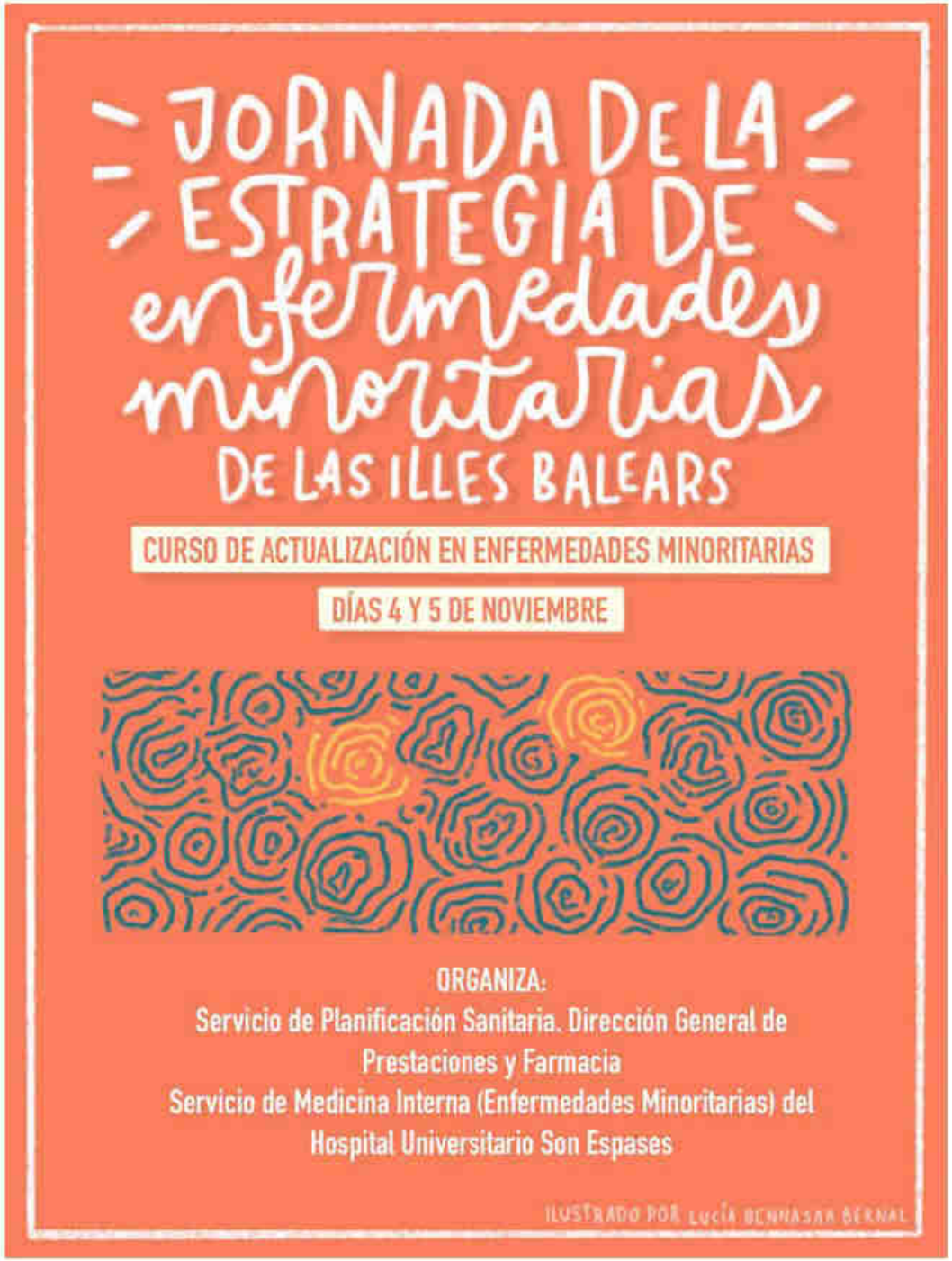

COMITÈ ORGANITZADOR

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Dr. Atanasio García Pineda
Dr. Eusebi J. Castaño Riera
Sra. Yolanda Muñoz Alonso
Dra. Catalina Nadal Martí
Dra. Maria Villalonga Comas
Dra. Iciar Martínez López
Dra. Ángeles Ruiz Gómez

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Dra. Inés Losada López
Dr. Juan González Moreno
Dr Lucio Pallarés Ferreres

L'ORGANITZEN

Servei de Planificació Sanitària, Direcció General de Prestacions i Farmàcia
Servei de Medicina Interna (Malalties Minoritàries) de l'Hospital Universitari Son Espases

GOIB / CONSELLERIA SALUT I CONSUM

MEDICINA TRASLACIONAL EN LA TELANGIECTASIA HEMORÁGICA HEREDITARIA

A. Riera-Mestre, M.D., PhD.
Unidad de HHT
Servicio de Medicina Interna
Hospital Universitari de Bellvitge
5.11.2021

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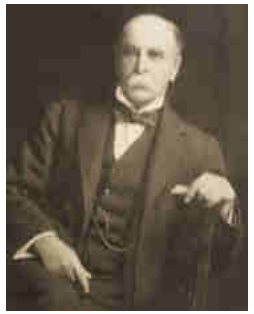
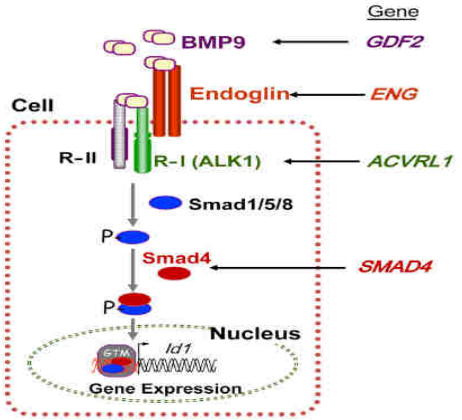
EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND
A WAY TO MAKE EUROPE

Instituto de Salud Carlos III





- ✓ **Enfermedad Minoritaria** (UE 1/2.000): Prevalencia 1/6.000
- ✓ Enfermedad **vascular de herencia autosómica dominante**
  - ✓ Caracterizada por **telangiectasias y otras MV de mayor tamaño**
- ✓ **Variantes patogénicas en *ENG* ó *ACVRL1*** son detectadas en **85-90%**
  - ✓ ***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 **Criterios de Curaçao:**

Criterio	Descripción
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*

- ✓ **Enfermedad edad-dependiente**: inicio de los síntomas (**epistaxis**) y desarrollo de MV alrededor de la adolescencia con meseta alrededor de los 40-50 años.

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 <u>MULTIDISCIPLINAR</u> →

INTERPROFESIONALIDAD

Medicina Clínica

Título: Las enfermedades minoritarias en España: una mirada hacia adelante.
Title: Rare diseases in Spain: a look into the future.

multidisciplinar. Esta multidisciplinariedad debe considerarse en el sentido más profundo, no sólo con la incorporación de distintas especialidades médicas, sino hacia la interprofesionalidad, incluyendo también a otros profesionales de la salud. En este

fundamental para la difusión y estabilización estas Unidades. Caminar de unas Unidades multidisciplinares a equipos sólidos interprofesionales, tal y como exigen los estándares internacionales, contribuirá a modernizar y aportar valor añadido al manejo de los pacientes con EE.MM., acorde con sus necesidades.

Riera-Mestre A. Med Clin 2021 (*en prensa*)

Bellvitge

Bellvitge Hospital Universitari

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

Activitat assistencial | Índex

Enviar a un amic

metropolitana sud

infoIDIBELL

InfoFlash

ICO Notícies

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.

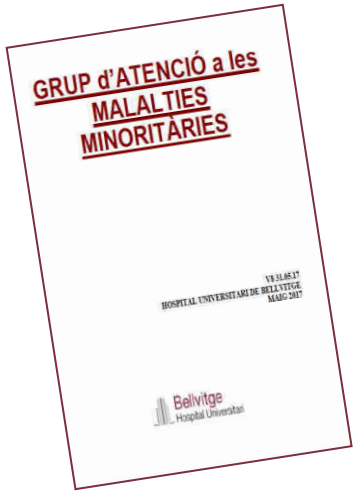
Els seus responsables assistencials són el Dr. Francesc Cruellas, del Servei d'Otorinolaringologia, i el Dr. Antoni Riera-Mestre, del Servei de Medicina Interna.

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

Bellvitge Hospital Universitari
Professionals de Referència
Highly Qualified Professionals

https://curehht.org/

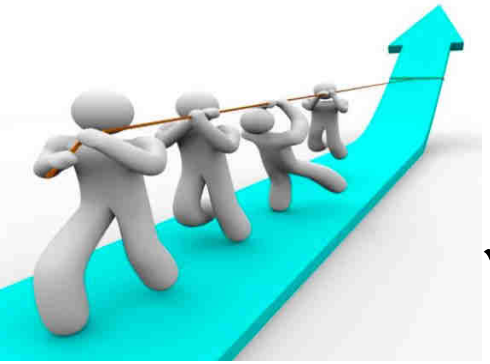
curehht



MEMBRES DEL GRUP

1 de maig de 2017

CASASNOVAS PONS, CARLOS (NRL); DÍEZ LOPEZ, CARLES (CAR); GASCÓN BAYARRI, JORDI (NRL); MAÑÁ REY, JOAN (MIR); MOLINA MOLINA, MARIA (NML); NARVAEZ GARCIA, JAVIER (REU); OLIVÉ PLANA, MONTSE (NRL); POVEDANO PANADES, MÒNICA (NRL); RAMA ARIAS, INÉS (NEF); RIBAS SOLA, JESÚS (NML); RIERA MESTRE, ANTONI (MIR); SOLANICH MORENO, XAVIER (MIR); TORRAS AMBRÓS, JOAN (NEF)



OBJECTIVOS del GRUPO de EEMM:

Interprofesionalidad
Terciarismo
Excelencia
Referencia
Innovación
Tecnología

- ✓ SINERGIAS
  - ✓ Entre los profesionales que atienden EEMM HUB
  - ✓ Características comunes de EEMM
  - ✓ **PROYECTO del HUB**
- ✓ POTENCIAR ASISTENCIA de pacientes con EEMM
  - ✓ Prioridad de Salud
- ✓ INVESTIGACIÓN
  - ✓ Acceso a redes locales, nacionales i europeas en EEMM
    - ✓ **UEC**, CSUR i European Reference Networks (ERN)
    - ✓ CIBERER (isciii)
  - ✓ IDIBELL → potenciar sinergias con básica (**MEDICINA TRASLACIONAL**)
- ✓ RELACIÓN CON ASOCIACIONES DE PACIENTES
  - ✓ FEDER, European Organisation for Rare Diseases (EURORDIS)
- ✓ VISIBILIDAD - DIFUSIÓN - COMPETITIVIDAD

L'Acadèmia
FUNDACIÓ ACADÈMIA DE CIÈNCIES MÈDIQUES I DE LA SALUT DE CATALUNYA I DE BALEARS

Societat Catalana de Malalties Minoritàries

ACTA REUNIÓ 01/2018

COMISSIÓ GESTORA DE LA FUTURA SOCIETAT DE MM

Data: 15.11.18 a les 16h

Assistents: Paco Palau, Jordi Gascón, Mònica Povedano, Joan Torras, Antoni Riera-Mestre

S'excusen: Jaume Coll, Guillem Pintos, Rafa López

- ✓ S'aprova el Pla d'Acció de la Comissió gestora, descrit en el document prèviament enviat a tothom. L'hem signat els que hem assistit a la reunió, però mancaria la signatura d'en Guillem i en Jaume. L'Odina us enviarà les 2 pàgines escanejades, que haurieu de signar i reenviar escanejat a la mateixa Odina, per tal que ho pugui presentar en la Junta de l'ACCMM el proper 11.12.18, sigui aprovat, validin aquesta Comissió Gestora i poguem començar a caminar.
- ✓ Tothom em vist la grandesa i exclussivitat del projecte, que de ben segur aportarà sinèrgies entre els seus membres i contribuirà en la difusió de les MM, que repercutirà en benefici de la societat.
- ✓ Tothom ha estat d'acord en fer el projecte el màxim d'inclusiu i atractiu per tal que tot aquell amb interès per les MM (metges, infermeres, psicòlegs, investigadors de bàsica,...) vulgui participar-hi (i fer-se'n socis).
- ✓ Pepe, tots em estat d'acord en que proposis una persona del HCP perque formi i part i vingui a aquestes reunions de la Comissió Gestora.
- ✓ L'Odina ens enviarà els estatuts establerts de tota Societat ens enviarà, i que haurem d'adaptar d'aquí a un any, al que serà la proposta d'estatuts de la nostra Societat.
- ✓ Hem acordat fer una segona reunió el 31 de gener a les 16h a l'ACCMM on haurìem de concretar una primera activitat científica, per fer-la al voltant de maig, que serveixi de difusió d'aquesta Comissió Gestora i escolti les vagi escoltant les suggerències de tothom.

Finalitza la reunió a les 17:30.

Societat Catalana de Malalties Minoritàries

I Jornada de la Societat Catalana de Malalties Minoritàries

Dijous, 26 de setembre de 2019 | 18:00 | Sala 2 L'Acadèmia - Can Caralleu

- 18:00 - 18:10 Benvinguda
- 18:10 - 19:00 Taula I: Particularitats dels models d'atenció a les MM

Multidisciplinarietat
Ponent: Dr. Antoni Riera Mestre

Genètica
Ponent: Dr. F. Palau

Transició complexe
Ponent: Dr. G. Pintos

Complexitat
Ponent: Dr. G. Espinosa

- 19:00 - 20:00 Taula II: Perspectives actuals en les MM

Punt de vista del pacient. FEDER

Necessitats psicosocials i models d'atenció psicològica als pacients en MM
Ponent: Dra. Laura Gonzalez
HSJD
Ponent: Dra. Mireia Forner
HVH
Ponent: Dra. Laura Baget

Teràpies avançades.
Ponent: Cristina Fillat Fonts
IDIBAPS

Acta SOCAMM 27/02/2020

Acte de constitució de la Societat Catalana de Malalties Minoritàries (SOCAMM)

De 17 a 19.15h es realitza un acte amb dues parts:

1.- El dr. Riera explica l'origen de la societat i les activitats organitzades per la junta gestora, que permeten que avui finalment es constitueixi.

És la primera societat científica específicament dedicada a l'estudi multidisciplinar de les malalties minoritàries, que en tinguem constància, donat que hi ha grups dins de societats específiques, o associacions i federacions de pacients, tot i que puguin incloure metges, infermers o d'altres professions científic-sanitàries.

Proposem establir aliances amb les altres societats científiques, amb la realització d'actes conjunts per donar-nos a conèixer, i fomentar la col·laboració entre tots.

2.- El dr. Grau fa una presentació sobre la seva experiència de 40 anys en la recerca de la patologia muscular.

Assemblea. Ordre del dia

1. Elecció de la junta directiva de la Societat Catalana de Malalties Minoritàries

   Amb el suport de tots el presents i l'absència de candidatura alternativa, a les 19.15h en segona convocatòria, es constitueix la junta directiva de la SOCAMM:

   - President: Antoni Riera Mestre. Hospital Universitari de Bellvitge
   - Vice-President: Francesc Palau Martínez. Hospital Sant Joan de Deu
   - Secretari: Rafael López Urdiales. Hospital Universitari de Bellvitge
   - Vocal 1: Josep Maria Grau Junyent. Hospital Clínic
   - Vocal 2: Guillem Pintos Morell. Hospital Universitari Vall d'Hebrón
   - Tresorer: Joan Torras Ambros. Hospital Universitari de Bellvitge

2. Aprovació dels estatuts de la societat

   Es revisen de nou els estatuts i es decideix la seva aprovació per unanimitat.

   Es clausura l'assemblea a les 19.40h sense més punts a tractar.

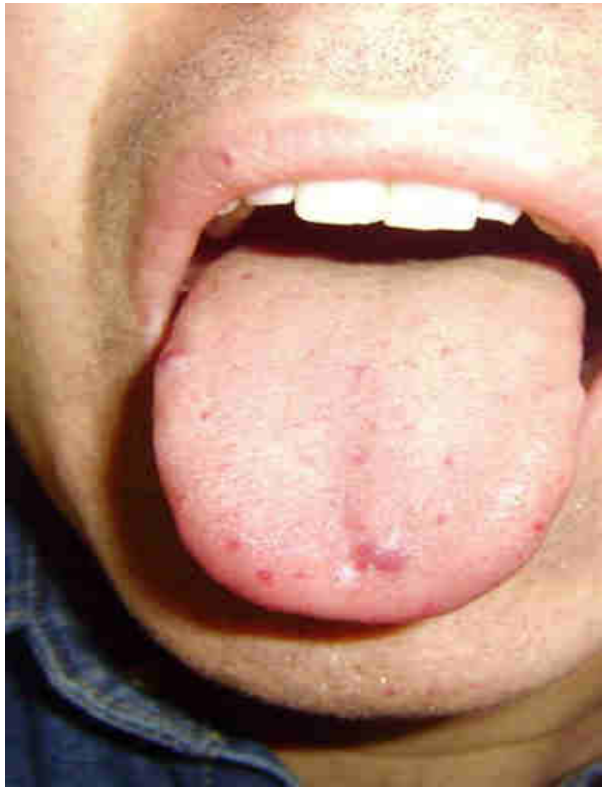
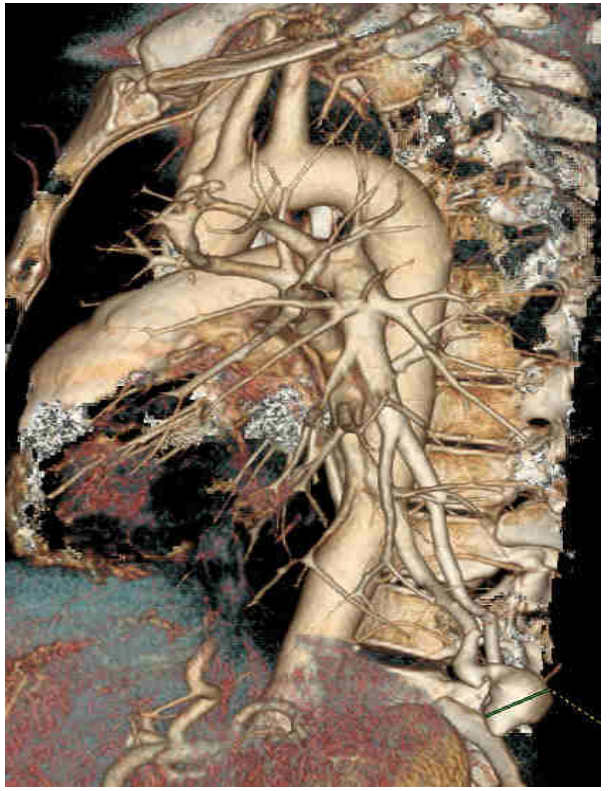
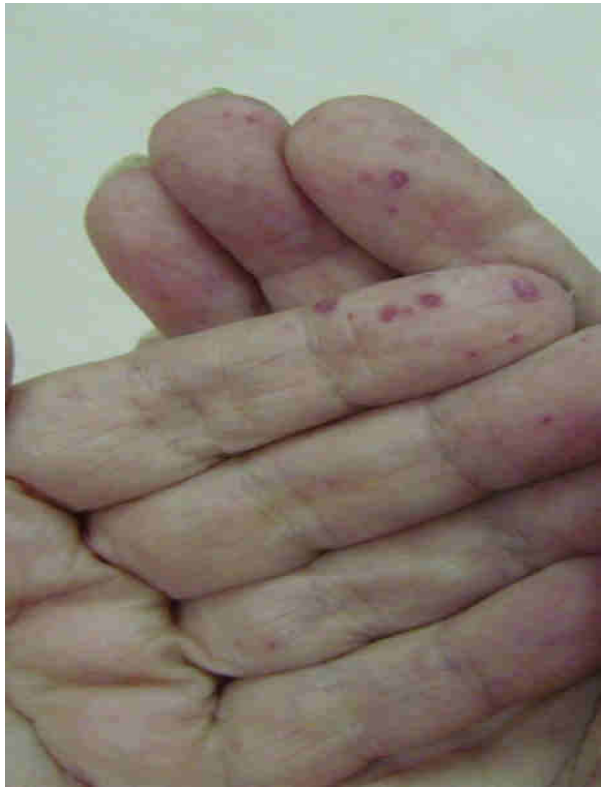
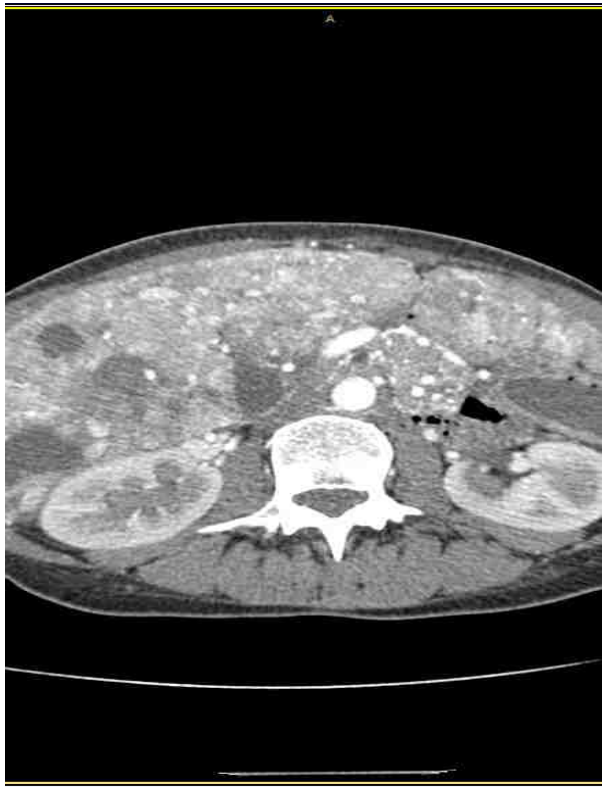
Vist-i-plau,
Dr. Antoni Riera Mestre
President SOCAMM

Dr. Rafael López Urdiales
Secretari SOCAMM

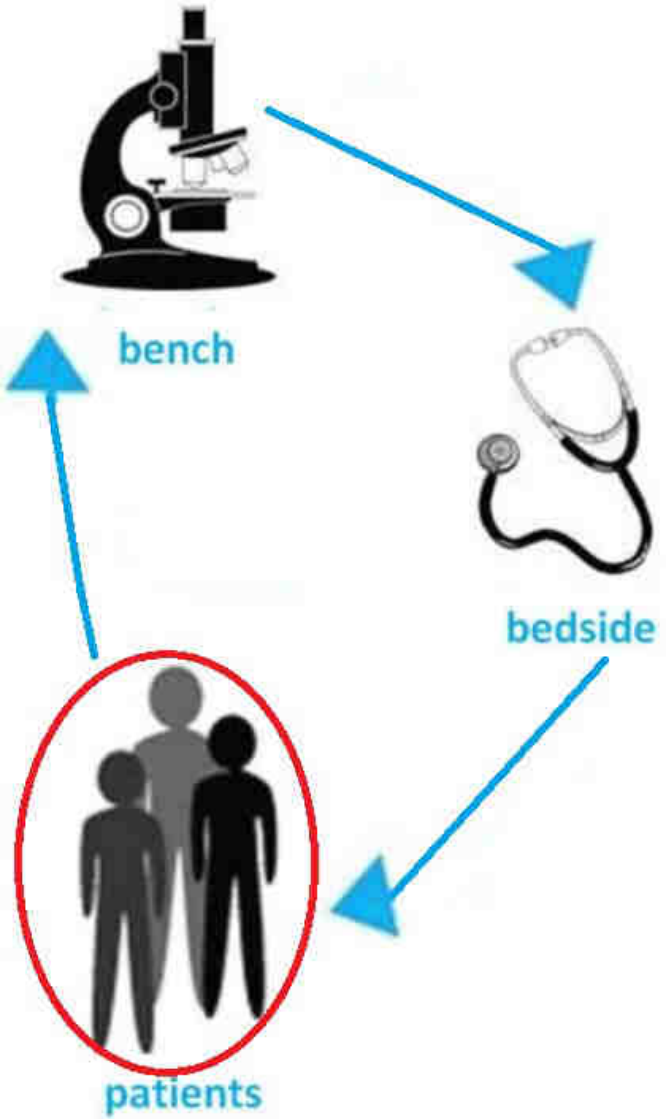
Junta Directiva

President	Antoni Riera Mestre
Vicepresident	Francesc Palau Martinez
Secretari	Rafael Lopez Urdiales
Vocal 1	Josep M. Grau Junyent
Vocal 2	Guillem Pintos Morell

Generalitat de Catalunya Salut/ Bellvitge Hospital Universitari
BELLVITGE HOSPITAL EN XARXA
IDI BELL
UNIVERSITAT DE BARCELONA

380 pacientes en seguimiento


bench
bedside
patients

Article

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

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,*]

Journal of *Clinical Medicine*

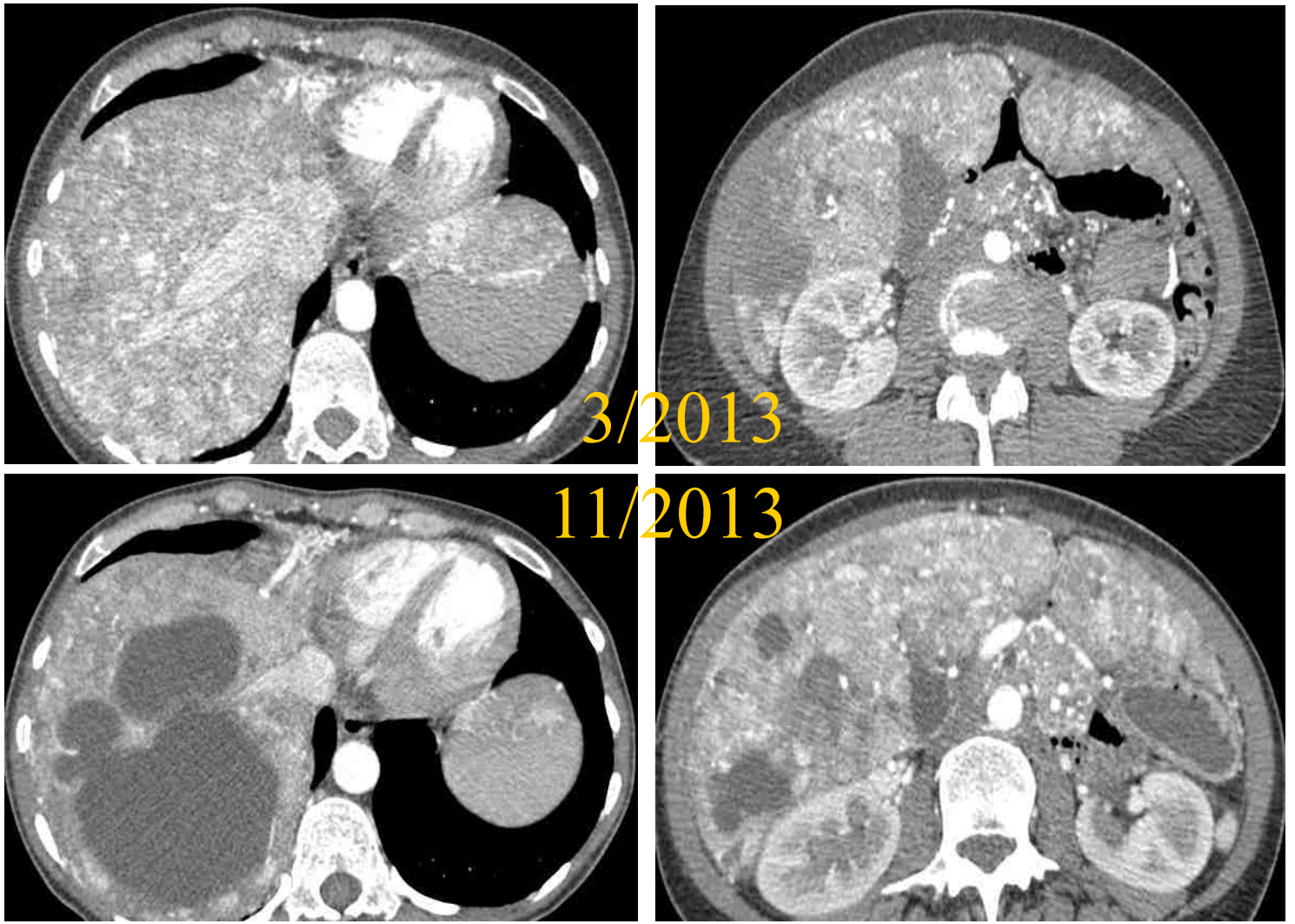
J. Clin. Med. 2020, 9, 82; doi:10.3390/jcm9010082

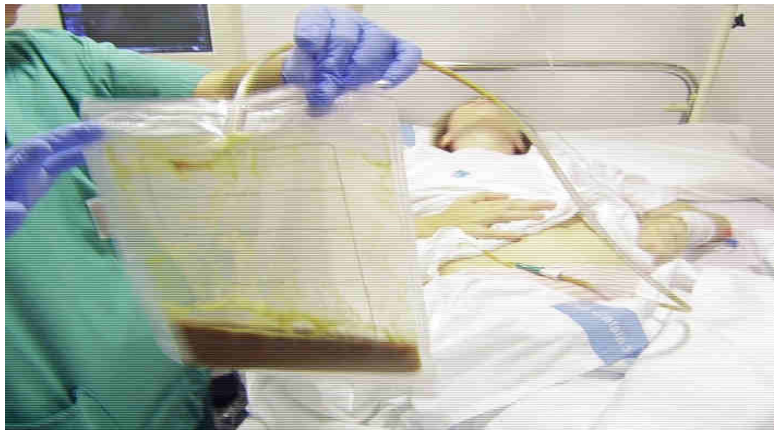
Table 2. Uni- and multivariable logistic regression analyses for gastrointestinal bleeding in patients with HHT.

	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

Among patients with GI involvement, those with hemoglobin levels < 8 g/ dL and/ or transfusion requirements (n=44) compared to the remaining patients (n=23), showed ***larger telangiectases (> 3 mm)*** *more frequently (65.7% vs 20%)*

Mujer de 38 años con HHT2 (ACVRL1)





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

- ✓ <3: low-risk (<5%)
- ✓ 3–5: intermediate risk (5-80%)
- ✓ ≥ 6: high-risk (>80%) for clinically significant liver disease

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

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

CLÍNIC BARCELONA Hospital Universitari

Bellvitge Hospital Universitari
Professionals de Referència
Highly Qualified Professionals

RiTHHA

REGISTRO INFORMATIZADO TELANGIECTASIA HEMORRAGICA HEREDITARIA

Empezó en JUNIO 2016

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

RiHHTa

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

Grupo de Enfermedades Minoritarias

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)

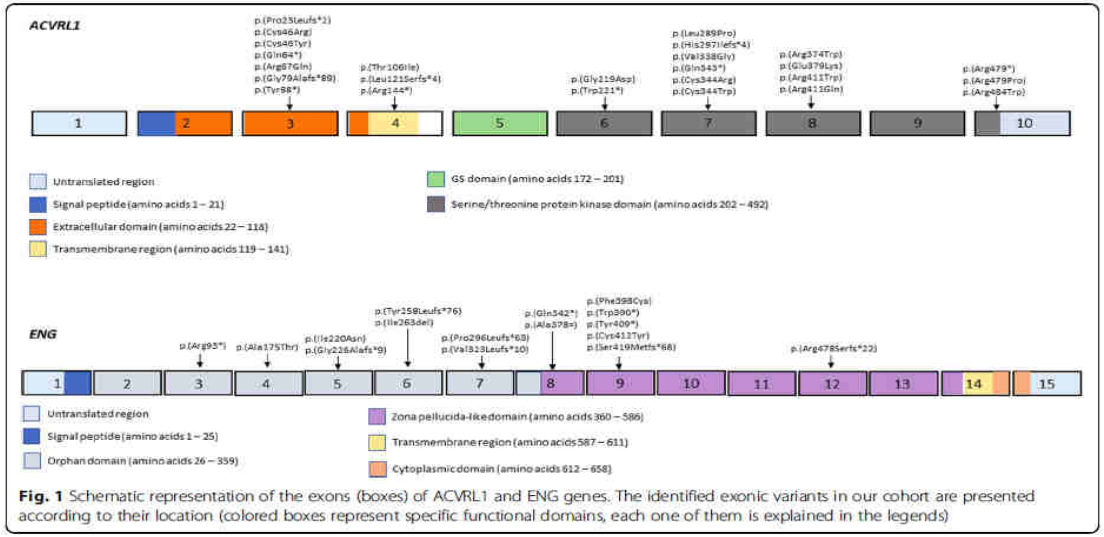


Fig. 1 Schematic representation of the exons (boxes) of ACVRL1 and ENG genes. The identified exonic variants in our cohort are presented according to their location (colored boxes represent specific functional domains, each one of them is explained in the legends)

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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.

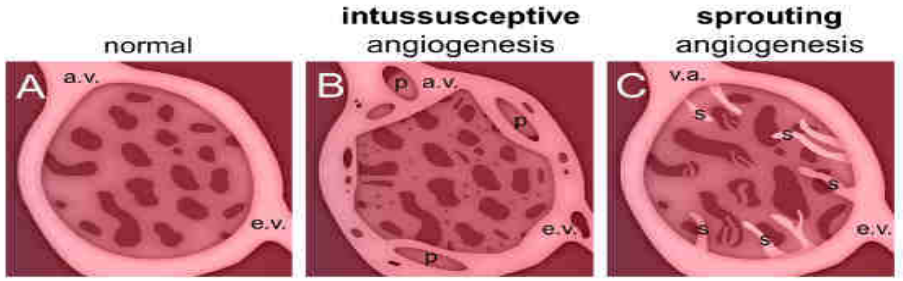
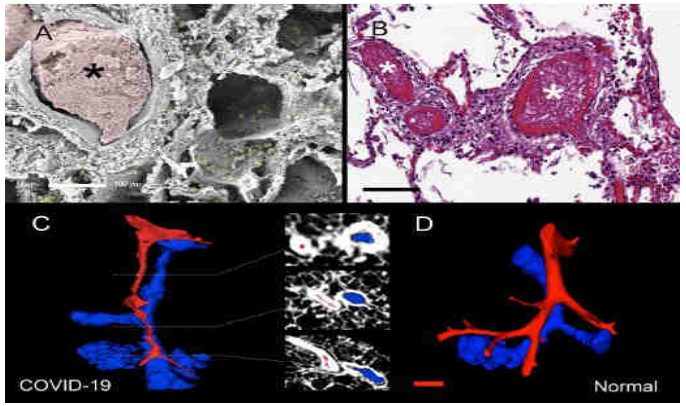


Figure S 4. Schematic of intussusceptive and sprouting angiogenesis. (A) The regular vasculature consists of an afferent (a.v.) and an efferent vessel (e.v.) and the intervening pulmonary alveolar capillary plexus (diameters not to scale). (B) Intussusceptive angiogenesis is found in COVID19-pulmonary 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.

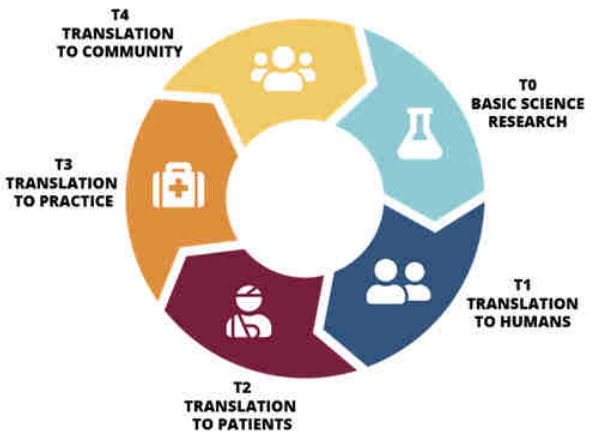


RiHHTa (Computerized Registry of Hereditary Hemorrhagic Telangiectasia) is an open, multicenter, prospective, observational registry including adult patients with HHT and developed within the Rare Diseases Working Group of the Spanish Society of Internal Medicine [1]. RiHHTa has an online design (accessible 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.

Angiogenesis 2021; 24:13-15

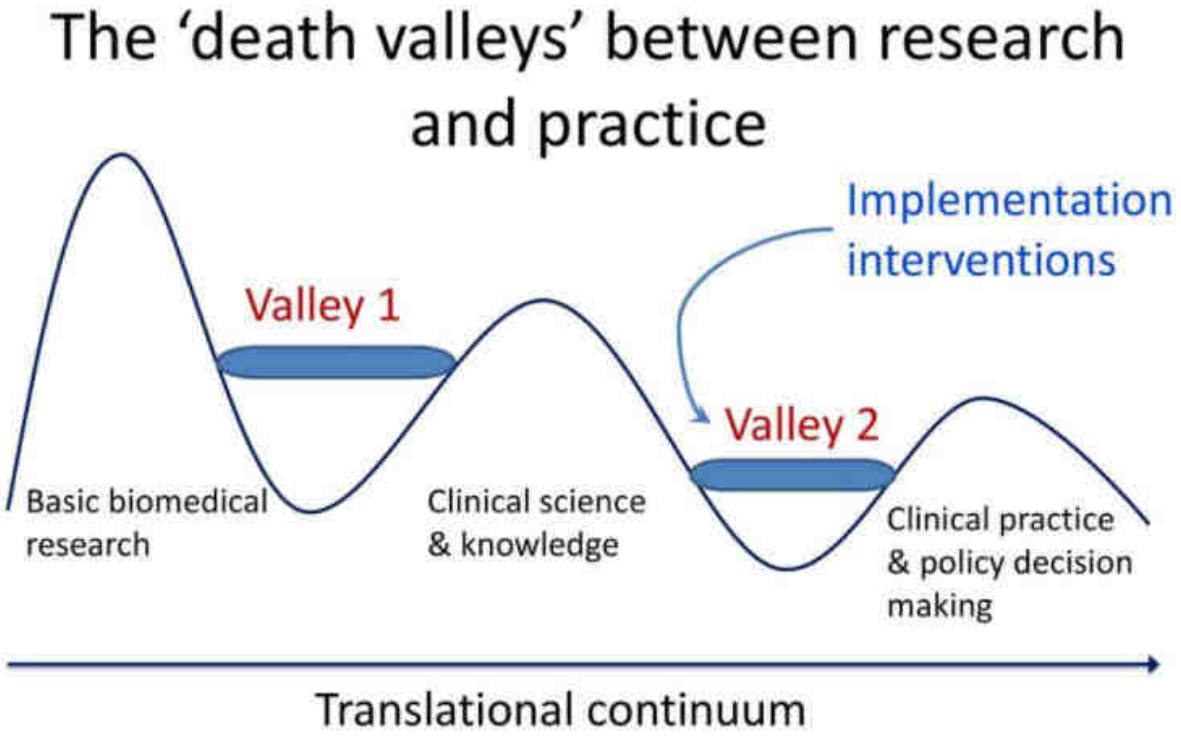
- ✓ La **MEDICINA TRASLACIONAL** es un esfuerzo para crear nuevas terapias o procedimientos diagnósticos, basadosen estudios de **procesos** de enfermedades (con modelos celulares o animales)
  - ✓ El adjetivo "traslacional" se refiere a ”trasladar” estos hallazgos desde un entorno de laboratorio a posibles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

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



CENTRO: PACIENTE

- ✓ 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 el laboratorio y la clínica.
- ✓ Los experimentos de laboratorio no siempre reflejan las necesidades de los pacientes.



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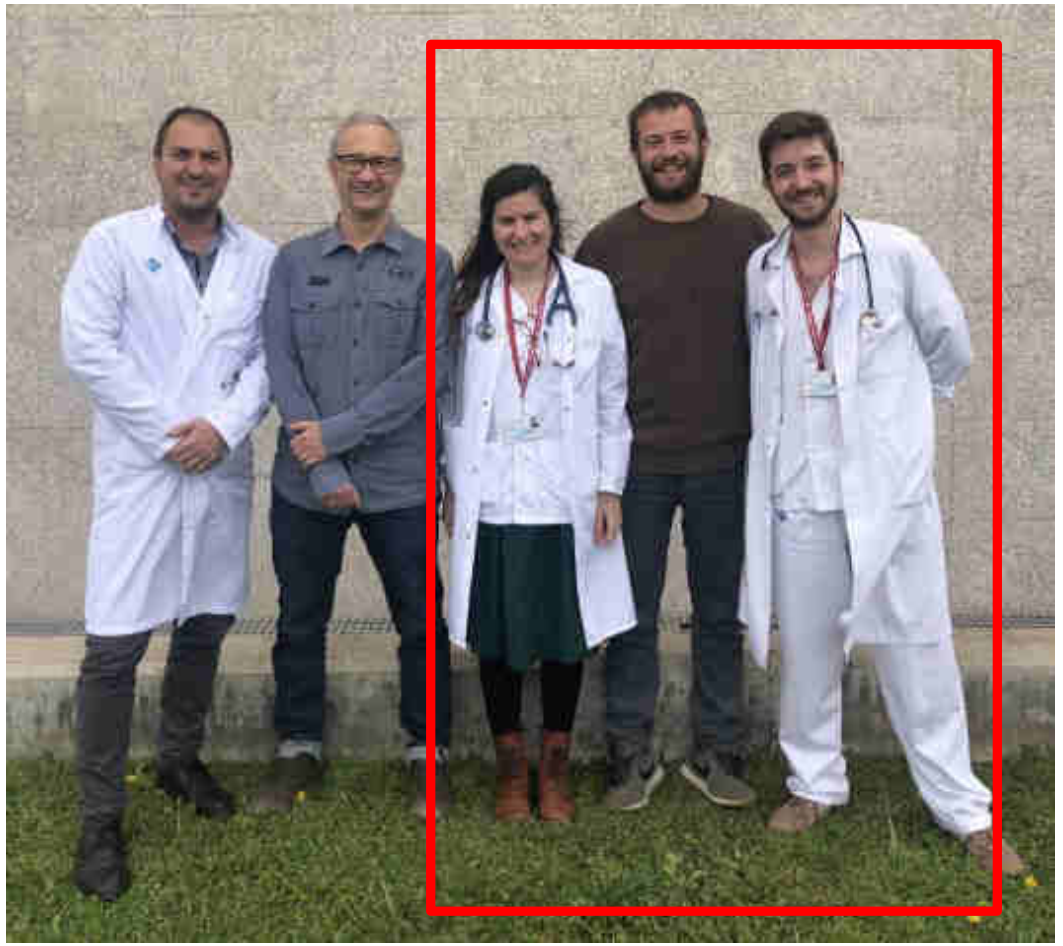

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PROYECTOS DE INVESTIGACIÓN EN SALUD 2018 – 2020

"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, A. Jucglà, A. Martins Figuereido, J. Ribas, E. Alba Rey

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, A. Jucglà, A. Iriarte, J. Ribas, Q. Ordi, J. Salazar, P. Mur Molina

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MDPI

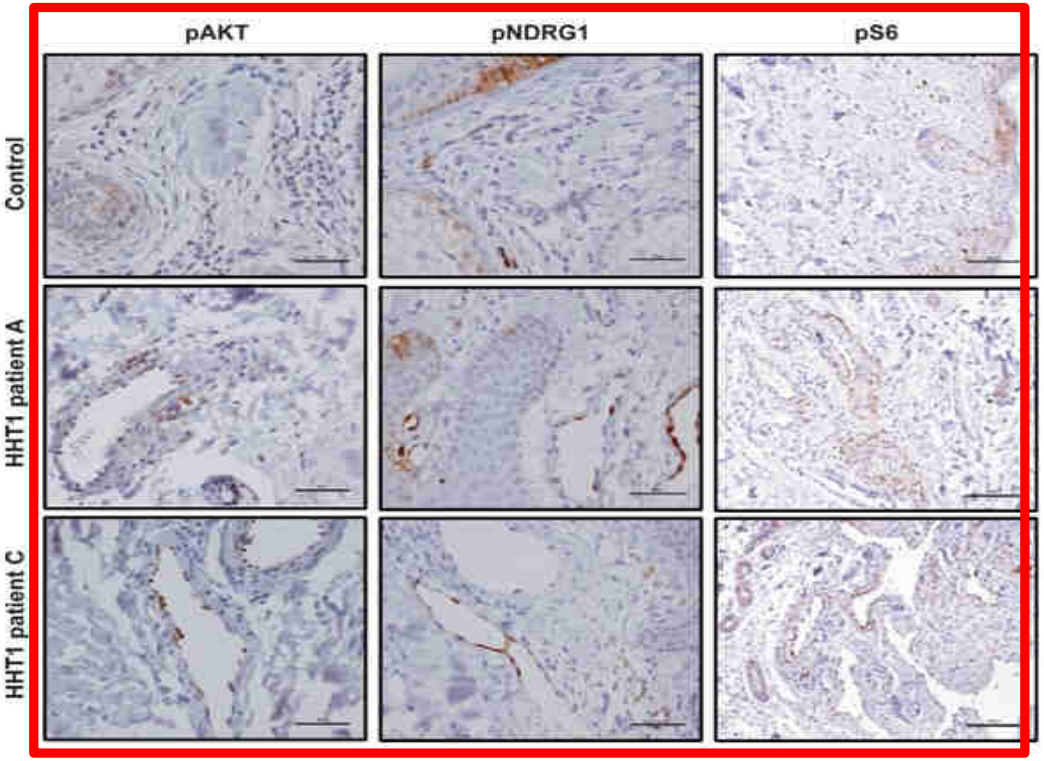
Article

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 Penin [3,7], Francesc Viñals [4,5,6,*,‡] 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 vía de la PI3K → puede ser inhibida con inhibidores de la mTOR (sirolimus)

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

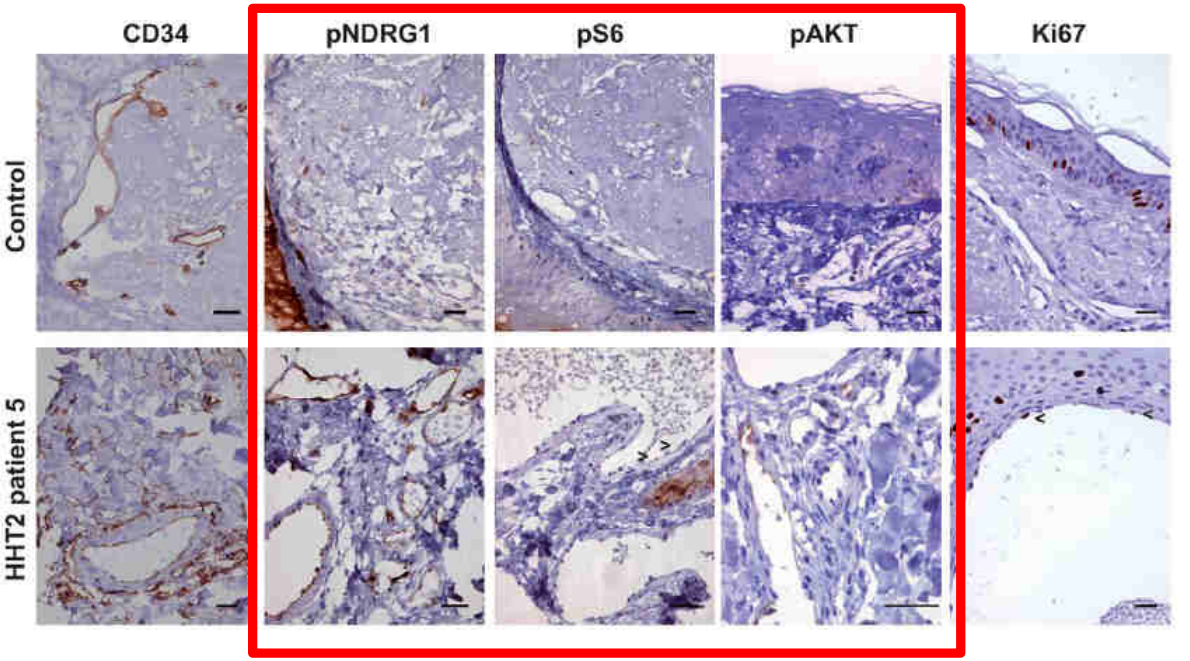
Elisenda Alsina-Sanchís,* Yaiza García-Ibáñez,* Ana M. Figueiredo, Carla Riera-Domingo, Agnès Figueras, Xavier Matias-Guiu, Oriol Casanovas, Luisa M. Botella, Miquel A. Pujana, Antoni Riera-Mestre, Mariona Graupera,† Francesc Viñals†

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 vía de la PI3K → puede ser inhibida con inhibidores de la mTOR (sirolimus)

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,*]

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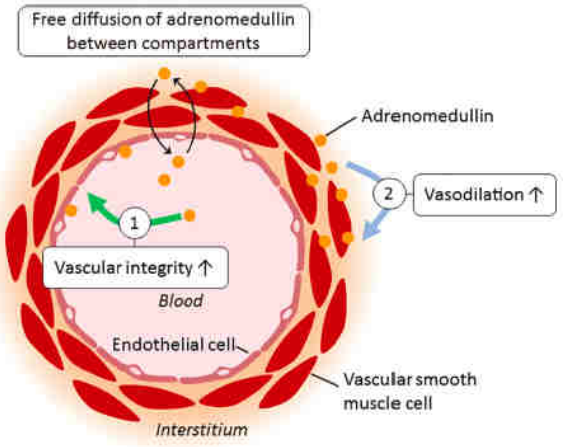

- ✓ Adrenomedullin (AM) is a vasoactive peptide mostly secreted by endothelial cells with important role in preserving endothelial integrity.
- ✓ We aimed to compare AM serum levels and tissue expression between HHT and controls.

- ✓ Serum AM levels were measured by radioimmunoassay and compared between both groups

	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

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

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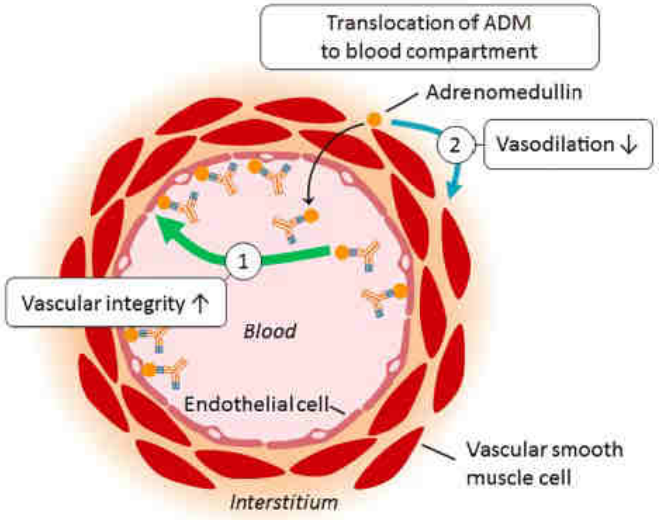
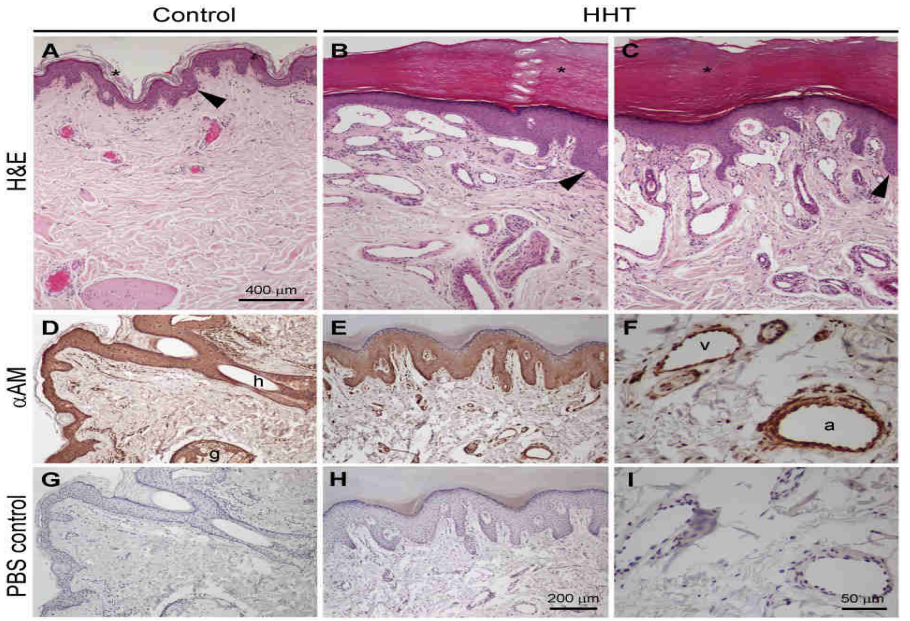


AM immunohistochemistry was performed on biopsies of cutaneous telangiectasia from 8 HHT patients and on healthy skin from 5 controls.



AM immunoreactivity was found with high intensity in the abnormal blood vessels of HHT biopsies.

Conclusions: Higher serum levels and tissue expression of AM were detected in patients with HHT than in healthy controls. Whether AM may constitute a novel therapeutic target in HHT (adrecizumab), needs further investigation.

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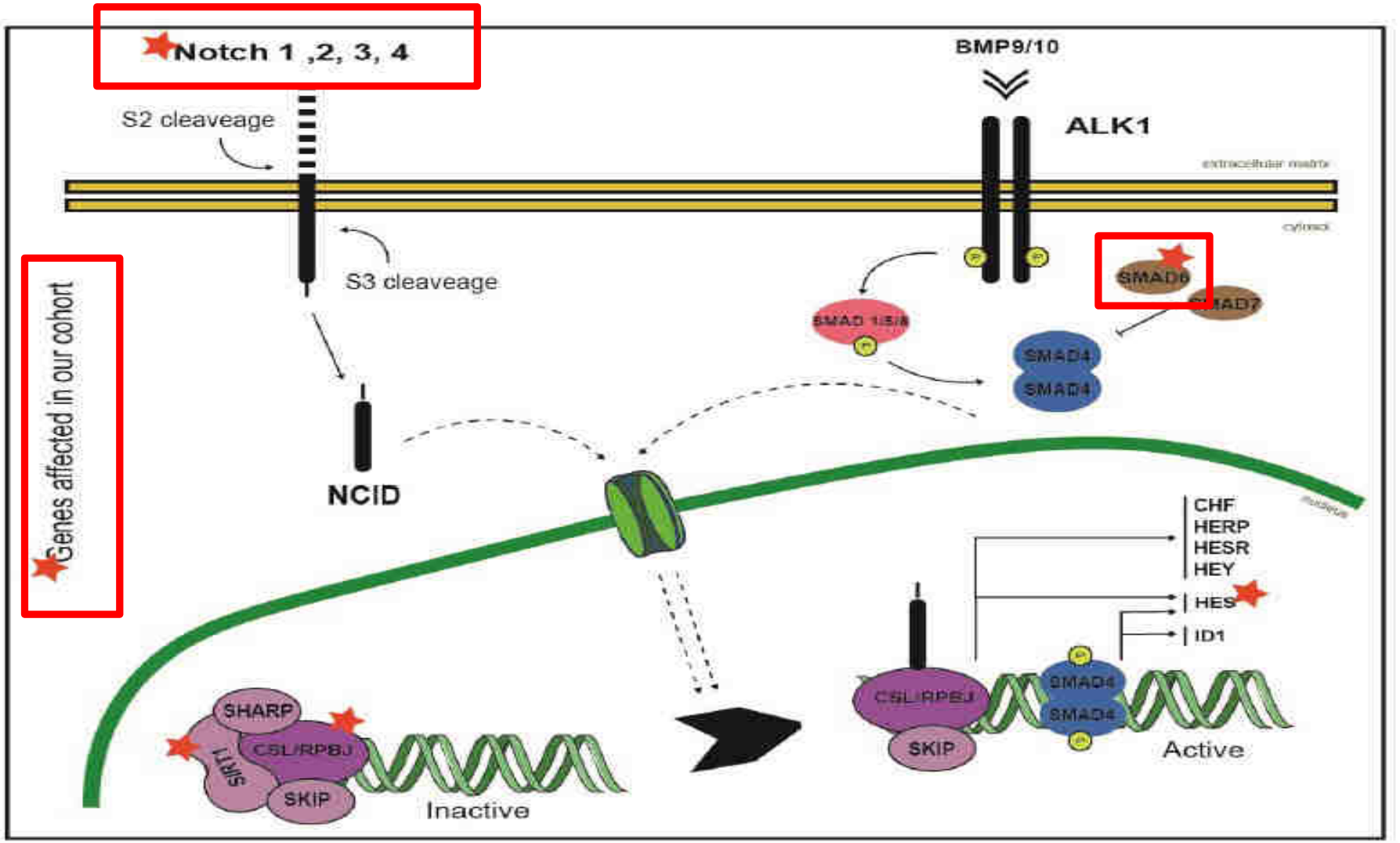
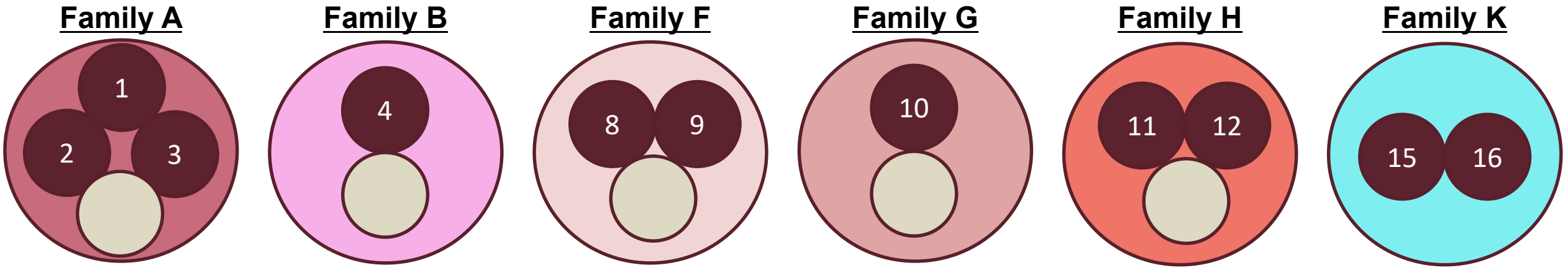
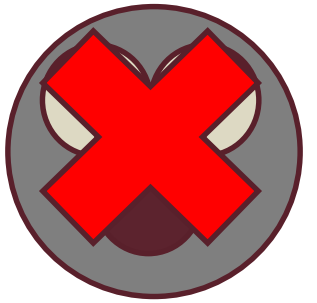
11 familias





One member families

ACVRL1



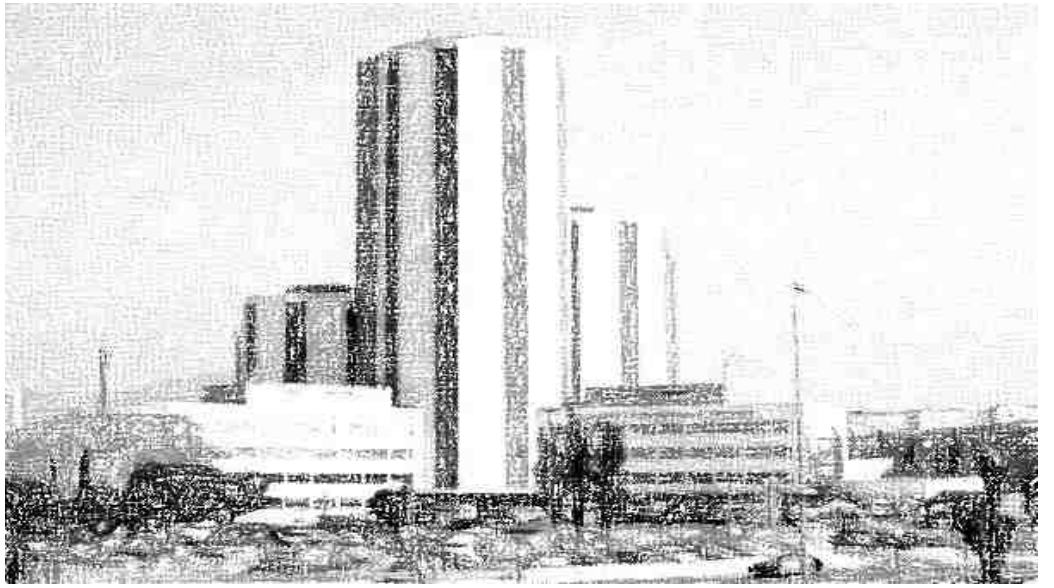
HHT patients

Unaffected relatives

Family ID	Patient ID	Kinship	Sex	Age	Curaçao Criteria										Nº of VUS per family
					AF	Epistaxis	Telangiectasia					Visceral VMs			
							A	F	L	T	N	GI	Lu	Li	Oth	
A	1	Proband	F	78	X	X		X	X	X	X	n/a		X	X	16
	2	Twin	F	78	X	X		X	X	X	X	X		X	X	
	3	Son	M	51	X	X		X	X	X	X	X			X	
	Daughter		F	47		Unaffected										
B	4	Proband	M	72		X					X	X		X		8
	Son		M	43		Unaffected										
C	5	Proband	M	66	X	X	X	X	X	X	X	X	X			33
D	6	Proband	F	51		X			X					X		29
E	7	Proband	M	57	X	X		X	X		X					36
F	8	Proband	F	23		X	X		X			X		X		14
	9	Brother	M	19	X	X		X			X					
	Sister		F	14		Unaffected										
G	10	Proband	M	60	X	X	X		X		X	X		X		3
	Son		M	18		Unaffected										
H	11	Proband	F	44	X	X					X			X	X	5
	12	Brother	M	59	X	X		X	X		X	n/a				
	Nephew		M	19		Unaffected										
I	13	Proband	F	54	X	X	X	X			X	X	X			15
J	14	Proband	M	60	X	X	X	X	X			n/a		X		20
K	15	Proband	F	63	X	X		X	X	X	X	n/a	X			9
	16	Daughter	F	36	X			X	X			n/a		X		

	Family A	Family B	Family F	Family G	Family H	Family K
Total genes	**17**	**9**	**13**	**3**	**6**	**10**
Candidate genes	**INHA ASB16**	**TMEM129 HIF1A**	**JAK2 LAMTOR5**	**F2**	**FOXM1 GH1**	**POSTN FOXO1 ANGPTL4**
GO biological process	protein ubiquitination	protein ubiquitination	ubiquitin protein ligase binding	positive regulation of receptor signaling pathway via JAK-STAT	negative regulation of TGFβ receptor signaling pathway	regulation of Notch signaling pathway
	SMAD protein signal transduction	angiogenesis	positive regulation of SMAD protein signal transduction	positive regulation of PI3K signaling	receptor signaling pathway via JAK-STAT	cellular response to TGFβ stimulus
		positive regulation of blood vessel endothelial cell migration	regulation of receptor signaling pathway via JAK-STAT		positive regulation of PI3K signaling	negative regulation of stress-activated MAPK cascade
		positive regulation of tyrosine phosphorylation of STAT protein	positive regulation of vascular associated smooth muscle cell proliferation		negative regulation of stress-activated MAPK cascade	angiogenesis
		vascular endothelial growth factor production	positive regulation of PI3K signaling			

	Family C5	Family D6	Family E7	Family I13	Family J14
Total genes	**32**	**29**	**36**	**15**	**21**
Candidate genes	**PVLD2 INPP5J MARVELD2 CHD7**	**GBP1 ARHGAP35 MIOS**	**SIRT2 FOXN1 KIAA1462 JAK1**	**ANPEP CHD8 LATS1 ANTXR1 PYCARD ESR1**	**SIRT3 PDE1A**
GO biological process	protein ubiquitination	protein ubiquitination	receptor signaling pathway via JAK-STAT	angiogenesis	negative regulation of ERK1 and ERK2 cascade
	establishment of endothelial barrier	negative regulation of vascular permeability	positive regulation of blood vessel endothelial cell proliferation involved in sprouting angiogenesis	regulation of ubiquitin-dependent protein catabolic process	regulation of smooth muscle cell proliferation
	blood vessel remodeling	negative regulation of ERK1 and ERK2 cascade	blood vessel morphogenesis	blood vessel development	
	phosphatidylinositol biosynthetic process		PI3K signaling	positive regulation of ERK1 and ERK2 cascade	
				Hippo & Wnt signaling	



CONCLUSIONES:

- ✧ Promover **sinergias intra e interhospitalarias**
- ✧ Se requiere un abordaje **interprofesional**, acorde con las necesidades de los pacientes con EEMM
- ✧ La medicina traslacional **debe partir de cuestiones clínicas delante de los enfermos** y debe retornar a ellos con mejoras en la clínica asistencial
- ✧ En las EEMM, la medicina traslacional permite aportar **nuevo conocimiento** de estas enfermedades y **nuevas dianas terapéuticas**

Modelo de atención centrado en 2 niveles: