CONGRESO HHT ESPAÑA
Del 3 al 5 de junio de 2022
Valencia

HHT
Asociación HHT España

# MEDICINA TRASLACIONAL EN LA TELANGIECTASIA HEMORÁGICA HEREDITARIA

**A. Riera-Mestre**

**Unidad de HHT**

**Servicio de Medicina Interna. Hospital Universitari de Bellvitge**

**04 de junio de 2022**

Salut/ Bellvitge Hospital Universitari

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EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND
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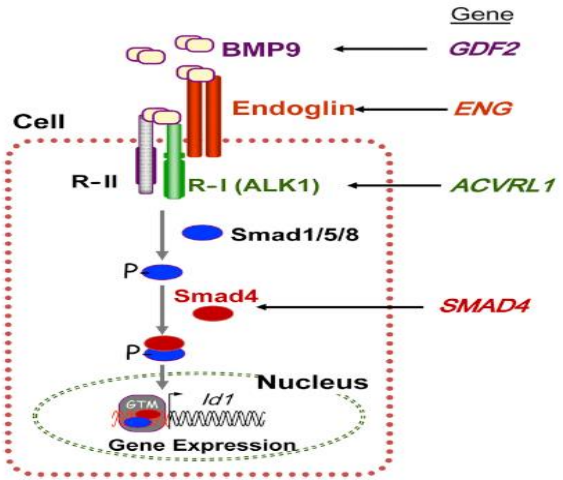
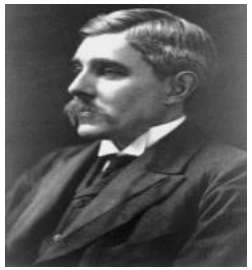
Instituto de Salud Carlos III



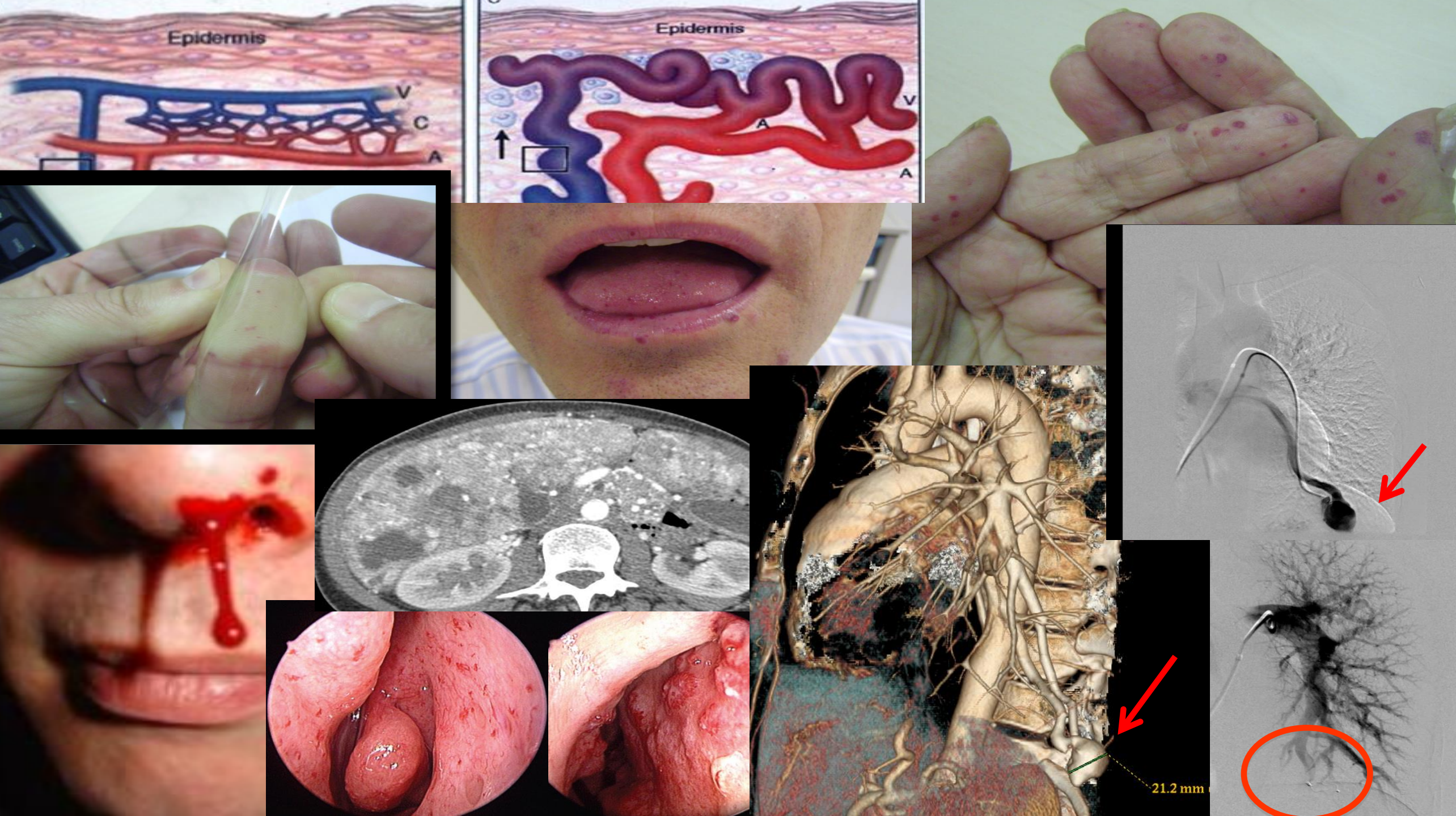
- ✓ **<u>Enfermedad Minoritaria</u>** (UE 1/2.000): Prevalencia 1/6.000
- ✓ Enfermedad **vascular de herencia autosómica dominante**
  - ✓ Caracterizada por **telangiectasias y otras MV de mayor tamaño**
- ✓ **<u>Variantes patogénicas en *ENG* ó *ACVRL1*</u>** son detectadas en > 85%
  - ✓ ***ENG* (HHT1)→** mayor prevalencia de FAV pulmonares y MV cerebrales
  - ✓ ***ACVRL1* (HHT2) →** mayor prevalencia de MV hepáticas
- ✓ HHT puede ser diagnosticada o vía molecular o clínica mediante los **<u>Criterios de Curaçao:</u>**

| Criterio | Descripcion |
|---|---|
| 1. Epistaxis | Espontaneas y recurrentes |
| 2. Telangiectasia | Múltiples en sitios característicos: labios, cavidad oral, dedos, fosa nasal |
| 3. Lesiones viscerales | MAVs gastrointestinal, pulmonar, hepático, cerebral o espinal |
| 4. Historia familiar | Familiar de primer grado con HHT |

**≥ 3, *definitivo***
**2, *probable***
**0-1, *improbable***



- ✓ **<u>Enfermedad edad-dependiente</u>**: inicio de los síntomas (**epistaxis**) y desarrollo de MV alrededor de la adolescencia con meseta alrededor de los 40-50 años.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# Manifestaciones Clínicas

- ✧ **Telangiectasias** Muc-Cut 95%
- ✧ **Epistaxis** 95%
- ✧ **MV Hepáticas** 60-85%
- ✧ **FAV Pulmonares** 20-40%
- ✧ **GI** 15-30% (*afectación tardía*)
- ✧ **MV Cerebrales** 5-15%

***Necesidad de un abordaje***
***INTERPROFESIONAL***

# UNIDADES INTERPROFESIONALES de EEMM

Además de diferentes especialidades médicas, incorporar otros profesionales de la Salud de acuerdo a las distintas necesidades de los pacientes con EEMM:

- ✓ **Asesor genético** → falta de reconocimiento profesional acreditado (y también de la especialidad de **Genética Clínica**)
- ✓ **Psicologia clínica**
- ✓ **Enfermera clínica**
- ✓ **Fisoterapeuta**
- ✓ **Trabajador social**
- ✓ **Gestor de casos**
- ✓ **Investigadores de básica**

**Riera-Mestre A. Editorial. Las Enfermedades Minoritarias en España: una mirada hacia delante. Med Clin 2021 (*en premsa*)**

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Núm. 195 | 7 d'octubre de 2011 | Gerència Territorial ICS Metropolitana Sud

Activitat assistencial

Índex

Enviar a un amic

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ICONotícies

## L'HUB inaugura la primera unitat especialitzada en el tractament de la telangectàsia hemorràgica hereditària a Catalunya

L'Hospital Universitari de Bellvitge ha posat en funcionament, aquest 15 de setembre, la Unitat Funcional de la Telangectàsia Hemorràgica Hereditària, la primera unitat especialitzada en el tractament d'aquesta malaltia a Catalunya.

Els seus responsables assistencials són el Dr. Francesc Cruellas, del Servei d'Otorinolaringologia, i el Dr. Antoni Riera-Mestre, del Servei de Medicina Interna.

**Incluída como <u>International Center of Excellence</u>, por la Asociación internacional CURE**

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*https://curehht.org/*

curehht

e Bellvitge

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Núm. 245 23 de juliol de 2013 Gerència Territorial ICS Metropolitana Sud

Butlletí setmanal de l'Hospital Universitari de Bellvitge

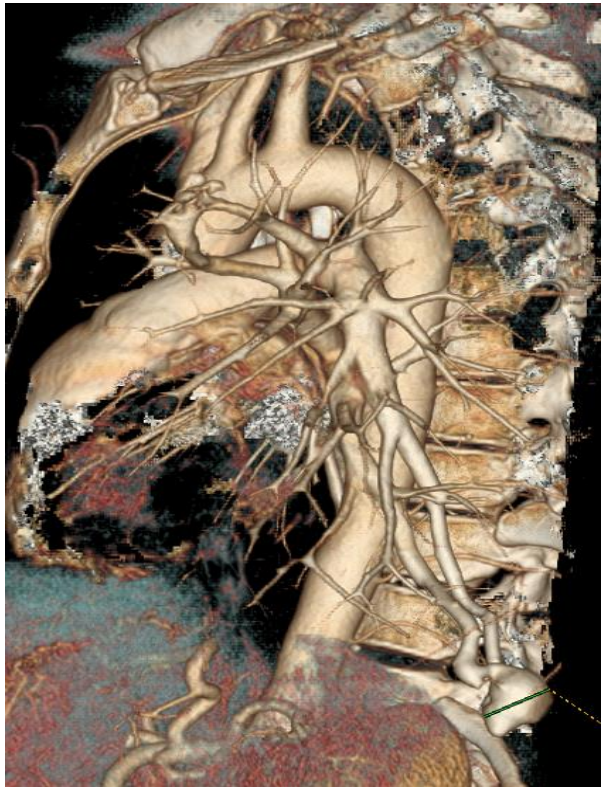
HHT

ASOCIACIÓN HHT ESPAÑA

# Noves línies de col·laboració com a centre referent en telangectàsia hemorràgica hereditària

Generalitat de Catalunya

El passat divendres 19 d'abril, van visitar l'Hospital Universitari de Bellvitge el Sr. Ángel Relancio, president de l'Associación de Enfermos con Telangectasia Hemorrágica Hereditaria (HHT), també anomenada malaltia de Rendu-Osler, i



# 450 pacientes en seguimiento

Bellvitge
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Professionals de Referència
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**Interprofesionalidad**
**Terciarismo**
**Excelencia**
**Referencia**
**Innovación**
**Tecnología**

## MIEMBROS DEL GRUPO de EEMM HUB

***1 de maig de 2017***

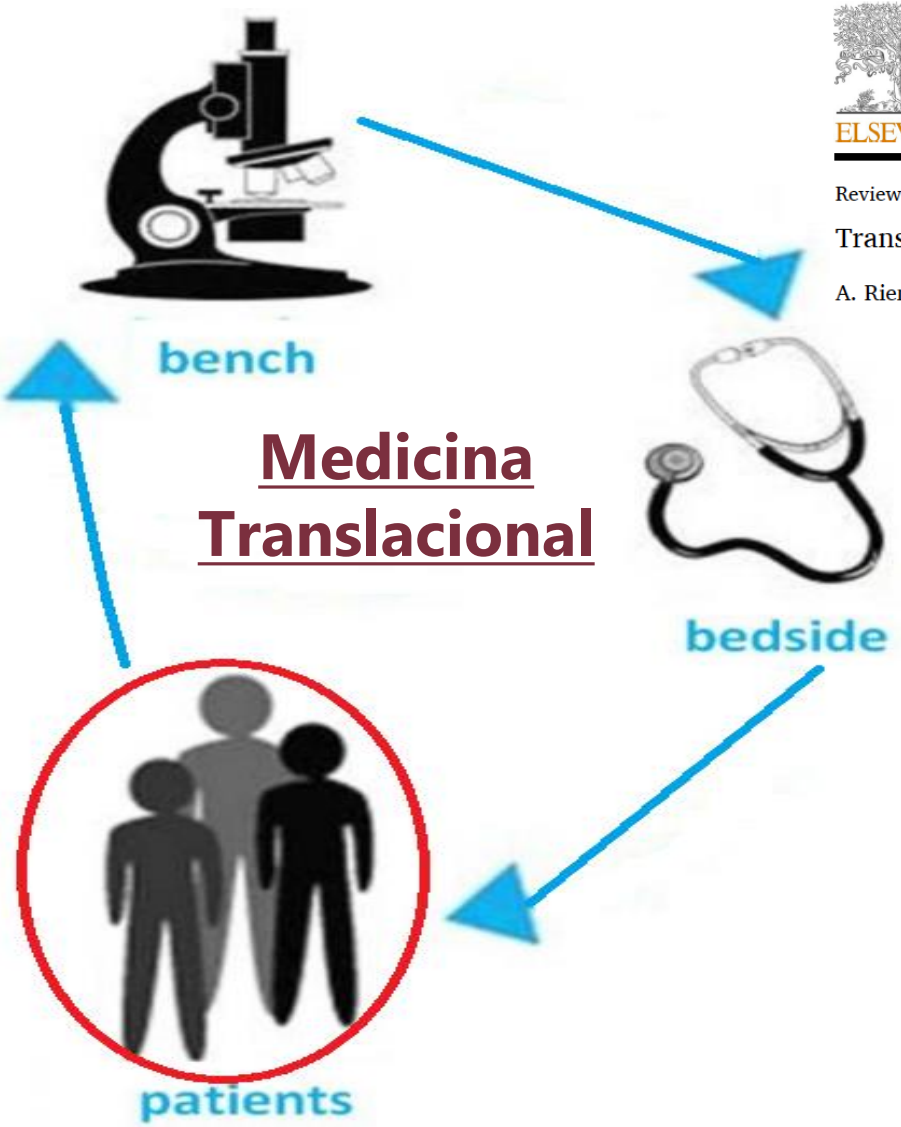
**CASASNOVAS PONS, CARLOS (NRL); COBOS MARTIN, ESTEFANIA (OFT); DÍEZ LOPEZ, CARLES (CAR); FALIP CENTELLAS, MERCÈ (NRL); GASCÓN BAYARRI, JORDI (NRL); LOPEZ URDIALES, RAFAEL (END); LLEONART BELLFILL, RAMON (ALE); MOLINA MOLINA, MARIA (NML); NARVAEZ GARCIA, JAVIER (REU); POVEDANO PANADES, MÒNICA (NRL); RAMA ARIAS, INÉS (NEF); RIBAS SOLA, JESÚS (NML); RIERA MESTRE, ANTONI (MIR); RUBIO RIBAS, MANUEL (MIR); SOLANICH MORENO, XAVIER (MIR); TORRAS AMBRÓS, JOAN (NEF)**

# OBJECTIVOS del GRUPO de EEMM:

**III JORNADA OCTUBRE 2022**

I Jornada II Jornada

- ✓ **SINERGIAS**
  - ✓ Más de 200 EEMM → > 3.000 pacientes con EEMM
- ✓ **POTENCIAR ASISTENCIA**
  - ✓ Características comunes de EEMM → **GENÈTICA**
  - ✓ Acceso a UEC, CSUR i ERN
- ✓ **INVESTIGACIÓN**
  - ✓ Dinamizar proyectos → CIBERER (isciii)
  - ✓ IDIBELL INSTITUT D'INVESTIGACIÓ BIOMÈDICA DE BELLVITGE → **MEDICINA TRASLACIONAL**
- ✓ **DOCENCIA** → sesiones, cursos, **ROTACIÓN** para residentes de toda España
- ✓ RELACIÓN amb **ASOCIACION DE PACIENTES**
  - ✓ FEDER, European Organisation for Rare Diseases (EURORDIS)
- ✓ **COMPETITIVIDAD - VISIBILIDAD - DIFUSIÓN** → **JORNADAS**




# Medicina Translacional

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Translational medicine in hereditary hemorrhagic telangiectasia

A. Riera-Mestre [a,b,c,*], P. Cerdà [a,b], A. Iriarte [a,b], M. Graupera [d,e], F. Viñals [f,g,h]

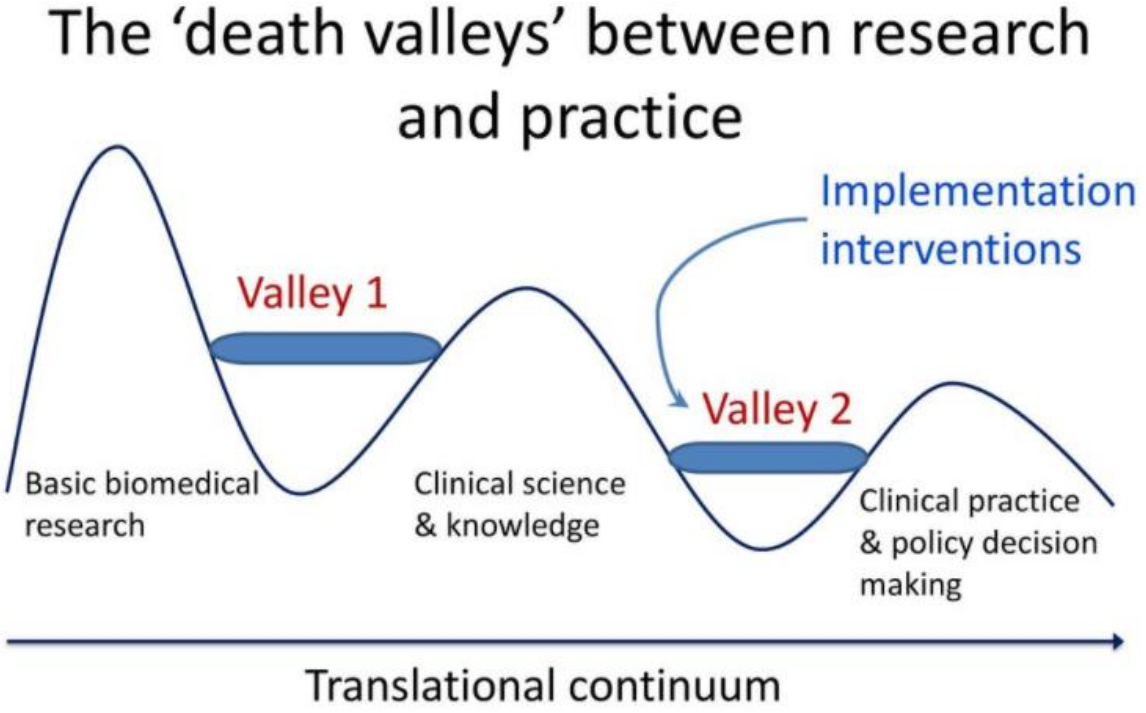
**Riera-Mestre A, et al. Translational medicine in HHT. Eur J Int Medicine 2021.**

- ✓ La **INVESTIGACIÓN** o **MEDICINA TRASLACIONAL** es un esfuerzo para crear nuevas terapias o procedimientos diagnósticos, basados en estudios de **procesos** de enfermedades (con modelos celulares)
  - ✓ El adjetivo "traslacional" se refiere a ”trasladar” estos hallazgos científicos básicos desde un entorno de laboratorio a posibles tratamientos para pacientes.

- ✓ De hecho, la Sociedad Europea de Medicina Traslacional la define como ***una medicina MULTIDISCIPLINAR apoyada por tres pilares: pacientes, laboratorio y comunidad, que promueve mejoras en prevención, diagnóstico y tratamiento, con el objetivo principal de MEJORAR la atención a los pacientes.***

A pesar del aumento de los esfuerzos e inversiones en investigación traslacional, la producción de nuevos medicamentos ha disminuido en los últimos años.

- ✓ Una de las razones de esta **brecha** es la difícil transición entre las etapas preclínicas ("básica") y clínicas.
  - ✓ Los experimentos de laboratorio deben reflejar las necesidades de los pacientes.



Mora-Luján et al. Orphanet Journal of Rare Diseases (2020) 15:63
https://doi.org/10.1186/s13023-020-1337-5

Orphanet Journal of Rare Diseases

RESEARCH Open Access

# Gender differences in hereditary hemorrhagic telangiectasia severity

J. M. Mora-Luján[1,2,3], A. Iriarte[1,2,3], E. Alba[1,3,4], M. A. Sánchez-Corral[1,3,5], P. Cerdà[1,2,3], F. Cruellas[1,3,6], Q. Ordi[1,3,4], X. Corbella[1,2,3,7], J. Ribas[1,3,8], J. Castellote[1,3,9,10] and A. Riera-Mestre[1,2,3,10*]

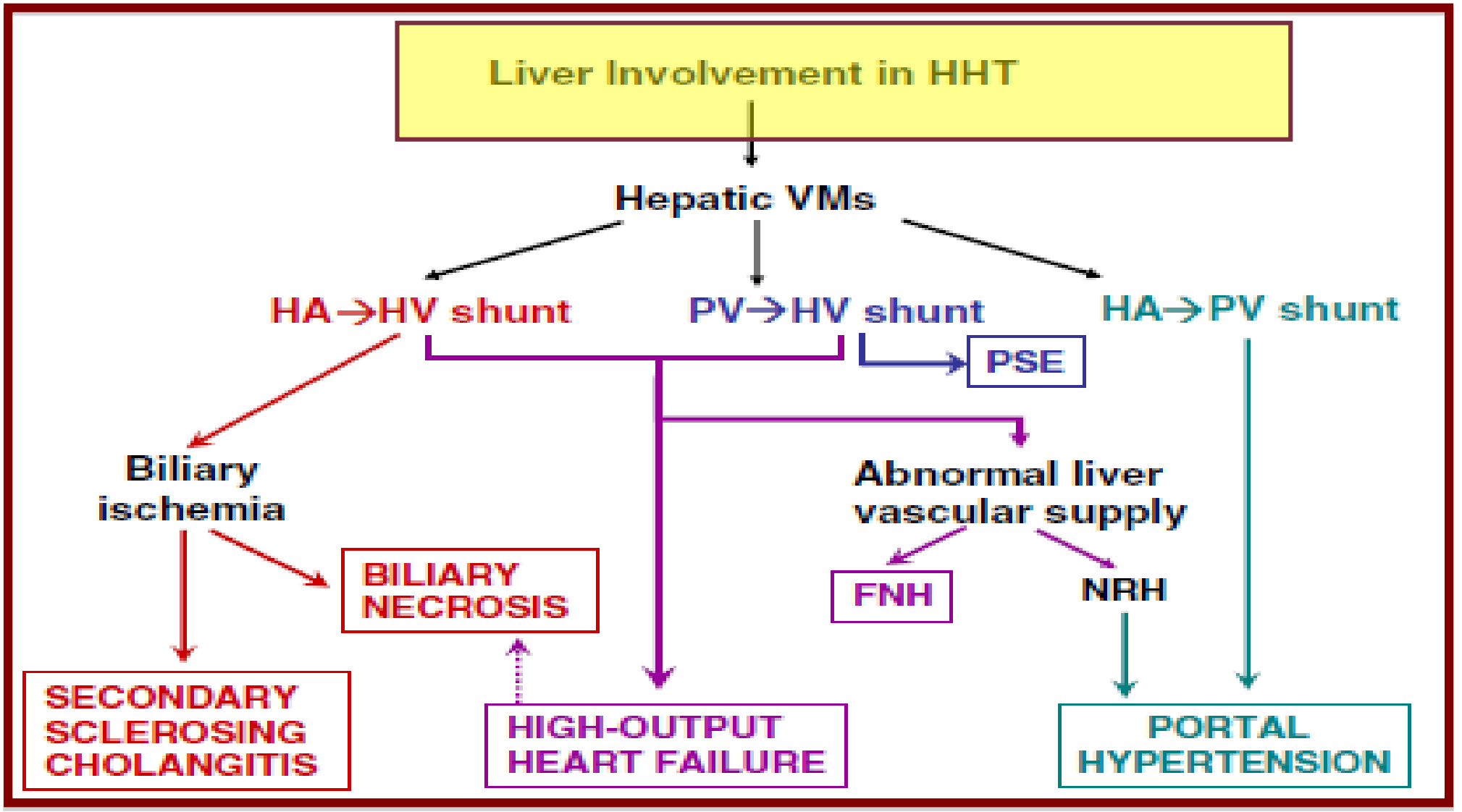
**Table 3** Gender differences in HHT severity

| | Female (n = 142) | Male (n = 100) | *P* value |
|---|---|---|---|
| ***Follow-up, months (mean ± SD)*** | 41.9 ± 25.8 | 40.4 ± 25.3 | 0.647 |
| ***ESS*** | | | |
| ESS at baseline (mean ± SD) | 3.47 ± 2.19 | 3.65 ± 2.12 | 0.536 |
| ESS during follow-up (mean ± SD) | 2.21 ± 1.76 | 2.52 ± 1.71 | 0.242 |
| ESS ≥ 4 | 61 (42.9%) | 37 (37%) | 0.379 |
| ESS ≥ 7 | 9 (6.3%) | 8 (8%) | 0.604 |
| ***Simple Clinical Scoring Index*** | 3.38 ± 1.20 | 2.03 ± 1.24 | < 0.001 |
| Low | 36 (25.3%) | 61 (61%) | < 0.001 |
| Intermediate | 90 (63.4%) | 31 (31%) | < 0.001 |
| High | 7 (4.9%) | 0 | 0.043 |
| ***HHT-score*** | 2.31 ± 1.06 | 2.09 ± 0.88 | 0.083 |
| Mild | 88 (62%) | 69 (69%) | 0.259 |
| Moderate | 47 (33.1%) | 29 (29%) | 0.532 |
| Severe | 7 (4.9%) | 1 (1%) | 0.245 |
| ***Invasive treatment*** | | | |
| Pulmonary embolization | 34 (23.9%) | 16 (16%) | 0.126 |
| Brain embolization | 2 (1.4%) | 0 | 0.470 |
| Liver transplantation | 2 (1.4%) | 0 | 0.513 |
| Young surgery | 3 (2.1%) | 0 | 0.270 |
| Anyone of the above | 40 (28.2%) | 16 (16%) | 0.027 |

## Simple Clinical Scoring Index

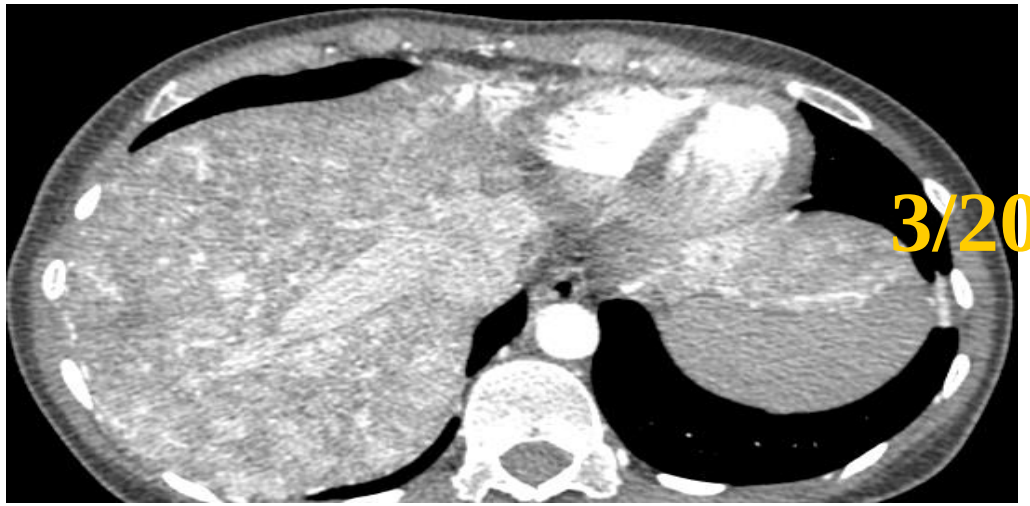
| Variable | Cut-off | Score |
|---|---|---|
| Age at presentation (yr) | >47 | 1 |
| | ≤47 | 0 |
| Sex | Female | 1 |
| | Male | 0 |
| Hemoglobin at presentation (g/dl) | <8 | 3 |
| | 8-12 | 2 |
| | 12-16 | 1 |
| | >16 | 0 |
| Alkaline phosphatase at presentation (IU/L) | >300 | 4 |
| | 225-300 | 3 |
| | 150-224 | 2 |
| | 75-149 | 1 |
| | <75 | 0 |

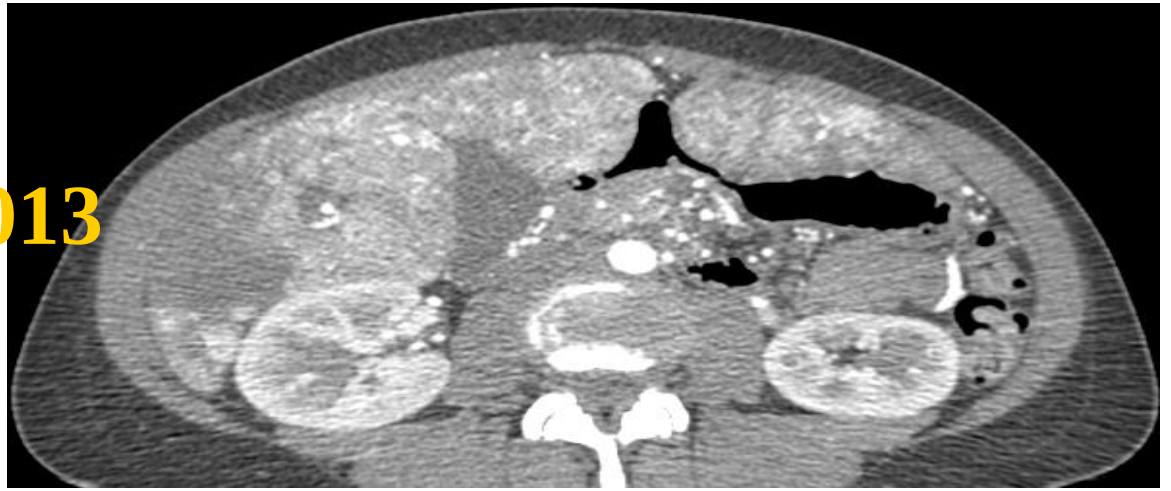
**Tanto en pacientes HHT1 (n=80) como HHT2 (n=75)**




*García-Tsao G. J Hepatology 2007*

# Mujer de 38 años con HHT2





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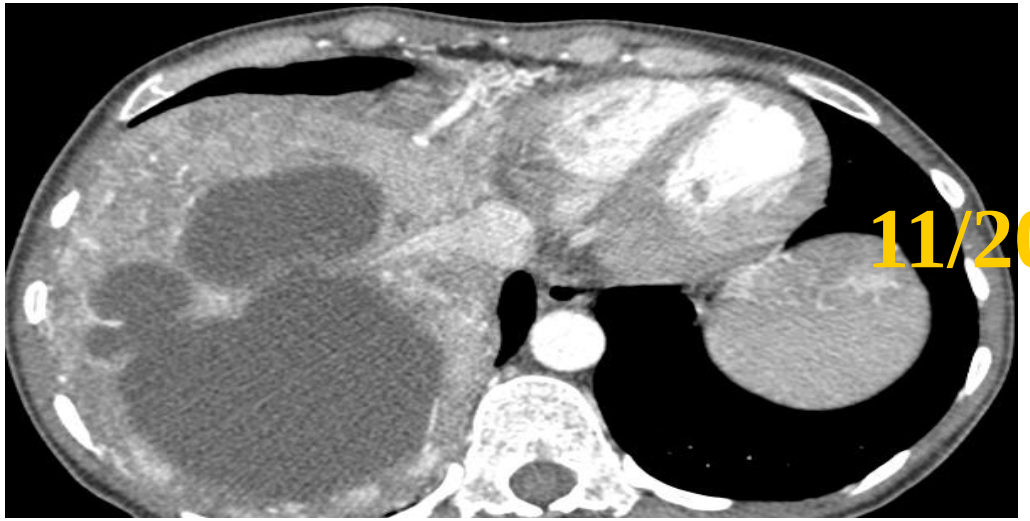
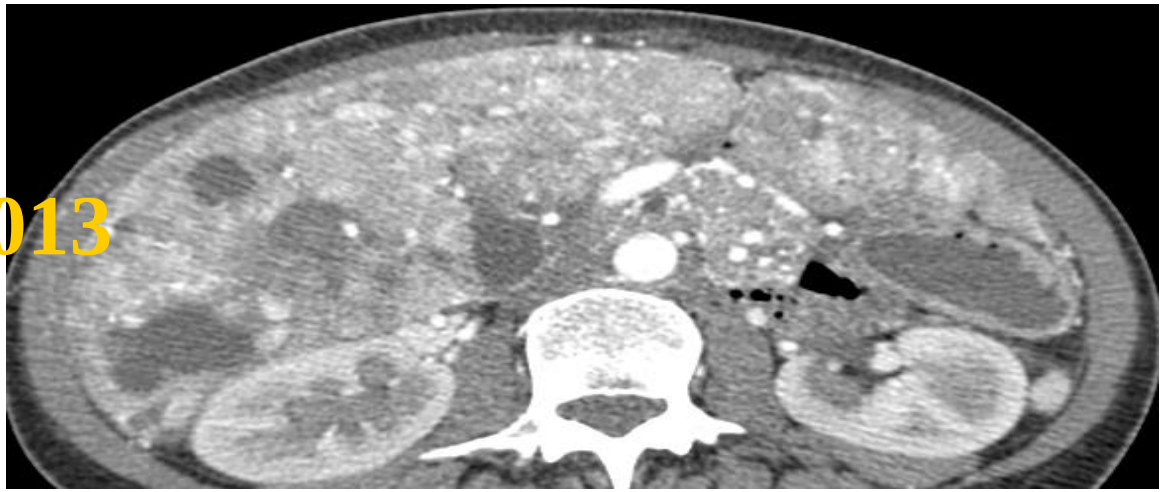
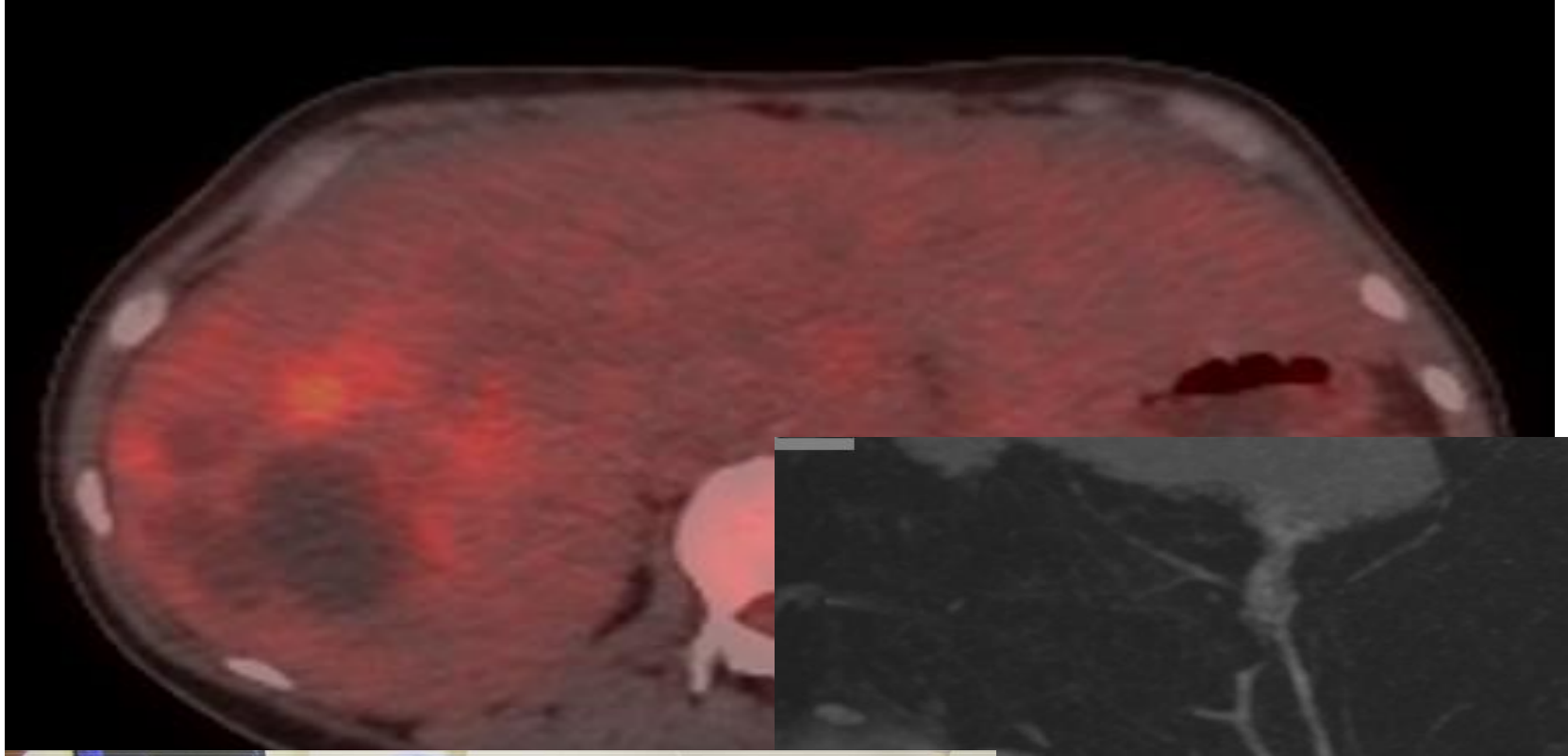
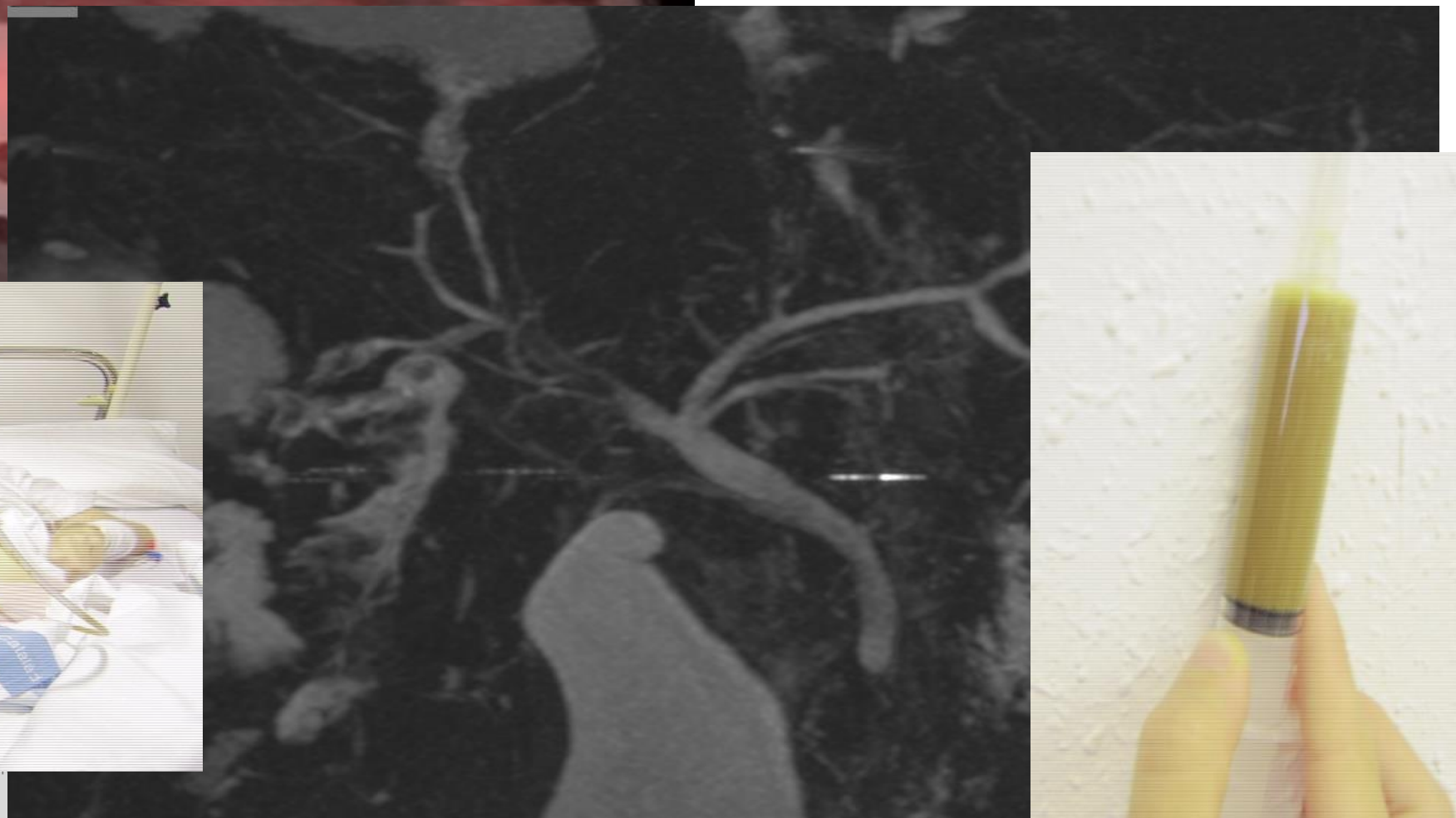




11/2013

# ColangioRM





15 de Diciembre, 2019
Fotografía autorizada por la paciente

Liver Transplantation for Hereditary Hemorrhagic Telangiectasia

*Report of the European Liver Transplant Registry*

**Lerut J, et al. Ann Surg 2006;244: 854–864**

**40 patients → 35 (87.5%) were female**

REVIEW ARTICLE

**Liver transplantation for hereditary hemorrhagic telangiectasia: a systematic review**

Emanuele Felli, Pietro Addeo, François Faitot, Gennaro Nappo, Constantin Oncioiu & Philippe Bachellier

**HBP 2017;19:567-572**

**57 patients → 51 (90%) were female**

**Liver Transplantation Trends and Outcomes for Hereditary Hemorrhagic Telangiectasia in the United States**

Vivek N. Iyer, MD,[1] Behnam Saberi, MD,[2] Julie K. Heimbach, MD,[3] Joseph J. Larson,[4] Suresh Raghavaiah,[5] Ivo Ditah, MD,[6] Karen Swanson, MD,[7] Patrick S. Kamath, MD,[3] KD Watt, MD,[3] Timucin Taner, MD,[3] Michael J. Krowka, MD,[3] and Michael D. Leise, MD[3]

**Transplantation 2019;103:1418-1424**

**24 patients → 20 (83.3%) were female**

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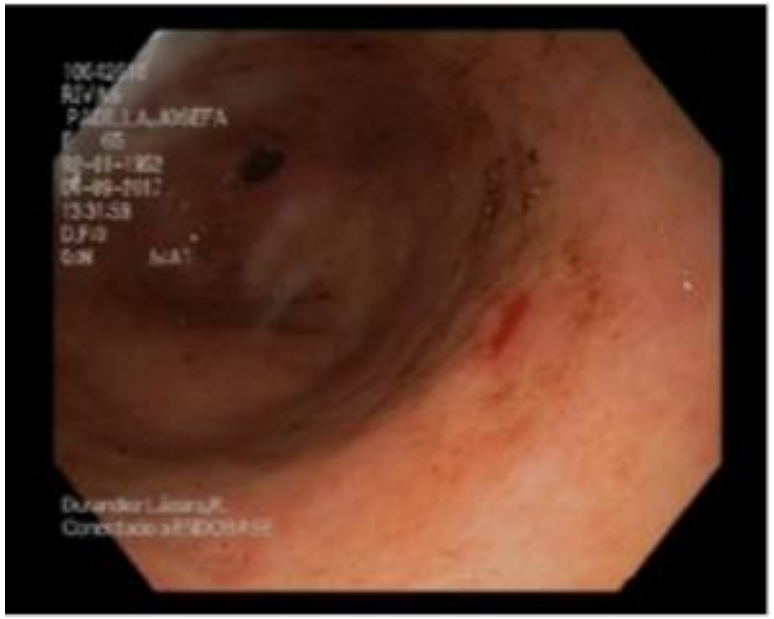
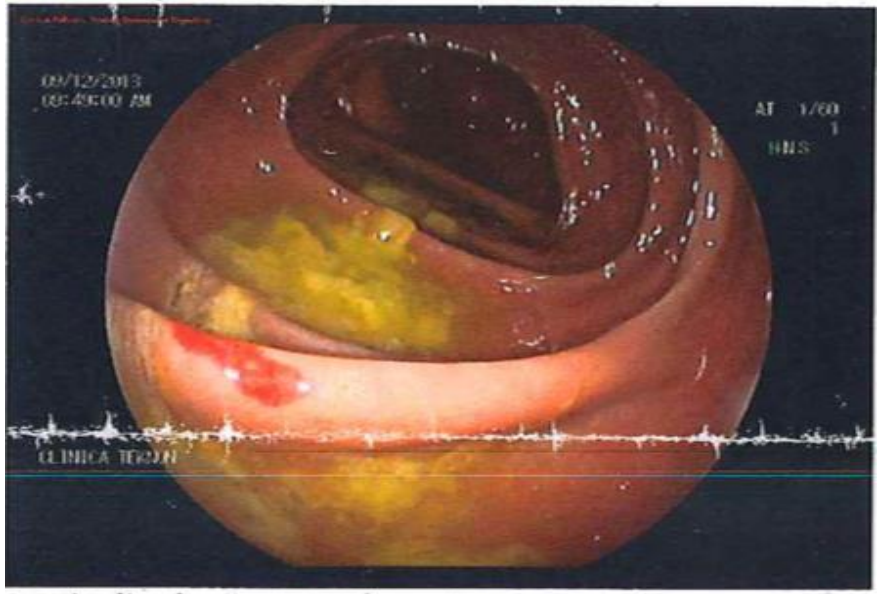
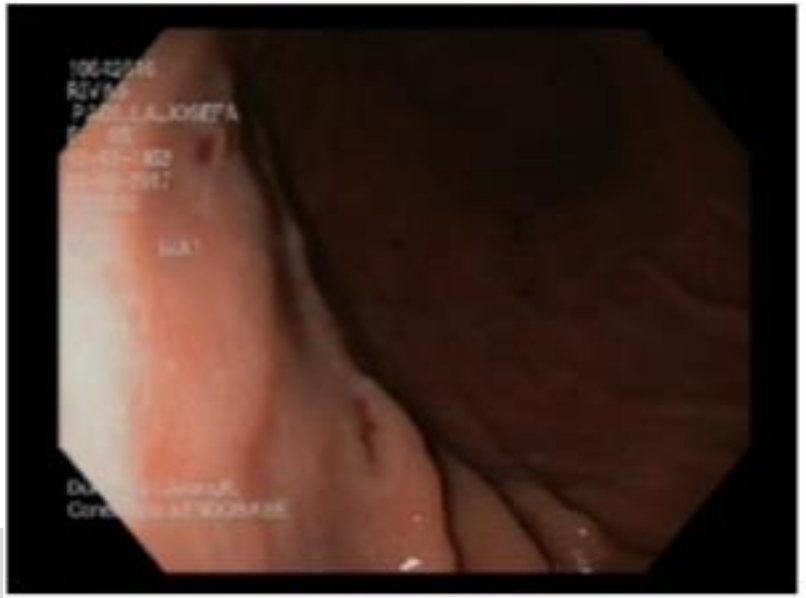
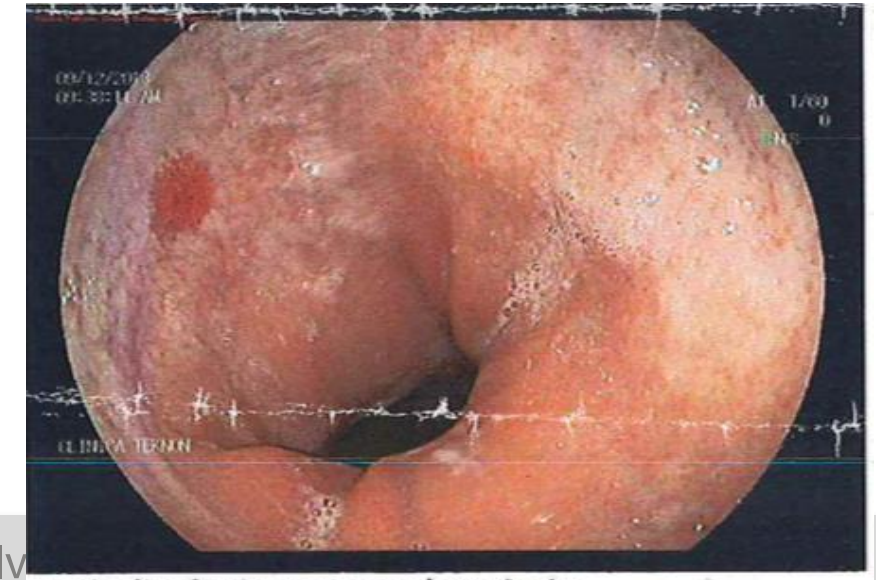


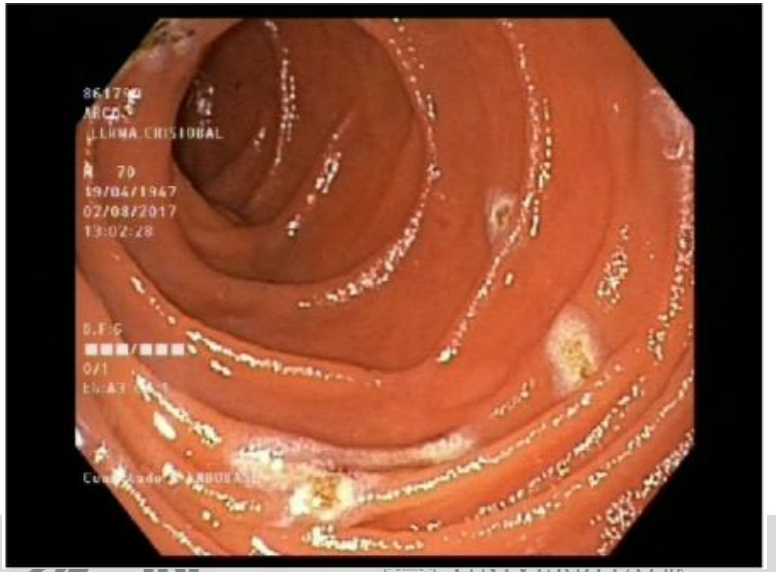


angiodisplasia en colon





angiodisplasia en saco herniario



*Article*

# Gastrointestinal Bleeding in Patients with Hereditary Hemorrhagic Telangiectasia: Risk Factors and Endoscopic Findings

Journal of *Clinical Medicine*

*J. Clin. Med.* 2020, *9*, 82; doi:10.3390/jcm9010082

José María Mora-Luján [1,2,3], Adriana Iriarte [1,2,3], Esther Alba [1,3,4], Miguel Ángel Sánchez-Corral [1,3,5], Ana Berrozpe [3,6], Pau Cerdà [1,2,3], Francesc Cruellas [1,3,7], Jesús Ribas [1,3,8], Jose Castellote [1,3,6] and Antoni Riera-Mestre [1,2,3,9,*]

Table 4. Clinical outcomes during follow-up according to gastrointestinal involvement.

| | GI Involvement (n = 67) | No GI Involvement (*n* = 28) | *p* Value | Unsuspected GI Involvement (*n* = 145) | *p* Value * |
|---|---|---|---|---|---|
| Follow-up (months), mean (SD) | 33.6 (21.9) | 29.2 (20.5) | 0.354 | 35.4 (23.6) | 0.585 |
| Outcomes, | | | | | |
| RBC transfusion, *n* (%)<br>Number of transfusions, mean (range) | 41 (61.2)<br>26.2 (1–218) | 8 (28.6)<br>8.9 (2–35) | 0.004<br>0.042 | 22 (15.4)<br>9.1 (1–50) | <0.001<br>0.101 |
| ED visit, *n* (%) | 40 (59.7) | 7 (25) | 0.002 | 42 (29) | <0.001 |
| Hospital admission, *n* (%) | 28 (41.8) | 5 (17.9) | 0.025 | 16 (11) | <0.001 |
| Mortality, *n* (%) | 2 (3%) | 0 | 1.000 | 3 (2.1) | 0.652 |

GI: gastrointestinal; SD: standard deviation; RBC: red blood cells; ED: Emergency Department; * Comparison between GI involvement and unsuspected GI involvement groups.

*Article*

# Gastrointestinal Bleeding in Patients with Hereditary Hemorrhagic Telangiectasia: Risk Factors and Endoscopic Findings

Journal of *Clinical Medicine*

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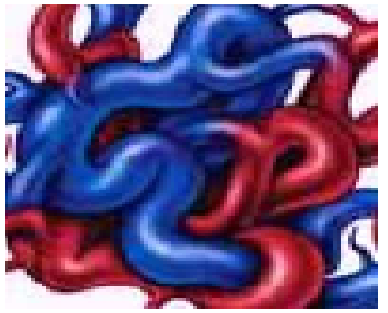
José María Mora-Luján [1,2,3], Adriana Iriarte [1,2,3], Esther Alba [1,3,4], Miguel Ángel Sánchez-Corral [1,3,5], Ana Berrozpe [3,6], Pau Cerdà [1,2,3], Francesc Cruellas [1,3,7], Jesús Ribas [1,3,8], Jose Castellote [1,3,6] and Antoni Riera-Mestre [1,2,3,9,*]

**Table 2.** Uni- and multivariable logistic regression analyses for gastrointestinal bleeding in patients with HHT.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Male | 1.64 | 0.66–4.08 | 0.283 | 0.90 | 0.15–5.32 | 0.910 |
| Age, years | 1.02 | 0.98–1.05 | 0.339 | 1.07 | 1.06–1.14 | 0.033 |
| Age > 50 years | 2.30 | 0.86–6.16 | 0.095 | 2.06 | 0.07–61.42 | 0.676 |
| Smoking | 3.27 | 1.26–8.48 | 0.015 | 7.82 | 1.37–44.52 | 0.020 |
| *ENG* mutations | 4.42 | 1.25–15.57 | 0.021 | 5.72 | 1.02–31.93 | 0.047 |
| *ACVRL1* mutations | 0.31 | 0.10–0.99 | 0.049 | 1.99 | 0.07–54.84 | 0.685 |
| Ferritin levels < 15 ug/L | 4.07 | 1.5–11.03 | 0.006 | 3.09 | 0.55–17.5 | 0.202 |
| Hemoglobin, g/dL | 0.97 | 0.95–0.99 | 0.003 | 0.96 | 0.93–0.96 | 0.033 |
| Hemoglobin levels < 8 g/dL | 2.18 | 0.83–5.76 | 0.112 | 0.75 | 0.09–6.55 | 0.801 |
| ESS ≥ 4 | 2.20 | 0.87–5.57 | 0.095 | 1.57 | 0.26–9.66 | 0.624 |

**Entre los pacientes con afectación GI aquellos con Hb < 8 g/dL y/o necesidad de transfusión requirements (n=44) comparado con el resto (n=23), mostraban telangiectasias más grandes (> 3 mm)**

# RiTHHA



REGISTRO INFORMATIZADO TELANGIECTASIA HEMORRAGICA HEREDITARIA

**Primer paciente… JUNIO 2016**

**Actualmente 366 pacientes**

Grupo de Enfermedades Minoritarias

health[in]code

# Empezó en JUNIO 2016

RiTHHA

REGISTRO INFORMATIZADO TELANGIECTASIA HEMORRAGICA HEREDITARIA

ACCESIBLE en **https://RiHHTa.healthincode.com**

RiHHTa

REGISTRO INFORMATIZADO TELANGIECTASIA HEMORRAGICA HEREDITARIA

Welcome, ariera | Logout

Unidad HHT. Servicio de Medicina Interna

Patients | Export Data | Participants | Documents

Personal data | Demographics | Clinical diagnosis | Personal history | Family & Family history | Physical examinations | Additional tests | Treatments | Events | Report

**Group:** HUB-HHT / **Family:** 3 / **Patient:** HUB-003 (PID: HUB-HHT-0003)

Save to review | Save | Cancel

## Clinical diagnosis

| | |
|---|---|
| Diagnosis | Affected or posibly affected |
| Symptoms start date | 01/01/1986 |
| Initial symptoms | Epistaxis |
| HHT diagnosis date | 01/01/1993 |
| Baseline Curacao criteria | 4 (Definitive) |
| Recurrent epistaxis | Yes |
| Start date | 01/01/1986 |
| Mucous cutaneos telangiectasias | Yes |
| Start date | 01/01/1993 |
| Visceral involvement | Yes |
| Hepatic | Yes |
| Cerebral | No |
| Digestive | No |
| Spinal | Unknown |
| Pulmonary | |
| Start date | 01/04/2011 |
| First degree family history | Yes |

RiTHHA

REGISTRO INFORMATIZADO TELANGIECTASIA HEMORRAGICA HEREDITARIA

ORIGINAL ARTICLE

## Computerized registry of patients with hemorrhagic hereditary telangiectasia (RiHHTa registry) in Spain: Objectives, methods, and preliminary results☆

A. Riera-Mestre[a,b,c,*], J.M. Mora Luján[a,c], R. Sanchez Martínez[c,d], M.A. Torralba Cabeza[c,e], J.L. Patier de la Peña[c,f], M.C. Juyol Rodrigo[c,g], D. Lopez Wolf[c,h], A. Ojeda Sosa[c,i], L. Monserrat[c,j], M. López Rodríguez[c,k], on behalf of the Researchers of the RiHHTa Registry◊

Rev Clin Esp. 2018;218(9):468–476

Sánchez-Martínez et al. Orphanet Journal of Rare Diseases (2020) 15:138
https://doi.org/10.1186/s13023-020-01422-8

Orphanet Journal of Rare Diseases

RESEARCH Open Access

## Current HHT genetic overview in Spain and its phenotypic correlation: data from RiHHTa registry

Rosario Sánchez-Martínez[1,2], Adriana Iriarte[2,3], José María Mora-Luján[2,3], José Luis Patier[2,4], Daniel López-Wolf[2,5], Ana Ojeda[2,6], Miguel Angel Torralba[2,7], María Coloma Juyol[2,8], Ricardo Gil[2,9], Sol Añón[2,10], Joel Salazar-Mendiguchía[11,12,13], Antoni Riera-Mestre[2,3,14*] and for the RiHHTa Investigators of the Rare Diseases Working Group from the Spanish Society of Internal Medicine

**Table 2** Summary of the variants analysis

| GENE mutation | ENG, n (%) | ACVRL1, n (%) |
|---|---|---|
| Patients, n | 36 | 77 |
| Sequencing method, n (%) | | |
| Sanger | 20 (55.5) | 45 (58.4) |
| NGS | 12 (33.3) | 26 (33.8) |
| Others | 4 (11.1) | 6 (7.8) |
| Variant type, n (%) | | |
| Nonsense | 10 (27.7) | 39 (50.6) |
| Frameshift | 13 (36.1) | 20 (25.9) |
| Splice-site | 4 (11.1) | 3 (3.9) |
| Missense | 9 (25) | 15 (19.4) |

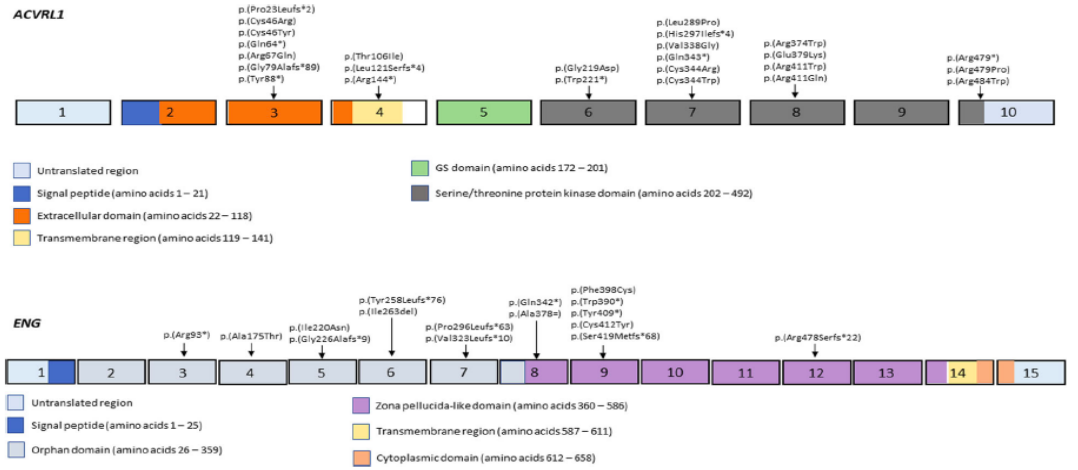



**Fig. 1** Schematic representation of the exons (boxes) of ACVRL1 and ENG genes. The identified exonic variants in our cohort are presented according to their location (colored boxes represent specific functional domains, each one of them is explained in the legends)

## Evidencia del daño endotelial y sus citas bibliográficas.

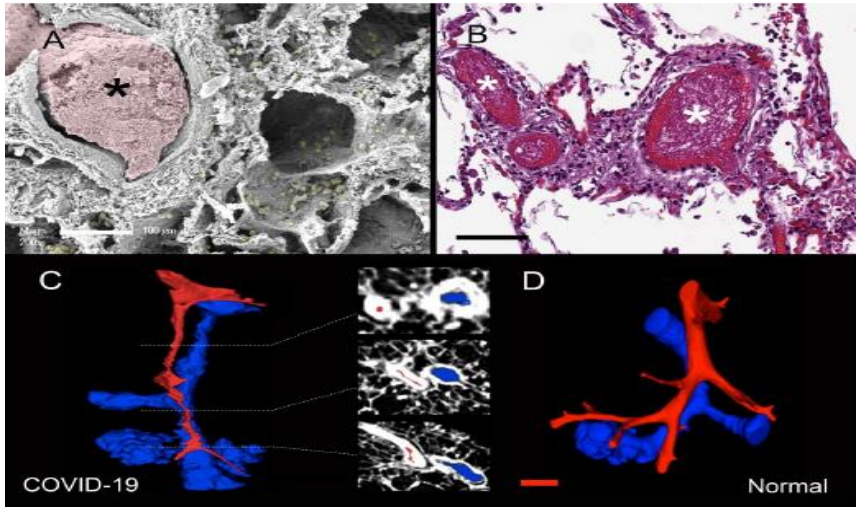
| Evidencia | Citas |
|---|---|
| Elevación del VEGF y menor actividad ADAMTS13 en formas más graves y relación con mortalidad a 60 días. | Rovas *et al*. Microvascular dysfunction in COVID-19: the MYSTIC study. *Angiogenesis*. 2020;1-13. |
| Elevación del Factor von Willebrand y menor actividad ADAMTS13. | Mancini *et al*. The ADAMTS13-von Willebrad factor axis in COVID-19 patients. *J Thromb Haemost* 2020. Doi: 10.1111/JTH.15191. |
| Elevación de VEGF en pacientes en la UCI. | Huang *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. |
| Elevación de células endoteliales circulantes en pacientes en la UCI. | Guervilly *et al*. Circulating Endothelial Cells as a Marker of Endothelial Injury in Severe COVID-19. *J Infect Dis*. 2020;222(11):1789-93. |
| Elevación de adrenomedulina. | Hupf *et al*. RNA-expression of adrenomedullin is increased in patients with severe COVID-19. *Crit Care*. 2020;24(1):527. |
| Evidencia histológica de daño e inflamación. | Ackermann *et al*. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*. 2020;383(2):120-8. |
| Evidencia histológica de inclusiones virales e infiltrado inflamatorio (endotelitis) en células endoteliales. | Varga *et al*. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-8. |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.



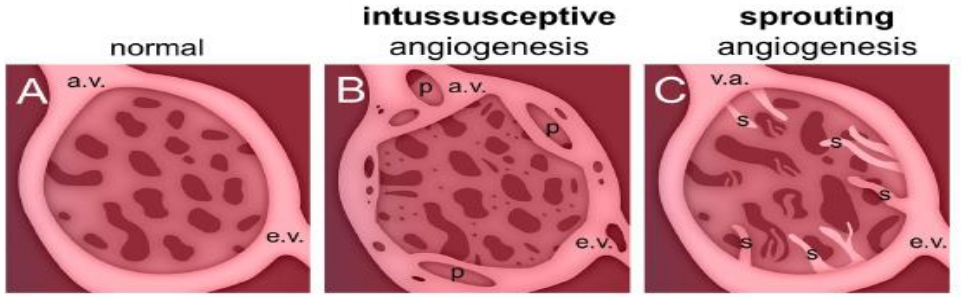




**Figure S 4. Schematic of intussusceptive and sprouting angiogenesis.** (A) The regular vasculature consists of an afferent (a.v.) and an efferent vessel (e.v.) and the intervening pulmonary alveolar capillary plexus (diameters not to scale). (B) Intussusceptive angiogenesis is found in COVID19-pulmonary plexuses characterized by the separation of preexisting blood vessels into two via the formation of an intravascular pillar (p). This allows a rapid expansion of the vascular plexuses to inflammatory and metabolic adaptations, and recruitment and incorporation of circulating progenitor cells from the bone marrow due to mechanosensitive regulations of shear stress and blood flow velocity. (C) The hallmark of sprouting angiogenesis is the formation of new "daughter" channels (s) composed of endothelial cells directly from an existing vessel extending to form tip and stalk cells, regulated by hypoxia and growth factors.

***J. Trujillo, A. Riera-Mestre. Enfermedad tromboembólica venosa en la COVID-19. Thromb Med 2020***

# RiTHHA

REGISTRO INFORMATIZADO TELANGIECTASIA HEMORRAGICA HEREDITARIA

## Angiogenesis, hereditary hemorrhagic telangiectasia and COVID-19

Antoni Riera-Mestre[1,2,3] · Adriana Iriarte[1,3] · Manuela Moreno[3,4] · Raul del Castillo[3,5] · Daniel López-Wolf[3,6]

*Angiogenesis 2021; 24:13-15*

RiHHTa (Computerized Registry of Hereditary Hemorrhagic Telangiectasia) is an open, multicenter, prospective, observational registry including adult patients with HHT and developed within the Rare Diseases Working Group of the Spanish Society of Internal Medicine [1]. RiHHTa has an online design (accessible from https://rihhta.healthincode.com) available in Spanish or English with individual encoded access for each researcher and counted on the nonremunerated collaboration of the genetic studies company Health in Code (A Coruña, Spain). The design of the RiHHTa registry was approved by the Ethics Committee of the Hospital Universitari de Bellvitge. The rationale and methodology of RiHHTa have been published elsewhere [1]. For this study, we focused in those HHT patients who required admission for COVID-19 pneumonia, so we created a 27-item survey that captured clinical data of hospitalized patients with both diseases. From June 8th to June 24th 2020, an electronic survey was distributed to all RiHHTa investigators. The survey was responded by investigators from 22 (79.3%) out of the 29 Spanish hospitals collaborating with RiHHTa registry and include 1177 HHT patients followed-up by the RiHHTa investigators. Overall, only one patient was admitted for COVID-19 pneumonia. She is a 74 years-old woman with a pathogenic variant in *ACVRL1* gene and hepatic vascular involvement. Her clinical course did not involve mechanical ventilation or worsening epistaxis, and she was successfully discharged after 2 weeks.

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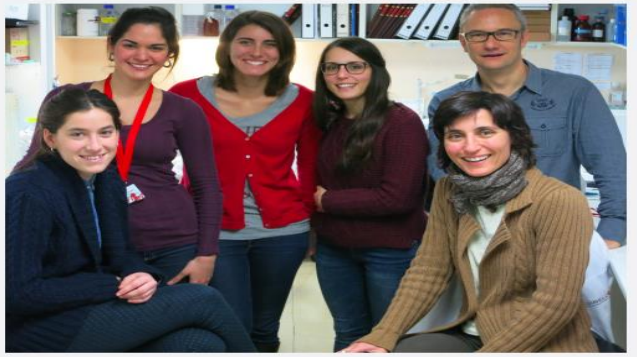
## Angiogenic factors



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Francesc Viñals

Collaborators
Agnes Figueras

Predoctoral researchers
Elisenda Alsina, Alicia Mansilla

Master and grade students
Zachary chanell Croes, Carla Riera

## Signaling Pathways in Angiogenesis

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Predoctoral researchers
Ana Angulo, Ana raquel Martins, Erika Monelli, Adriana Soler

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# PROYECTOS DE INVESTIGACIÓN EN SALUD 2018 – 2020

**“Estudio de alteraciones en vías de señalización del endotelio vascular y su correlación clínica en la Telangiectasia Hemorrágica Hereditaria”**

**Expediente Nº: PI17/00669**

*A. Riera-Mestre, JM Mora Luján, A. Jucglà Serra, A. Martins Figuereido, J. Ribas Sola, E. Alba Rey*

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# PROYECTOS DE INVESTIGACIÓN EN SALUD 2021 – 2023

**“Nuevas vías de señalización clínicamente relevantes relacionadas con la HHT”**

**Expediente Nº: PI20/00592**

***A. Riera-Mestre, P. Cerdà, JM Mora Luján, A. Jucglà Serra, A. Iriarte, J. Ribas Sola, Q. Ordi, J. Salazar Mendiguchia, P. Mur Molina***

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cells
MDPI

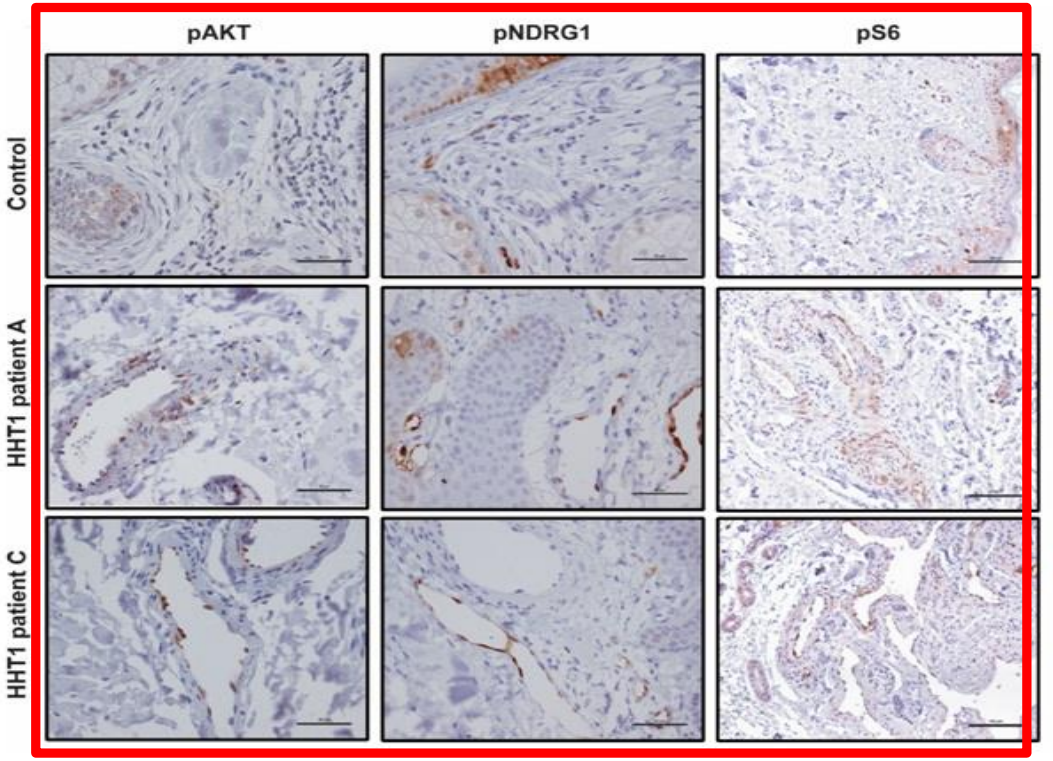
*Article*

# PI3K (Phosphatidylinositol 3-Kinase) Activation and Endothelial Cell Proliferation in Patients with Hemorrhagic Hereditary Telangiectasia Type 1

Adriana Iriarte [1,2,3,†], Agnes Figueras [4,5,†], Pau Cerdà [1,2,3], José María Mora [1,2,3], Anna Jucglà [1,3,6], Rosa Penín [3,7], Francesc Viñals [4,5,8,*,‡] and Antoni Riera-Mestre [1,2,3,9,*,‡]

Received: 31 July 2019; Accepted: 21 August 2019; Published: 24 August 2019

**Abstract:** Hemorrhagic hereditary telangiectasia (HHT) type 2 patients have increased activation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway in telangiectasia. The main objective is to evaluate the activation of the PI3K pathway in cutaneous telangiectasia of HHT1 patients. A cutaneous biopsy of a digital hand telangiectasia was performed in seven HHT1 and eight HHT2 patients and compared with six controls. The study was approved by the Clinical Research Ethics Committee of our center. A histopathological pattern with more dilated and superficial vessels that pushed up the epidermis was identified in HHT patients regardless of the type of mutation and was associated with older age, as opposed to the common telangiectasia pattern. The mean proliferation index (Ki-67) was statistically higher in endothelial cells (EC) from HHT1 than in controls. The percentage of positive EC for pNDRG1, pAKT, and pS6 in HHT1 patients versus controls resulted in higher values, statistically significant for pNDRG1 and pS6. In conclusion, we detected an increase in EC proliferation linked to overactivation of the PI3K pathway in cutaneous telangiectasia biopsies from HHT1 patients. Our results suggest that PI3K inhibitors could be used as novel therapeutic agents for HHT.




**Hiperactivación de la via de la PI3K → puede ser inhibida por inhibidores de la mTOR (sirolimus)**

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UNIVERSITAT DE BARCELONA

# ALK1 Loss Results in Vascular Hyperplasia in Mice and Humans Through PI3K Activation

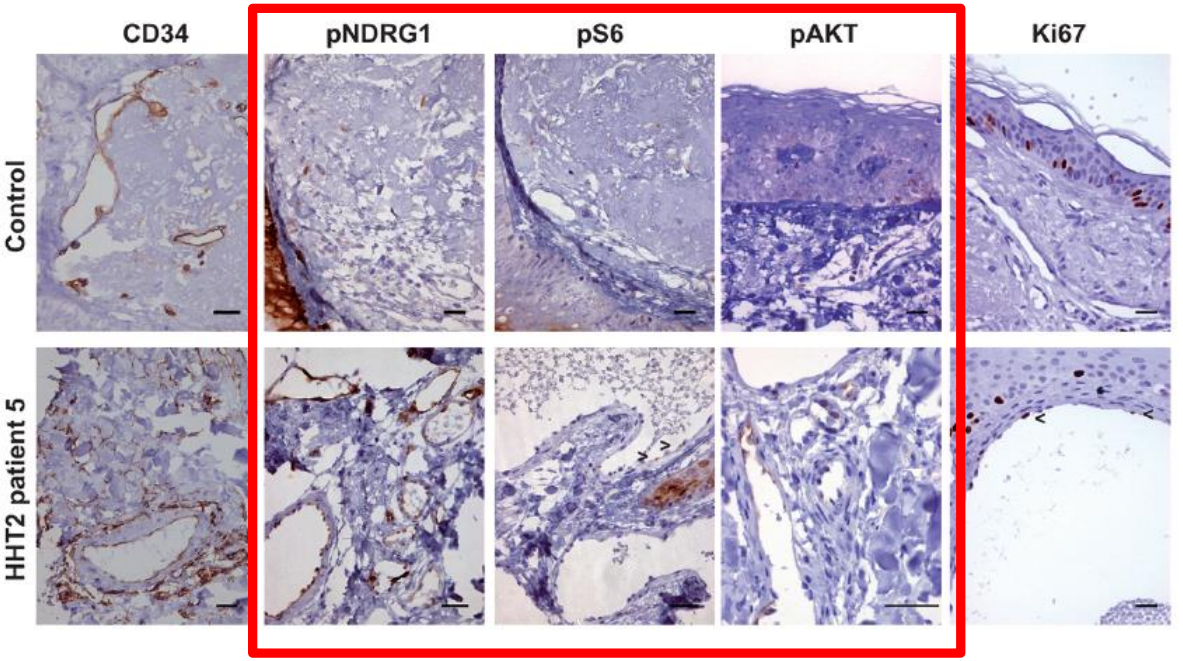
Elisenda Alsina-Sanchís,* Yaiza García-Ibáñez,* Ana M. Figueiredo, Carla Riera-Domingo, Agnès Figueras, Xavier Matias-Guiu, Oriol Casanovas, Luisa M. Botella, Miquel A. Pujana, Antoni Riera-Mestre, Mariona Graupera,† Francesc Viñals†

***Objective***—ALK1 (activin-receptor like kinase 1) is an endothelial cell-restricted receptor with high affinity for BMP (bone morphogenetic protein) 9 TGF-β (transforming growth factor-β) family member. Loss-of-function mutations in ALK1 cause a subtype of hereditary hemorrhagic telangiectasia—a rare disease characterized by vasculature malformations. Therapeutic strategies are aimed at reducing potential complications because of vascular malformations, but currently, there is no curative treatment for hereditary hemorrhagic telangiectasia.

***Approach and Results***—In this work, we report that a reduction in ALK1 gene dosage (heterozygous ALK1$^{+/-}$ mice) results in enhanced retinal endothelial cell proliferation and vascular hyperplasia at the sprouting front. We found that BMP9/ALK1 represses VEGF (vascular endothelial growth factor)-mediated PI3K (phosphatidylinositol 3-kinase) by promoting the activity of the PTEN (phosphatase and tensin homolog). Consequently, loss of ALK1 function in endothelial cells results in increased activity of the PI3K pathway. These results were confirmed in cutaneous telangiectasia biopsies of patients with hereditary hemorrhagic telangiectasia 2, in which we also detected an increase in endothelial cell proliferation linked to an increase on the PI3K pathway. In mice, genetic and pharmacological inhibition of PI3K is sufficient to abolish the vascular hyperplasia of ALK1$^{+/-}$ retinas and in turn normalize the vasculature.

***Conclusions***—Overall, our results indicate that the BMP9/ALK1 hub critically mediates vascular quiescence by limiting PI3K signaling and suggest that PI3K inhibitors could be used as novel therapeutic agents to treat hereditary hemorrhagic telangiectasia.

***Visual Overview***—An online visual overview is available for this article. (***Arterioscler Thromb Vasc Biol*. 2018;38: 1216-1229. DOI: 10.1161/ATVBAHA.118.310760.**)




**Hiperactivación de la via de la PI3K → puede ser inhibida por inhibidores de la mTOR (sirolimus)**

VADERIS Therapeutics AG

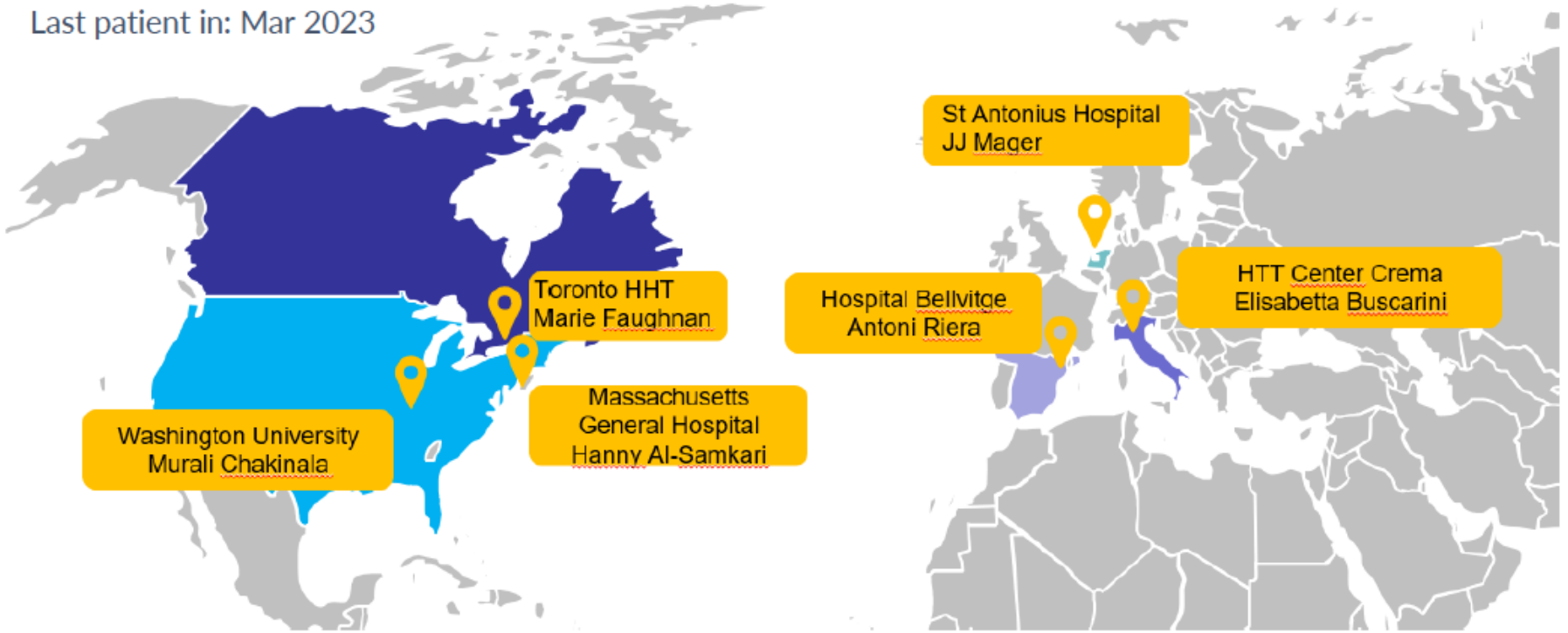
# Project timelines and study sites

Vaderis THERAPEUTICS

**A randomised, placebo controlled, double blind, multicentre proof of concept study to assess the safety and efficacy of two doses of VAD044 in patients with hereditary haemorrhagic telangiectasia (HHT)**

Investigator Meeting 30 May 2022

A maximum of **80 patients** will be randomised over **10 months** recruitment period.
First patient in: May 2022
Last patient in: Mar 2023



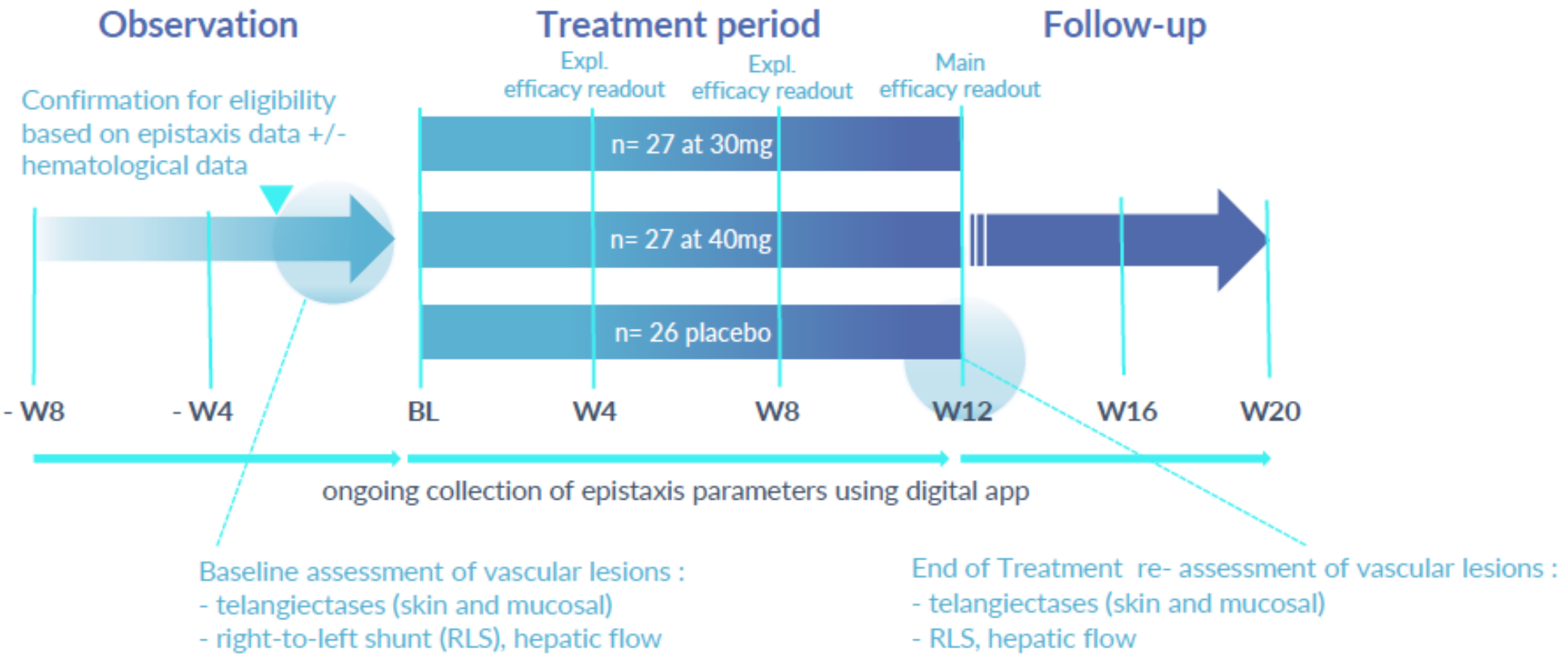
VADERIS Therapeutics AG

# Study design

## Randomized, 3 parallel arms, placebo controlled, double blind, to investigate the safety and tolerability of VAD044 in HHT

### Population characteristics

- Significant epistaxis with minimum monthly frequency (≥20) and duration (≥80 min)
- Chronically iron deficient: anemia or significant iron supplementation



Original article

# Adrenomedullin as a potential biomarker involved in patients with hereditary hemorrhagic telangiectasia

A. Iriarte [a,b,c], L. Ochoa-Callejero [d], J. García-Sanmartín [d], P. Cerdà [a,b,c], P. Garrido [d], J. Narro-Íñiguez [d], JM. Mora-Luján [a,b,c], A. Jucglà [a,c,e], MA Sánchez-Corral [a,c,f], F. Cruellas [a,c,g], E. Gamundi [h], J. Ribas [a,c,i], J. Castellote [a,c,j,k], F. Viñals [k,l,m], A. Martínez [d,1], A. Riera-Mestre [a,b,c,n,1,*]

- ✓ Adrenomedulina (AM) es un péptido vasoactivo mayoritariamente secretado por las células endoteliales con un importante rol en preservar la integridad endotelial
- ✓ Comparar niveles séricos y expresión tisular de AM entre pacientes HHT y controles

- ✓ Niveles séricos de AM

| | HHT | Controls | P-value |
|---|---|---|---|
| Patients, n | 45 | 50 | |
| Age, years; mean (SD) | 50.7 (14.9) | 46.4 (9.9) | 0.102 |
| Sex (females), (%) | 27 (60%) | 19 (38%) | 0.032 |
| AM pg/mL, median [Q1–Q3] | 68.3 [58.1–80.6] | 47.7 [43.2–53.8] | <0.001 |

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Original article

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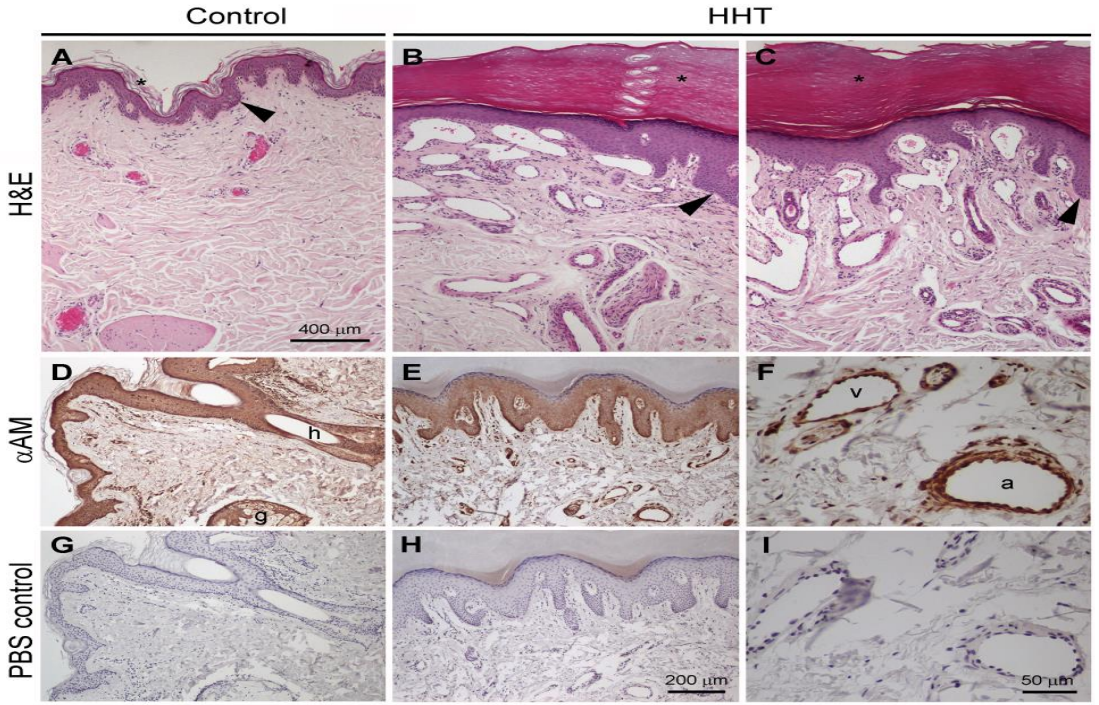
CIBR Centro de Investigación Biomédica de La Rioja

AM por inmunohistoquímica en biopsias de 8 pacientes HHT y 5 controles




**Mayor intensidad en la inmunoreactividad de AM en los vasos de pacientes con HHT**

**<u>Conclusiones</u>**: Se ha detectado niveles más elevados de AM en sangre y telangiectasias de pacientes HHT que controles

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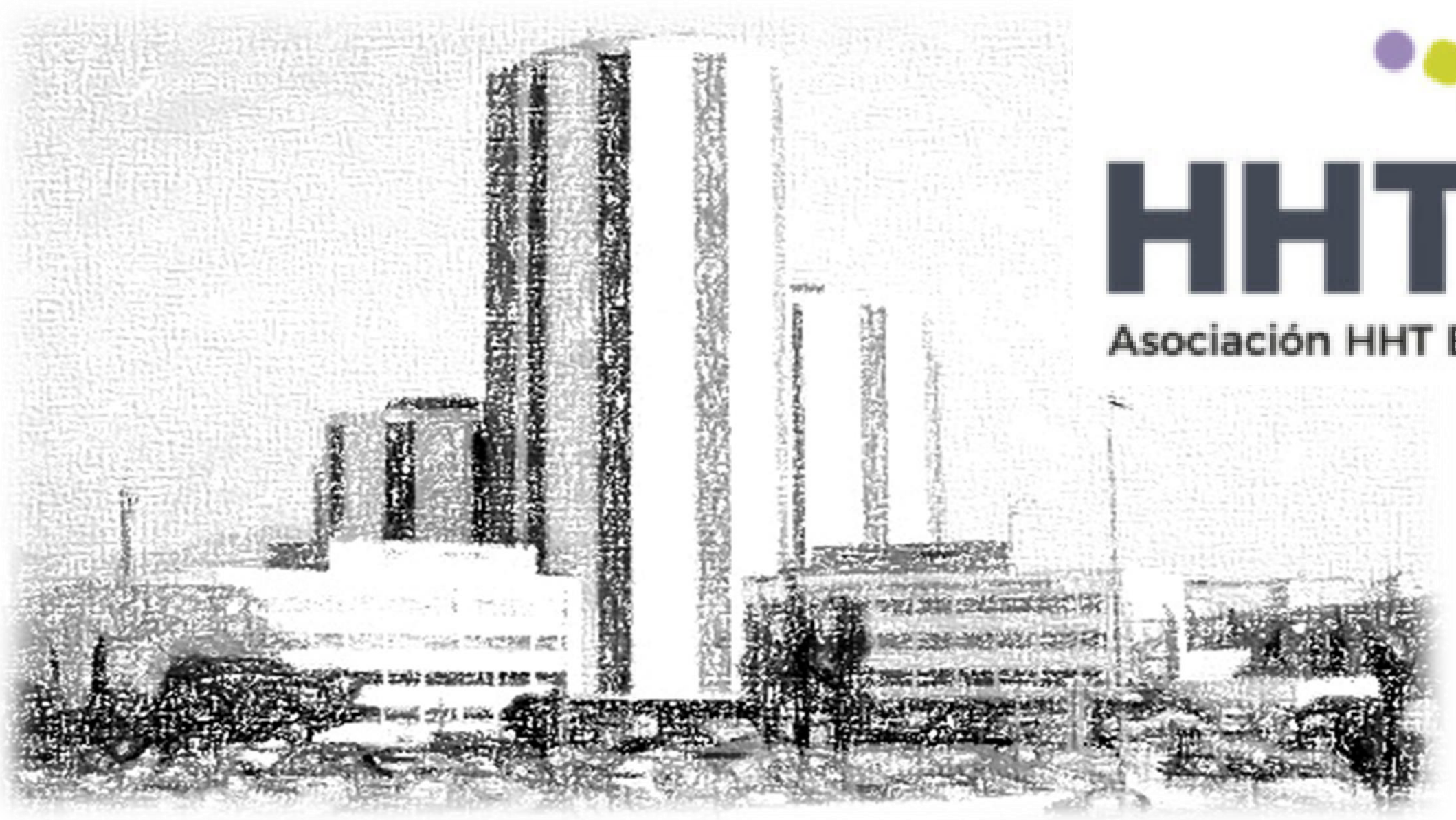
# 4 Tesis Doctorales en marcha → mayo 2023

JULIO 2020

JUNIO 2022



HHT

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