6to Congreso Argentino de Gastroenterología Pediátrica

Mesa Redonda

ENFERMEDAD INFLAMATORIA INTESTINAL TEMPRANA

- Visión del inmunólogo -

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Servicio de Inmunología y Reumatología
Hospital Nacional de Pediatría
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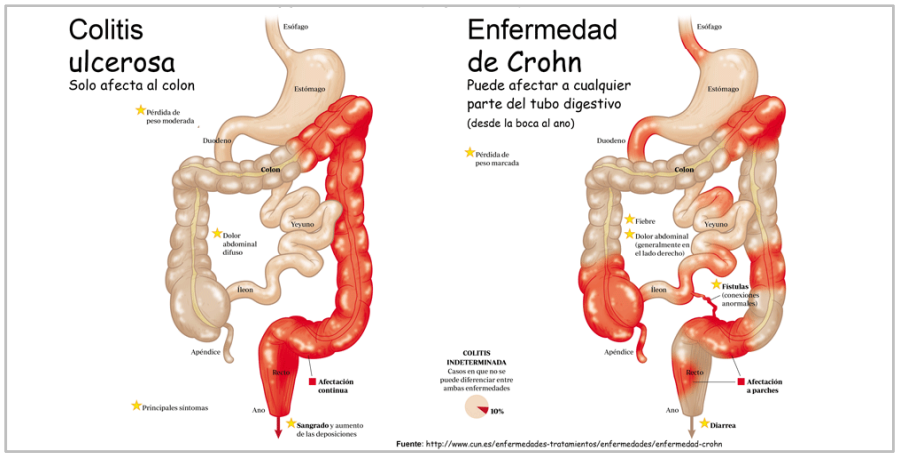
Buenos Aires, Argentina

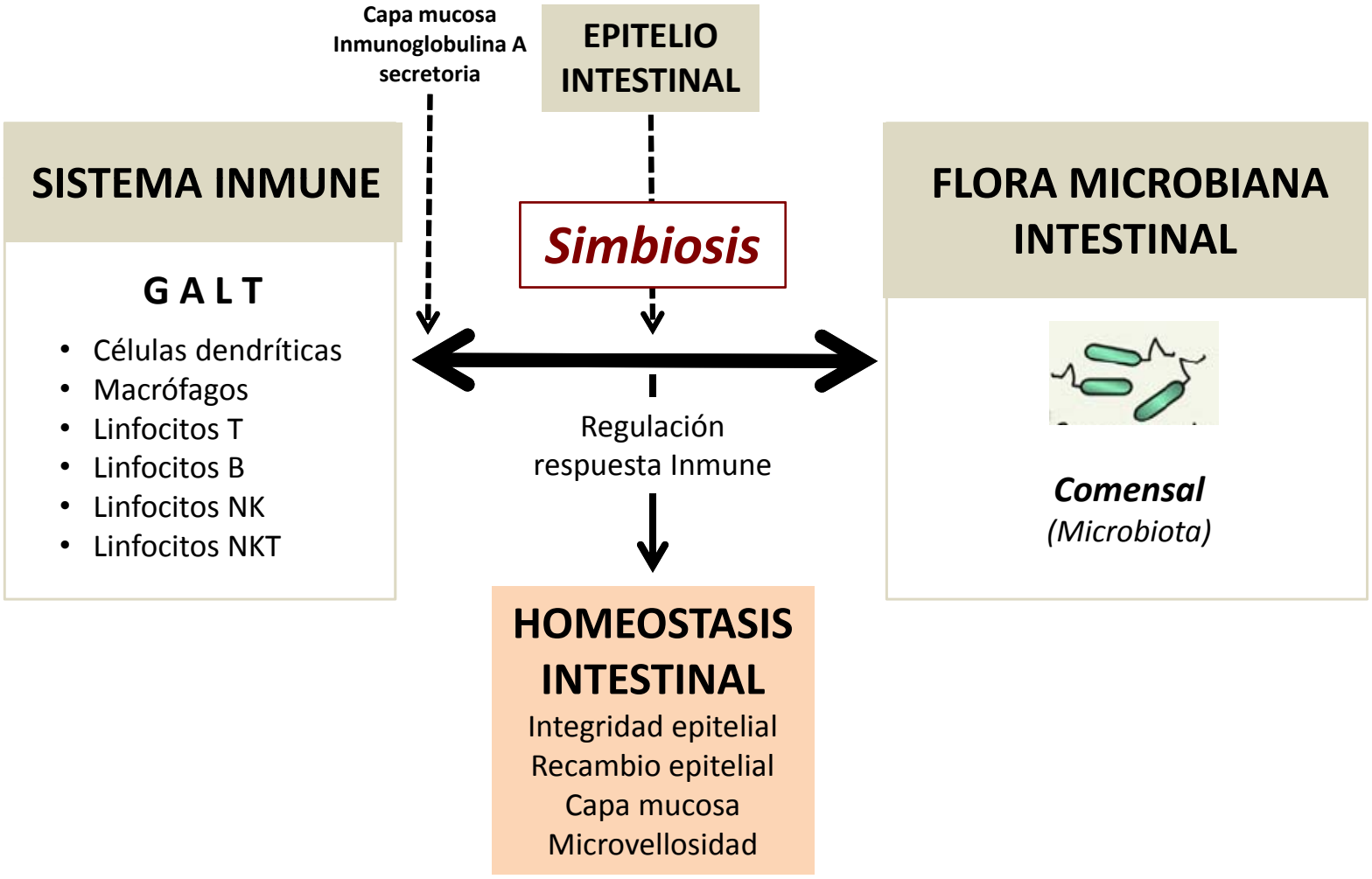
Enfermedad Inflamatoria Intestinal



ENFERMEDAD INTESTINAL INFLAMATORIA
Generalidades

CONDICIÓN NORMAL

HOMEOSTASIS INTESTINAL



ENFERMEDAD INTESTINAL INFLAMATORIA
Generalidades

- ***Definición***

  Enfermedad inflamatoria crónica, **inmuno-mediada**, de curso fluctuante
  Epidemiología: **20 – 30 años**
  Incidencia en aumento

- ***Entidades***
  - **Enfermedad de Crohn**
  - **Colitis Ulcerosa**
  - **Colitis indeterminada / no clasificable**

- ***Clasificaciones***

Pediatric Modification of the Montreal Classification for Inflammatory Bowel Disease: The Paris Classification

Arie Levine, MD, Anne Griffiths, MD,† James Markowitz, MD,‡ David C Wilson, MD,§ Dan Turner, MD, PhD,¶ Richard K Russell, MD, PhD,‖ John Fell, MD,** Frank M Ruemmele, MD, PhD,†† Thomas Walters, MD,† Mary Sherlock, MD,† Marla Dubinsky, MD,‡‡ and Jeffrey S Hyams, MD§§*

Inflamm Bowel Dis *2011;17:1314–1321*

TABLE 2. Montreal and Paris Classifications for Crohn's Disease

	Montreal	Paris
Age at Diagnosis	A1: below 17 y	A1a: 0–<10y A1b: 10–<17 y
	A2: 17-40 y	A2: 17–40 y
	A3: Above 40 y	A3: >40 y
Location	L1:terminal ileal± limited cecal	L1: distal 1/3 ileum + limited cecal
	B2: stricturing	B2: stricturing
	B3: penetrating	B3: penetrating
	p: perianal disease modifier	B2B3: both penetrating and and stricturing disease, either at the same or different times
		p: perianal disease modifier
Growth	n/a	G_0: No evidence of growth delay
		G_1: Growth delay

Table 1. Subgroups of Pediatric IBD According to Age

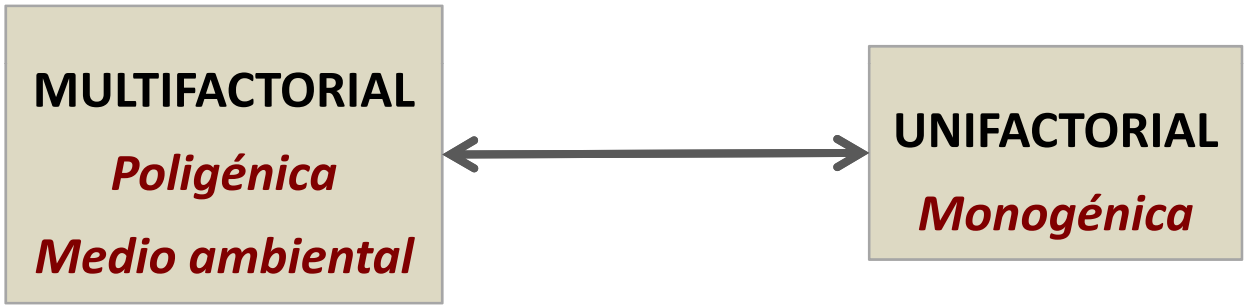
Group	Classification	Age range (*y*)
Pediatric-onset IBD	Montreal A1	Younger than 17
EOIBD	Paris A1a	Younger than 10
VEOIBD		Younger than 6
Infantile (and toddler) onset IBD		Younger than 2
Neonatal IBD		First 28 days of age

- ***Dificultades – Desafíos***
  - Fisiopatogénicos
  - Diagnósticos
  - Terapéuticos

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Vista del Inmunólogo

ENFERMEDAD



ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Vista del Inmunólogo

Enfermedad monogénica

COLITIS CRÓNICA DE PRESENTACIÓN TEMPRANA
EO-IBD
Menores de 17 años

Enfermedad Compleja

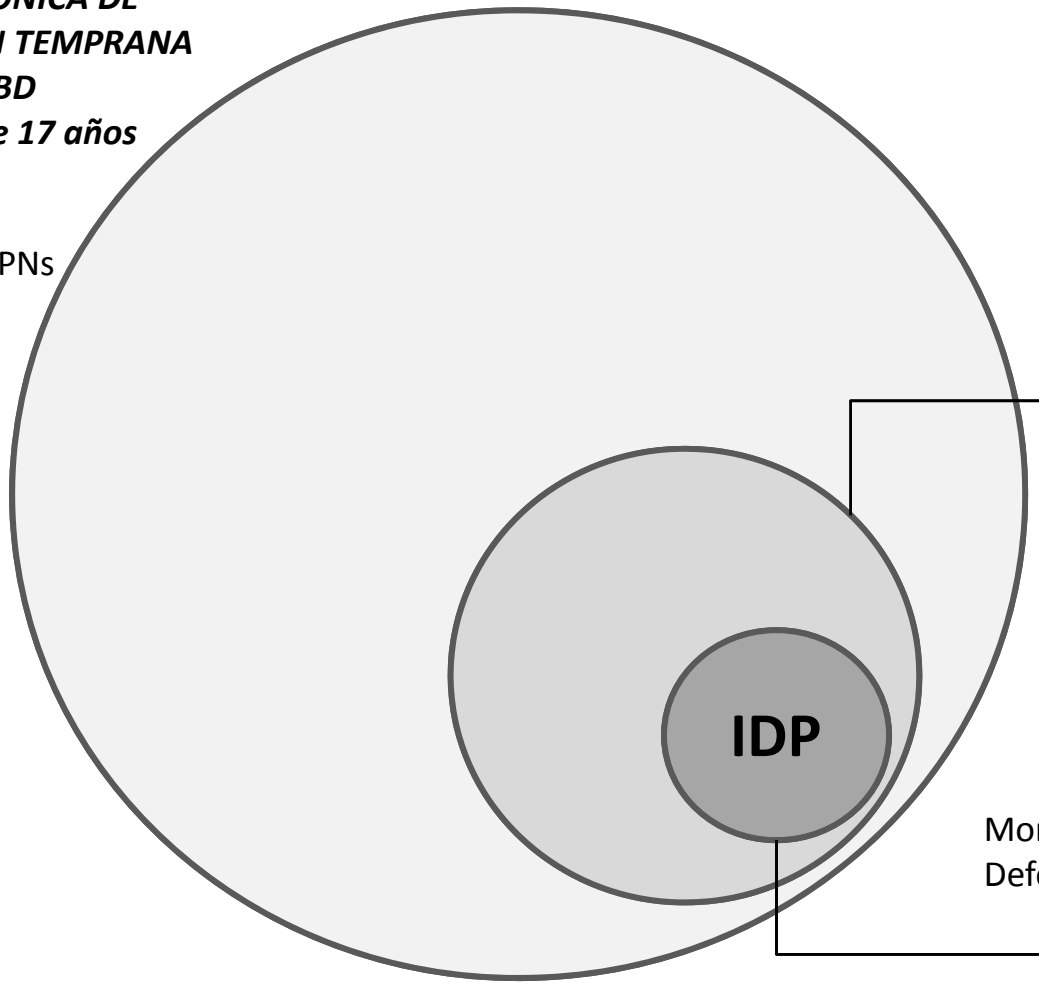
Predisposición genéca - SPNs
(más de 160 locus asociados)

Factor medioambiental
- Dieta
- Drogas
- Tabaquismo

Disbiosis

Respuesta Inmune
- IL10
- Th17
- Receptores NOD

…..



COLITIS CRÓNICA DE PRESENTACIÓN MUY TEMPRANA
VEO-IBD
Menores de 5 años

Monogénica
Defecto inmune primario

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Vista del Inmunólogo

Enfermedad monogénica

Published in final edited form as:
Annu Rev Pathol. 2016 May 23; 11: 127–148. doi:10.1146/annurev-pathol-012615-044152.

GENETICS AND PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

Ta-Chiang Liu and **Thaddeus S. Stappenbeck***
Department of Pathology and Immunology, Washington University School of Medicine, S
Louis, MO 63110

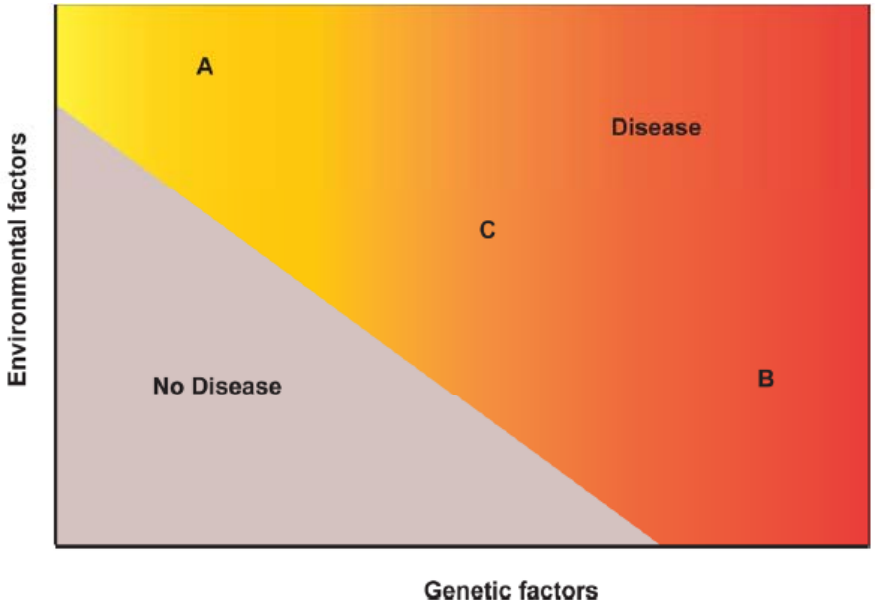


Figure 3.
Hypothetical thresholds for genetic and environmental factors required to trigger IBD. The three scenarios include (A) environmental factors are dominant and requires less genetic risk factors (similar to an infectious disease model); (B) genetic factors are dominant (e.g. VEO-IBD), which likely requires less environmental dosage; and (C) 'medium' dosage of genetic and environmental factors, similar to other autoimmune disorders.

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Vista del Inmunólogo

Enfermedad monogénica

INMUNODEFICIENCIAS PRIMARIAS - IDP

Enfermedades que resultan de defectos primarios del sistema inmune

- ✓ Unas 300 entidades bien definidas
- ✓ Más de 260 alteraciones génicas identificadas
- ✓ La gran mayoría enfermedades hereditarias
- ✓ Frecuencia global: 1 : 2500 - 5.000 individuos
- ✓ Deficiencia en uno o mas de los componentes:

① SISTEMA FAGOCÍTICO
② SISTEMA COMLEMENTO
③ LINFOCITOS NK
④ LINFOCITOS B
⑤ LINFOCITOS T

INMUNODEFICIENCIAS PRIMARIAS
Manifestaciones clínicas

INFECCIONES	**90 – 95 %**
INFLAMACIÓN	**30 - 60 %**
AUTOINMUNIDAD	**25 – 50 %**
LINFOPROLIFERACIÓN	**10 – 25 %**
HIPERSENSIBILIDAD ALERGIA	**10 – 25 %**
MANIFESTACIONES NO INMUNOLÓGICAS	**10 – 15 %**

EDAD DE PRESENTACIÓN
(inicio de las manifestaciones)

0 - 1 año	30 - 40 %
1 - 5 años	30 - 40 %
5 - 16 años	10 %
> 16 años	20 %

INMUNODEFICIENCIAS PRIMARIAS
Manifestaciones clínicas

INFLAMACIÓN

Aftas / úlceras cutáneo-mucosas
Eccema – Dermatitis tipo atópica
Edema subcutáneo, …..
Eritrodermia / exantemas – rash
Vasculitis/vasculopatía
Pioderma gangrenoso
Artritis inflamatoria: ARJ, Art seroneg.
Enfermedad intestinal inflamatoria
Enfermedad pulmonar inflamatoria
Enfermedad ocular inflamatoria

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Vista del Inmunólogo

Enfermedad monogénica

INMUNODEFICIENCIAS PRIMARIAS - IDP

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J Clin Immunol (2015) 35:696–726
DOI 10.1007/s10875-015-0201-1

ORIGINAL RESEARCH

Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015

1. **INMUNODEFICIENCIAS COMBINADAS (IDC)**
2. **IDC ASOCIADAS A SÍNDROMES**
3. **DEFICIENCIAS PREDOMINANTES DE ANTICUERPOS**
4. **ENFERMEDADES POR DESREGULACIÓN INMUNE**
5. **DEFICIENCIAS CONGÉNITAS DEL FAGOCITO** (Número y/o Función)
6. **DEFECTOS DE LA INMUNIDAD INNATA**
7. **DESÓRDENES AUTOINFLAMATORIOS**
8. **DEFICIENCIAS DEL SISTEMA COMPLEMENTO**
9. **FENOCOPIAS DE IDP**

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Manifestación inicial

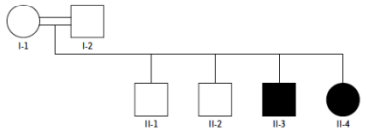
The NEW ENGLAND JOURNAL of MEDICINE

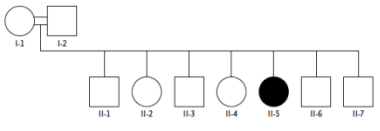
ORIGINAL ARTICLE

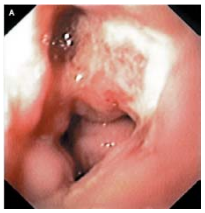
Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

Erik-Oliver Glocker, M.D., Daniel Kotlarz, M.D., Kaan Boztug, M.D., E. Michael Gertz, Ph.D., Alejandro A. Schäffer, Ph.D., Fatih Noyan, Ph.D., Mario Perro, M.Sc., Jana Diestelhorst, B.Sc., Anna Allroth, M.D., Dhaarini Murugan, M.Sc., Nadine Hätscher, B.Sc., Dietmar Pfeifer, M.D., Karl-Walter Sykora, M.D., Martin Sauer, M.D., Hans Kreipe, M.D., Martin Lacher, M.D., Rainer Nustede, M.D., Cristina Woellner, M.Sc., Ulrich Baumann, M.D., Ulrich Salzer, M.D., Sibylle Koletzko, M.D., Neil Shah, M.D., Anthony W. Segal, M.D., Axel Sauerbrey, M.D., Stephan Buderus, M.D., Scott B. Snapper, M.D., Ph.D., Bodo Grimbacher, M.D., ...I.D.

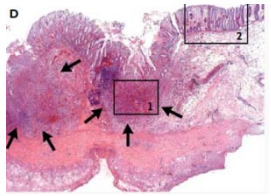
N Engl J Med 2009;361.



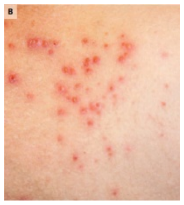




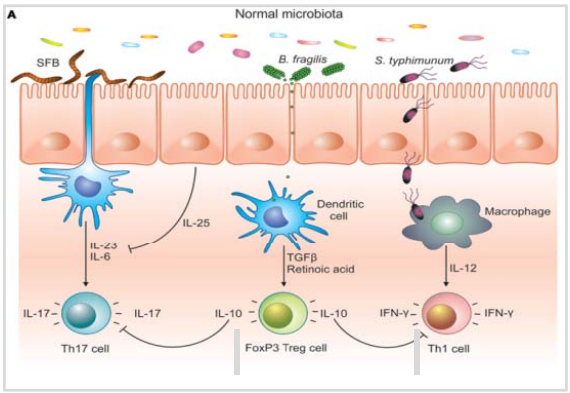
Lesión erosiva



Microabscesos intramurales
Infiltración linfoplasmocitaria



Foliculitis



Análisis de ligamiento para secuenciar gene candidato

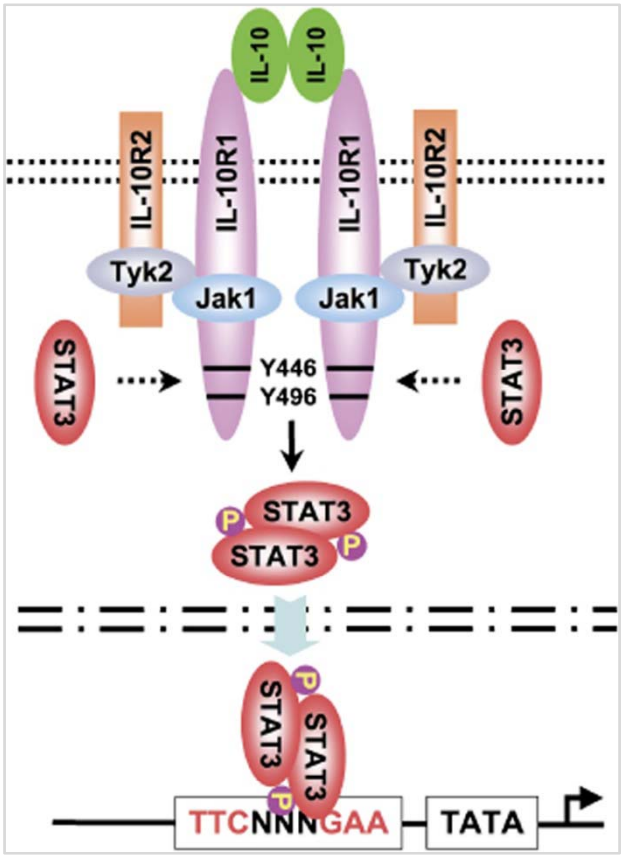
- Mutaciones en *IL-10RA* y *IL-10RB*
- FP: CM, falta de respuesta (producción de TNFα) estimulando con LPS e IL-10

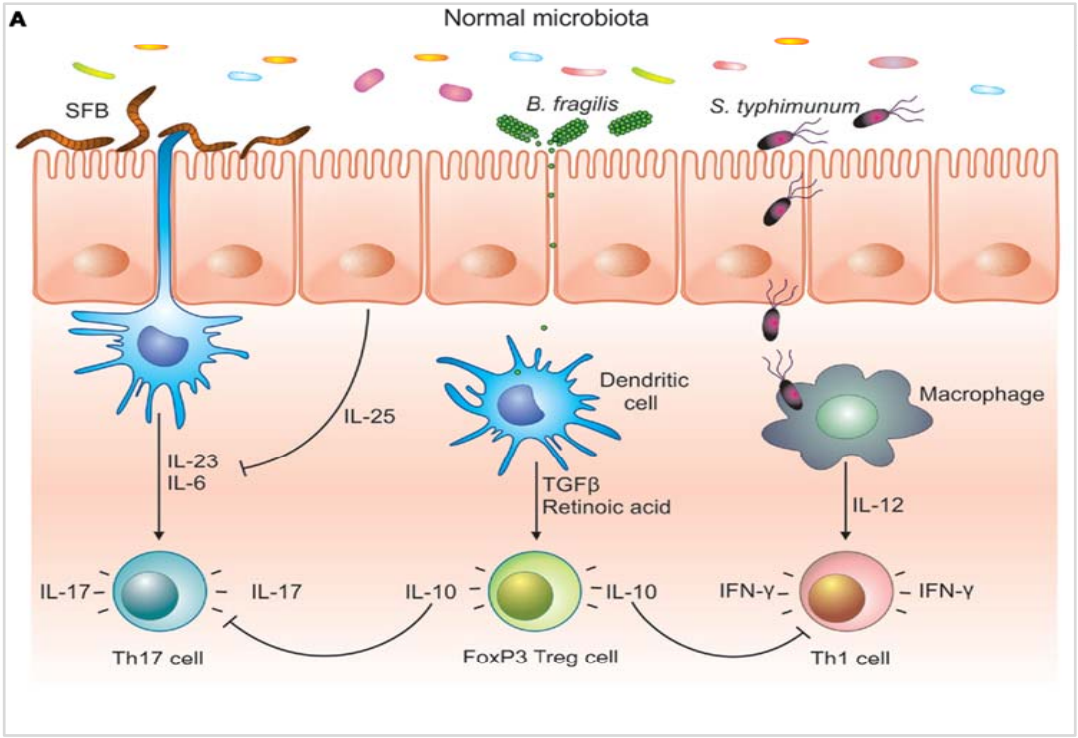
➢ 6 pacientes con EII de comienzo temprano **(<1 año)**

- 1 P^{te} Mutación homocigota en *IL-10RA*

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

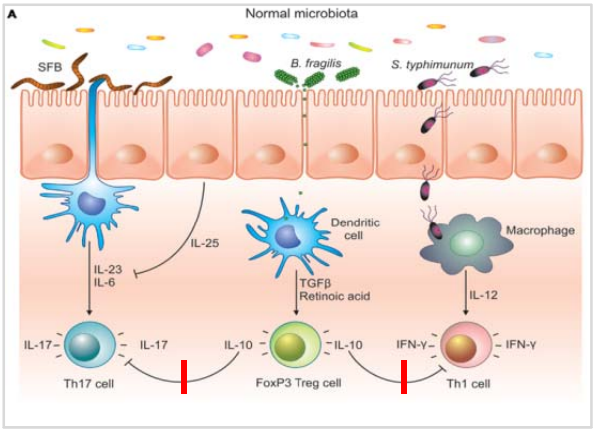
Sistema IL 10 – IL 10R





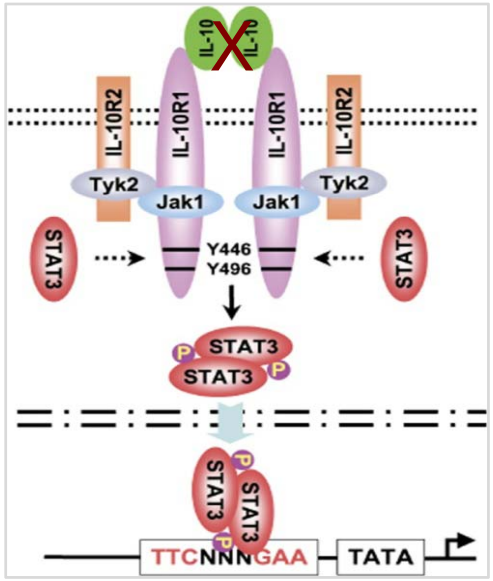
ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Manifestación inicial



Glocker EO, Frede N, Perro M, Sebire N, Elawad M, Shah N, et al. Infant colitis - it's in the genes.
Lancet 2010;376:1272.

11-month-old girl presented to us with **intractable inflammatory bowel disease**; she had **Crohn's-like colitis** with formation of perianal and rectovaginal fistulae. Colonoscopy and histology of biopsy samples showed extensive ulceration of the ileum and focal active colitis with areas of patchy cryptitis and polymorphs entering surface epithelium Her colitis was resistant to treatment with immunosuppressants, and she was treated surgically……



IDP	GEN (HERENCIA)	FP	OTRAS MANIFESTACIONES	Rta Tto Convencional	Tratamiento de Elección
Defecto en IL10R	*IL10R* (AR)	Pérdida Homeostasia intestinal	Foliculitis Abscesos Fístulas E-C-PA Fíitulas R-V	Refractario	Drenajes Colectomía TCHP
Defecto en IL10	*IL10* (AR)	Pérdida Homeostasia intestinal	Foliculitis Abscesos Fístulas E-C-PA Fíitulas R-V	Refractario	Drenajes Colectomía TCHP

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Defecto en IL10 – IL10R

Loss of Interleukin-10 Signaling and Infantile Inflammatory Bowel Disease: Implications for Diagnosis and Therapy

DANIEL KOTLARZ,[*,‡] RITA BEIER,[*] DHAARINI MURUGAN,[*,‡] JANA DIESTELHORST,[*,‡] OLE JENSEN,[*,‡] KAAN BOZTUG,[*] DIETMAR PFEIFER,[§] HANS KREIPE,[‖] EVA-DOREEN PFISTER,[¶] ULRICH BAUMANN,[¶] JACEK PUCHALKA,[‡] JENS BOHNE,[#] ODUL EGRITAS,[**] BUKET DALGIC,[**] KAIJA-LEENA KOLHO,[‡‡] AXEL SAUERBREY,[§§] STEPHAN BUDERUS,[‖‖] TAYFUN GÜNGÖR,[¶¶] AXEL ENNINGER,[##] YU KAR LING KODA,[***] GRAZIELLA GUARISO,[‡‡‡] BATIA WEISS,[§§§] SELIM CORBACIOGLU,[‖‖‖] PIOTR SOCHA,[¶¶¶] NURAY USLU,[###] AYSE METIN,[****] GHASSAN T. WAHBEH,[‡‡‡‡] KHALID HUSAIN,[§§§§] DINA RAMADAN,[‖‖‖‖] WALEED AL-HERZ,[‖‖‖‖] BODO GRIMBACHER,[¶¶¶¶] MARTIN SAUER,[*] KARL-WALTER SYKORA,[*] SIBYLLE KOLETZKO,[‡] and CHRISTOPH KLEIN[*,‡]

GASTROENTEROLOGY 2012;143:347–355

Al diagnóstico

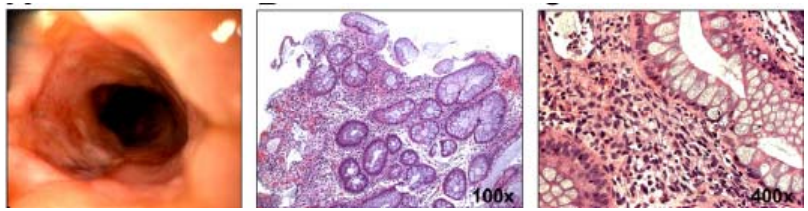


Figure 1. Clinical phenotype and defective IL-10-mediated signal transduction in IL-10R–deficient patients. (*A*) Representative colonoscopy image of patient 4 showing acute colitis accompanied by early cobblestone pattern and intermittent serpiginous ulcers with fibrin layers.(*B, C*) Histopathological analysis of colon biopsies of patient 4 revealed glandular distortion and a mild to moderate degree of inflammation with circumscribed and superficial mucosal defects. Infiltrate primarily consists of lymphocytes, macrophages, eosinophils, and polymorphonuclear granulocytes. (*D*)

Pos TCHP

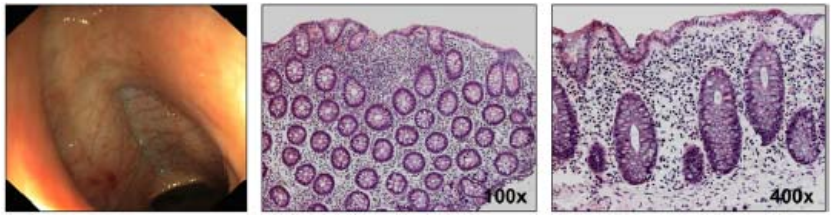


Figure 4. Clinical phenotype and reconstitution of the IL-10–mediated signal transduction in IL-10–deficient patients after allogeneic HSCT. (*A*) Representative colonoscopy of patient 4 demonstrates normal intestinal mucosa without evidence of inflammatory processes 13 months after HSCT. (*B, C*) Histopathological examination of colon biopsies after 13 months of HSCT revealed almost complete reduction of glandular distortion and an inconspicuous, sparse leukocytic infiltration within the lamina propria mucosa. (*D*) Representative Western blot analysis of signal transducer and

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Manifestación inicial

blood

2011 117: 1522-1529
Prepublished online November 30, 2010;
doi:10.1182/blood-2010-07-298372

Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency)

Jana Pachlopnik Schmid, Danielle Canioni, Despina Moshous, Fabien Touzot, Nizar Mahlaoui, Fabian Hauck, Hirokazu Kanegane, Eduardo Lopez-Granados, Ester Mejstrikova, Isabelle Pellier, Lionel Galicier, Claire Galambrun, Vincent Barlogis, Pierre Bordigoni, Alain Fourmaintraux, Mohamed Hamidou, Alain Dabadie, Françoise Le Deist, Filomeen Haerynck, Marie Ouachée-Chardin, Pierre Rohrlich, Jean-Louis Stephan, Christelle Lenoir, Stéphanie Rigaud, Nathalie Lambert, Michèle Milili, Claudin Schiff, Helen Chapel, Capucine Picard, Geneviève de Saint Basile, Stéphane Blanche, Alain Fischer and Sylvain Latour

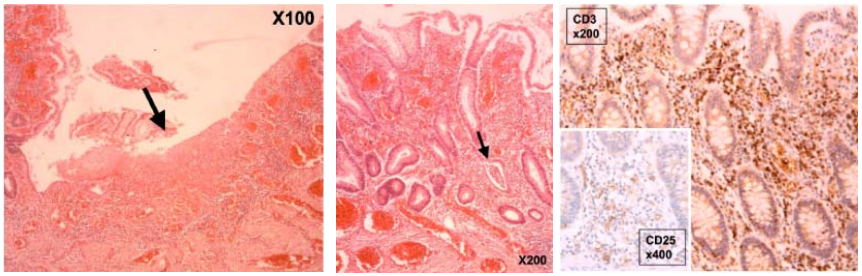


Figure 2. Histology of the large bowel of PX1.7 with XIAP deficiency. (Top left) On hematoxylin and eosin at low magnification (×100), a large ulceration is seen, indicated by an arrow. (Bottom left) Higher magnification (×200) shows a massive polymorphic inflammatory infiltrate associated with a crypt abscess (indicated by the arrow). (Central right) Immunostaining with anti-CD3 shows frequent lymphoid T cells (on the right, ×200), some of them express the activation marker CD25 (×400, inset).

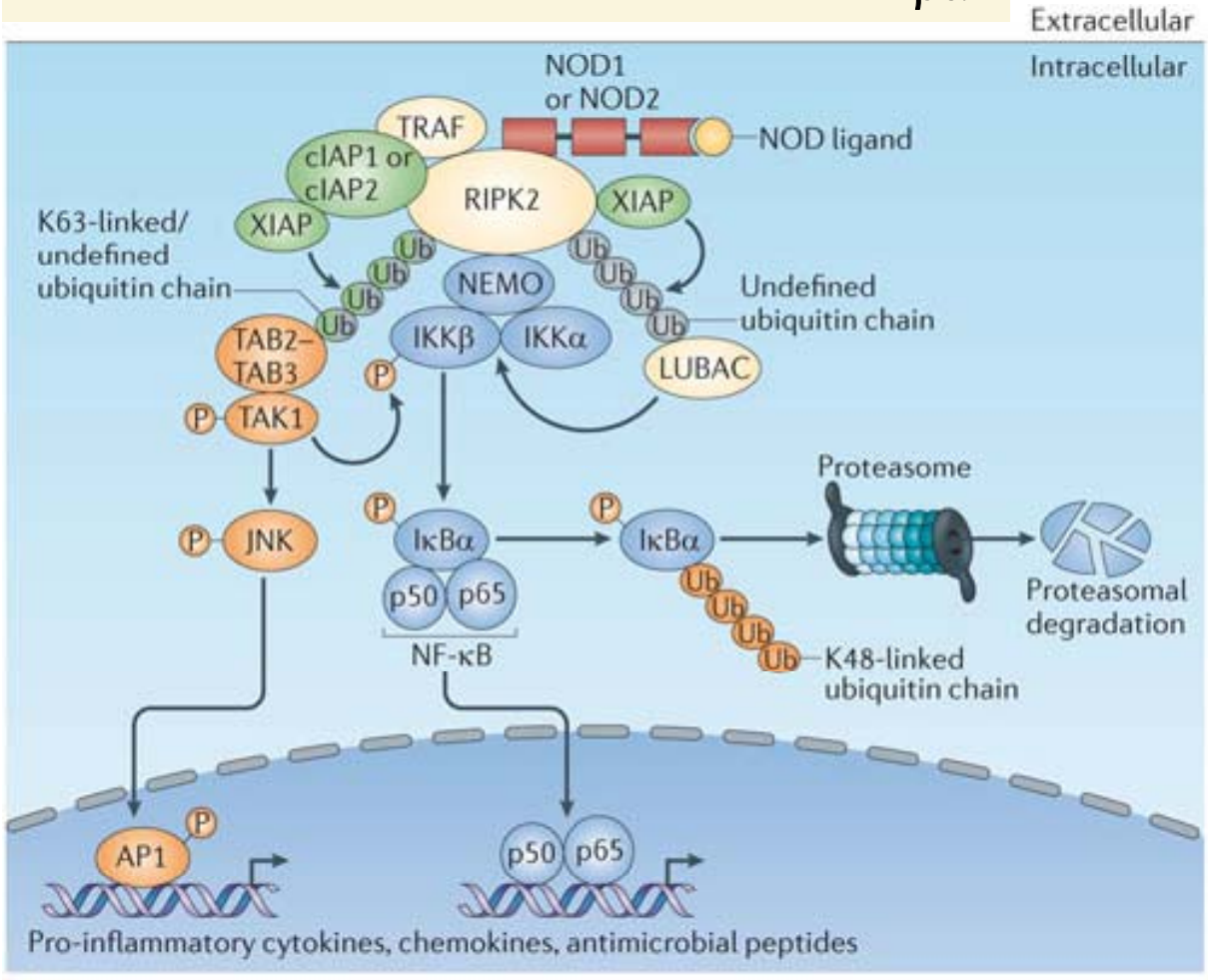
XLP 2 **Defecto en XIAP**	***BIRC4*** **(LX)**	**Deficiente activación de NOD2**	**HLH** **Hepatitis fulminate** **Colangitis** **EII**	**Parcial con recurrencias**	**TCHP**

o al sexo 2
XIAP: X linked inhibitor of apoptosis protein
NOD2: Nucleotide-binding oligomerization domain 2
HLH: Hewmophogacytic Lymphohistiocytosis

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Manifestación inicial

Señalización : XIAP – NEMO – IL10 – NOD - IKβα



ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Manifestación inicial - evolutiva

Clinical & Cellular Immunology

Broides et al., J Clin Cell Immunol 2014, 5:2
http://dx.doi.org/10.4172/2155-9899.1000204

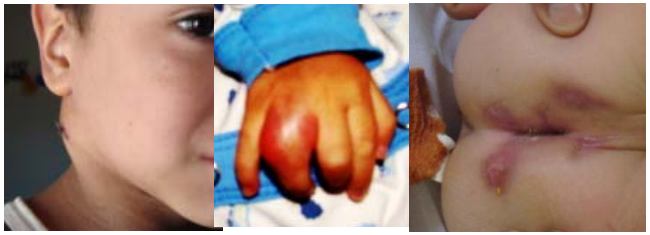
Research Article Open Access

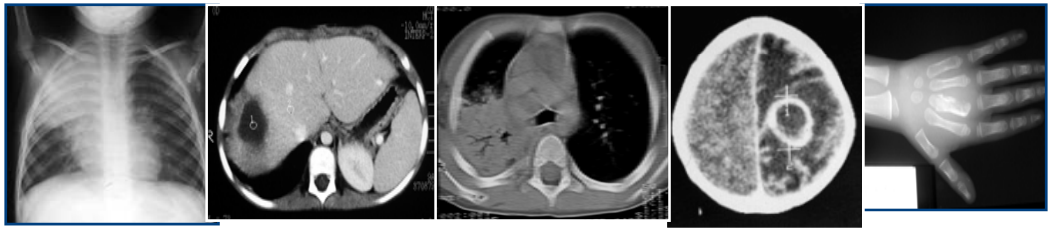
Gastrointestinal Abnormalities among Patients with Chronic Granulomatous Disease

Arnon Broides[1,2], Reem Mohammed[2], Brenda Reid[2], Chaim M. Roifman[2] and Eyal Grunebaum[2*]

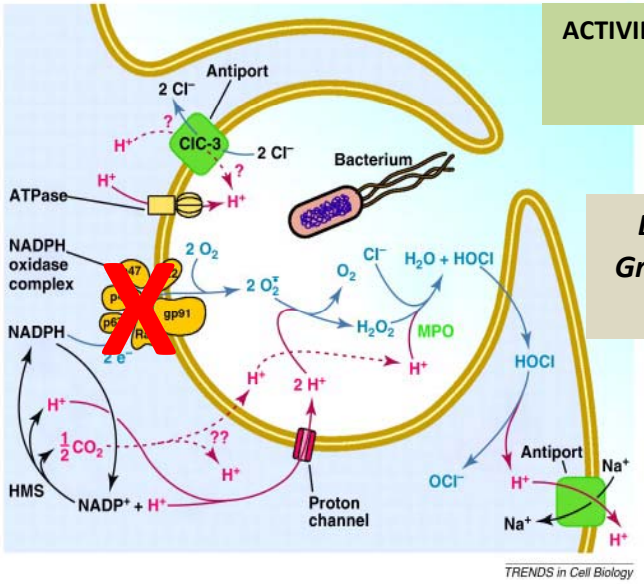
Inflammatory manifestations in a single-center of patients with chronic granulomatous disease

Alessandra Magnani, MD, PhD,[a,b,c] Pauline Brosselin, MD, MPH,[b,c] Julien Beauté, MD, MSc, MI
Nathalie de Vergnes, BS,[b,c] Richard Mouy, MD,[a] Marianne Debré, MD,[a] Felipe Suarez, MD, PhD
Olivier Hermine, MD, PhD,[b,c,d] Olivier Lortholary, MD, PhD,[b,c,e] Stéphane Blanche, MD,[a,b,c]
Alain Fischer, MD, PhD,[a,b,c,f] and Nizar Mahlaoui, MD, MSc, MPH[a,b,c,g] *Paris, France*





Reactivos Intermediarios de Oxígeno (RIOs)



ACTIVIDAD MICROBICIDA
Bactericida
Fungicida

Enfermedad Granulomatosa Crónica

Colitis leve
⬇
Enf. de Crohn like

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Enfermedad Granulomatosa Crónica

Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease

Alessandra Magnani, MD, PhD,[a,b,c] Pauline Brosselin, MD, MPH,[b,c] Julien Beauté, MD, MSc, MPH,[b] Nathalie de Vergnes, BS,[b,c] Richard Mouy, MD,[a] Marianne Debré, MD,[a] Felipe Suarez, MD, PhD,[b,c,d] Olivier Hermine, MD, PhD,[b,c,d] Olivier Lortholary, MD, PhD,[b,c,e] Stéphane Blanche, MD,[a,b,c] Alain Fischer, MD, PhD,[a,b,c,f] and Nizar Mahlaoui, MD, MSc, MPH[a,b,c,g] *Paris, France*

J ALLERGY CLIN IMMUNOL
2014

TABLE III. Inflammatory episode sites

	No. of episodes, all CGD, n	No. of patients with ≥1 episode: All CGD, n(%)	XL, n	AR, n	Unknown, n
No. of sites					
Single site	193	49 (72)	36	9	4
Two or more sites*	28	19 (28)	17	2	0
Total	221	68 (100)	53	11	4
Localization					
Gastrointestinal	156	60 (88.2)	46	10	4
Pulmonary	19	18 (26.4)	15	3	0
Genitourinary	20	12 (17.6)	9	2	1
Ocular	6	6 (8.8)	4	2	0
Autoimmune	7	7 (10.3)	6	1	0
Other†	16	13 (19.1)	10	2	1

*Twenty-six double sites (including 9 gastrointestinal + pulmonary episodes and 6 gastrointestinal + genitourinary episodes) and 2 triple sites (gastrointestinal + pulmonary + ocular and gastrointestinal + pulmonary + other episodes).
†Other sites: skin, central nervous system, and tympanum.

The GI tract was the most commonly involved organ (60 patients). There were 156 episodes in the GI tract alone or concurrently with other sites. The most frequent symptom was noninfectious diarrhea, followed by oral aphthae, anal fistulae, vomiting, anorexia, and abdominal pain.

different patients (at first episode in 2 cases). A total of 44 histological analyses were available. Acute and chronic inflammatory features were found in 56.8% and 47.7% of the samples, respectively, and mainly corresponded to an eosinophil-rich infiltrate, crypt abscesses, large pigment-containing macrophages in the lamina propria, and noncaseating granulomata (see Table E3 in

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Enfermedad Granulomatosa Crónica

Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease

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Paris, France

J ALLERGY CLIN IMMUNOL

2014

TABLE II. Inflammatory episodes and inheritance mode

Characteristic	Total (n = 98)	XL (n = 70)	AR (n = 20)	Unknown (n = 8)
≥1 Inflammatory episode, n (%)	68 (69.4)	53 (76)	11 (55)	4 (50)
1-2 Episodes, n (%)	32 (32.6)	22 (31.4)	8 (40)	2 (25)
≥3 Episodes, n (%)*	36 (36.7)	31 (44.3)	3 (15)	2 (25)
No inflammatory episodes, n (%)	30 (30.6)	17 (24.6)	9 (45)	4 (50)
Age at first inflammatory episode (y), median (min-max)				
All sites	3.2 (0.14-22.2)	3.2 (0.14-22.2)	5.4 (0.3-14.9)	2.0 (0.2-6.9)
Gastrointestinal	2.2 (0.1-22.2)	2.0 (0.1-22.2)	2.9 (0.3-14.9)	2.0 (0.2-6.9)
Pulmonary	6.9 (2.0-19.8)	6.9 (2.0-19.8)	8.3 (6.9-9.7)	—
Urogenital	4.8 (0.6-6.9)	4.8 (0.6-6.9)	—	—
Ocular	11.3 (0.6-12.8)	5.9 (0.6-11.3)	12.8	—
Autoimmune	4.1 (1.1-8.0)	4.9 (1.1-8.0)	3.3	—
Other	15.9 (0.2-19.8)	15.9 (0.2-19.8)	—	—

*P = .095 (Fisher exact test).

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Enfermedad Granulomatosa Crónica

Gastrointestinal Involvement in Chronic Granulomatous Disease

Beatriz E. Marciano, MD*; Sergio D. Rosenzweig, MD*; David E. Kleiner, MD‡; Victoria L. Anderson, MSN, CRNP*; Dirk N. Darnell, RN, MSN*; Sandra Anaya-O'Brien, RN, MSN*; Dianne M. Hilligoss, MSN, CRNP*; Harry L. Malech, MD*; John I. Gallin, MD*; and Steven M. Holland, MD*

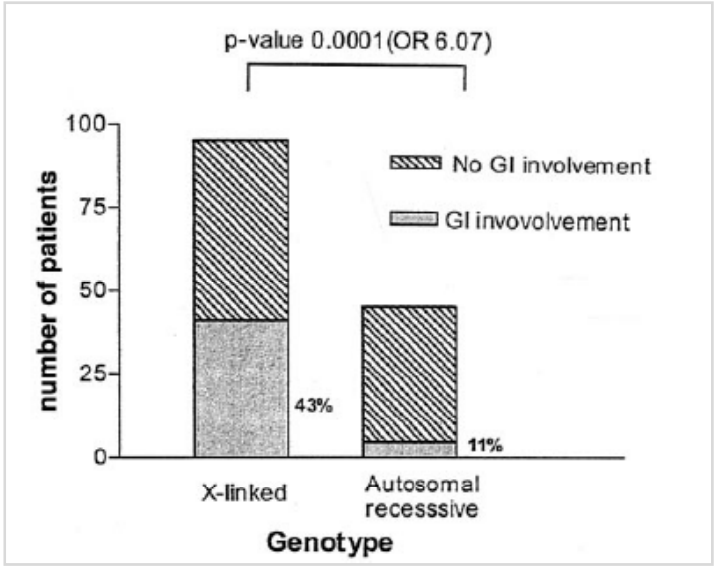
Pediatrics 2004;114;462-468

n 140 pacientes con EGC

TABLE 1. Clinical Manifestations in the Cohort of Patients With CGD and GI Involvement

	Patient (%)
Clinical Features	
Abdominal pain*	46 (100%)
Nausea and vomiting	11 (24%)
Diarrhea	15 (33%)
Bloody diarrhea	3 (6%)
Constipation	2 (4%)
Pathology features	
Granulomatous colitis	29 (63%)

* Abdominal pain as the sole symptom occurred in 33%.



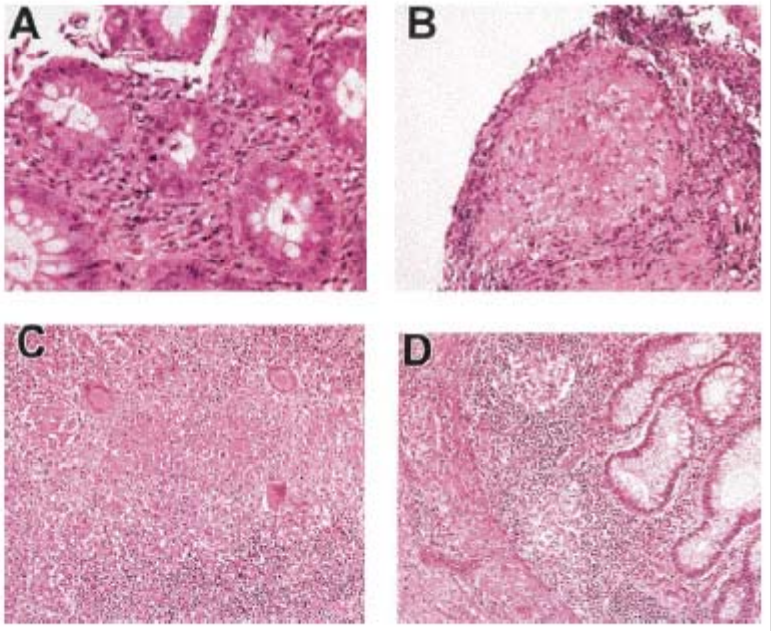


Fig 2. Colon biopsies in CGD patients. A, Focal cryptitis is a common finding. The crypt in the center of the field shows infiltration by neutrophils, but a crypt abscess has not formed. The lamina propria shows a dense infiltrate of lymphocytes, plasma cells, and occasional neutrophils and eosinophils (hematoxylin and eosin [H&E], ×600). B, Elsewhere in the same colon, there were discrete nonnecrotizing granulomas involving the lamina propria and superficial submucosa (H&E, ×400). C, A sigmoidectomy done on another patient to remove strictures showed large necrotizing granulomata deep in the submucosa (H&E, ×200). D, Nonnecrotizing granulomata were also present in the lamina propria and submucosa, associated with changes of chronic colitis (H&E, ×200).

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

CLINICAL IMMUNOLOGY

doi: 10.1111/j.1365-3083.2011.02658.x

Array-Based Sequence Capture and Next-Generation Sequencing for the Identification of Primary Immunodeficiencies

S. Ghosh*[1], F. Krux*[1], V. Binder*[1], M. Gombert*[1], T. Niehues†, O. Feyen‡, H.-J. Laws* & A. Borkhardt* on behalf of PID-NET: German Network on Primary Immunodeficiency Diseases

Para enfermedades humanas hereditarias
(Condiciones genéticas Mendelianas)

- ✓ Secuenciación masiva en paralelo de grandes proporciones del genoma
- ✓ Muestra ADN – Diferentes plataformas
- ✓ Paciente seleccionado con cuadro clínico de causa no caracterizada (especialmente si varios miembros afectados)
- ✓ Familiares (hermanos, padre, sin clínica)

- ✓ Fragmentación del ADN (diferentes métodos)
- ✓ Amplificación regiones seleccionadas:
  - **Whole exome Sequencing (WES)**
  - **Paneles genes candidatos**
- ✓ Secuenciación en paralelo
- ✓ Análisis – comparación genoma de referencia

➔ **Secuenciación por Sanger (confirmatorio)**

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Gastroenterology 2014;147:990–1007

REVIEWS IN BASIC AND CLINICAL GASTROENTE
AND HEPATOLOGY

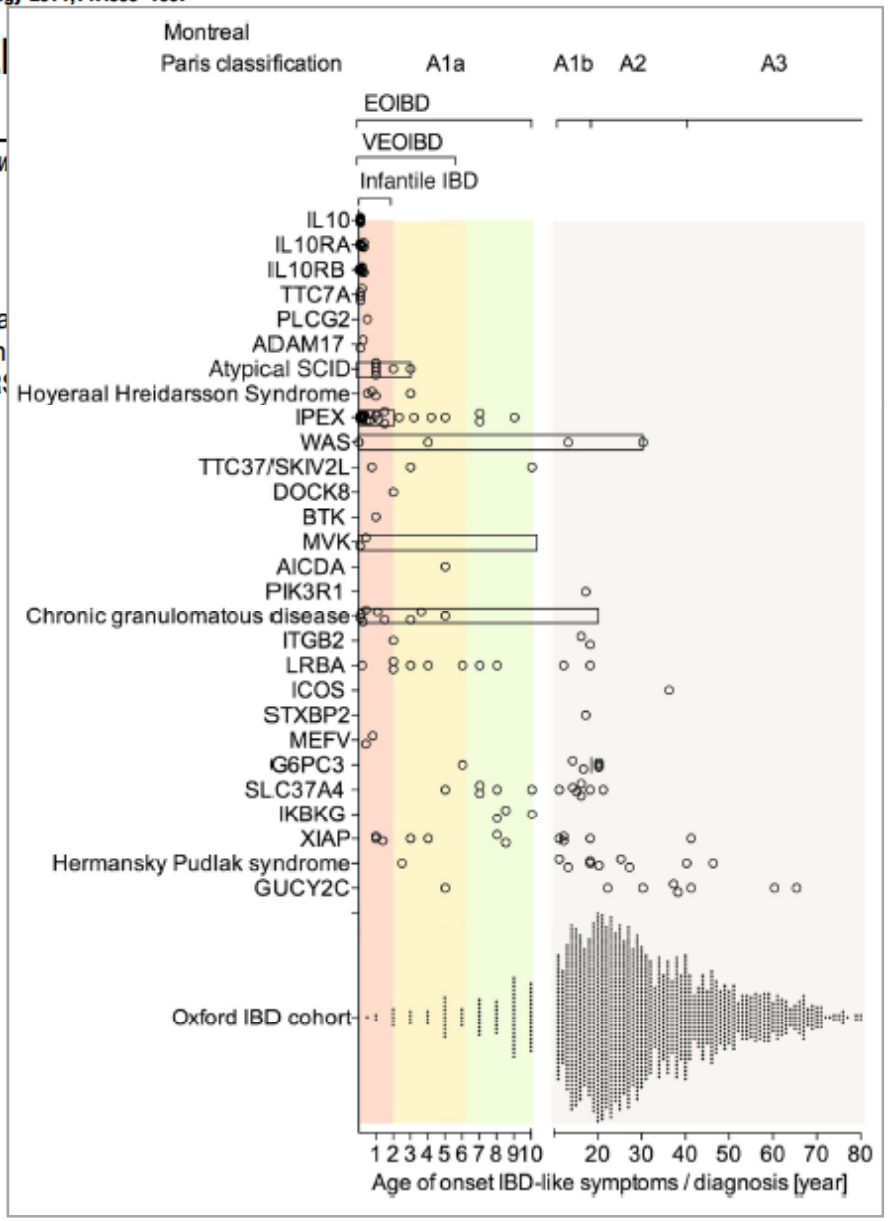
Robert F. Schwabe and John W

The Diagnostic Approach to Monogenic Very Early Onset Inflammatory Bowel Disease

Holm H. Uhlig,[1,2] Tobias Schwerd,[1] Sibylle Koletzko,[3] Neil Shah,[4,5] Jochen Ka
Abdul Elkadri,[6,7] Jodie Ouahed,[8,9] David C. Wilson,[10,11] Simon P. Travis,[1] Dan
Christoph Klein,[3] Scott B. Snapper,[8,9] and Aleixo M. Muise,[6,7] for the COLORS
Study Group and NEOPICS

Table 1. Subgroups of Pediatric IBD According to Age

Group	Classification	Age range (*y*)
Pediatric-onset IBD	Montreal A1	Younger than 17
EOIBD	Paris A1a	Younger than 10
VEOIBD		Younger than 6
Infantile (and toddler) onset IBD		Younger than 2
Neonatal IBD		First 28 days of age



ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Defectos inmunidad celular - Combinados
- IDC - IDCS – S. Omenn

ID Combinadas asociadas a Síndromes
- WAS (WASP)
- Disqueratosis congénita L´ X (Disqueratina)
- Defecto en TTC7A

Defectos inmunidad Predominantemente Ac
- Agamaglobulinemias
- IDCV
- Defecto en PLCγ2
- HIGM
- Defecto en LRBA
- Defecto en CD21
- Defectos PI3K

Desregulación inmune
- IPEX - IPEX like (CD25, STA5b, STAT1GOF, STAT3GOF, LRBA, CTLA4, MALT1)
- APECED (AIRE)
- LHF5 (STXBP2)
- S. Hermansky Pudlak tipo 2 (APB13)
- XLP 2 - Defecto en XIAP
- Defectos IL10 - IL10RA - IL10RB
- TGFRβ1 – TGFRβ2 , HSP1L , CARMIL2

Defectos fagocitos
- Neutropenia congénita
- EGC (CYBB)
- LAD (CD18)
- Glucogenosis 1b

Def. Inmunidad Innata
- Defecto en NEMO
- Defecto en IkBα
- Defectos en CARD9

Deficiencias del S. Complemento
- Defectos MAPS2

Síndromes auto inflamatorios
- MVK
- (Defectos IL10-IL10R - EOBID)
- Pyrin

Otros
- S. Trico-hepato-entérico *(TTC37-SKIVAL)*

Defectos barrera intestinal
- TTC7A
- ADAM11

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Center for Chronic Immunodeficiency
Universitats Klinikum Freiburg
Secuenciación de nueva generación
Paneles de genes candidatos (según fenotipo)

Panel para EII
53 genes candidatos con susceptibilidad a EII
Costo: 250 euros
Tiempo proceso: 1 a 4 meses

GENES CANDIDATOS – FENOTIPO EII			
ADAM17	CD40LG	NOD2	DEFB1
CYBA	CDX1	IL23R	DKC1
CYBB	CTLA4	ATG16L1	IKBKG
FOXP3	FUT2	IRGM	RTEL1
IL2RA	GATA2	IL17	TERC
IL10RA	GUCY2C	IL17RA	TERT
IL10RB	ICOS	P2RX7	TINF2
IL10	IKZF2	PLCG2	WRAP53
NCF1	IL1RL1	PTEN	IL23A
NCF2	IL4	TGFB2	IL33
NCF4	1L15	TGFB3	IRAK1
WASP	IL15RA	TGFB1	RORC
XIAP	STXBP2		SC2D1A
LRBA	TTC7A		

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia – Enfermedad Monogénica

Resumiendo

- *IL10R - IL10*
- *XIAP* (Síndrome Linfoproliferativo ligado al sexo ti
- *CYBB* (Enfermedad granulomatosa crónica)
- *ADAM17*

- *FOXP3* (Síndrome IPEX)
- *AIRE* (APECED)
- *WASP* (Síndrome de Wiskott aldrich)
- *Diskeratina* (Disqueratosis congénita)
- *Artemis* (ID Combinadas)
- Sistema Complemento
- *STX11BP2* (LHF tipo 5)
- *Lyst* (Síndrome de Chediak Higashi)
- *APB13* (Síndrome de Hermansky Pudlak)
- *CD18* (LAD tipo 1)
- *NEMO* (Displasia ectodérmica anhidrótica con ID)
- IkBα
- *LRBA* (ID Combinada – Ac)
- TTC37 - SKIV2L (Sme trico hepato entérico)
- EPAM
- CARMIL 2
- TGFRβ1 - 2
- HSP1L
- **ID Común Variable**

ESTUDIOS DISPONIBLES

Expresión, Señalización Células Mo estimuladas con LPS **con y sin IL10**. producción de IL 6 - TNFα- por ELISA. (LPS solo, estimula, LPS con IL10 debe disminuir)

- *Expresión, NKT, Sanger*
- *Prueba de DHR, Sanger*
- *ADAM17*

- *Expresión, Threg*
- *Sanger*
- *Expresión, Sanger*
- *Estudios telómero, Sanger*
- *Poblaciones Linfocitarias, Sanger*
- *C3, CH50, AP50*
- *CD107a, Sanger*
- *Pelo gris, gránulos, CD107a*
- *Pelo gris Disfunción plaquetaria*
- *Expresión*
- *Expresión, Señalización, Sanger*
- *Expresión, Señalización, Sanger*
- *Expresión*
- *TTC37 - SKIV2L (Sme trico hepato entérico)*
- *EPAM*
- *CARMIL 2*
- *TGFRβ1 - 2*
- *HSP1L*
- ***Igs Acs CD19***

Secuenciación génica de nueva generación
WES - Paneles

6to Congreso Argentino de Gastroenterología Pediátrica

MUCHAS GRACIAS

Dr. Matías Oleastro

Jefe Clínica Médica en Inmunología
Servicio de Inmunología y Reumatología
Hospital Nacional de Pediatría
"Prof. Dr. Juan P Garrahan"
Buenos Aires, Argentina

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

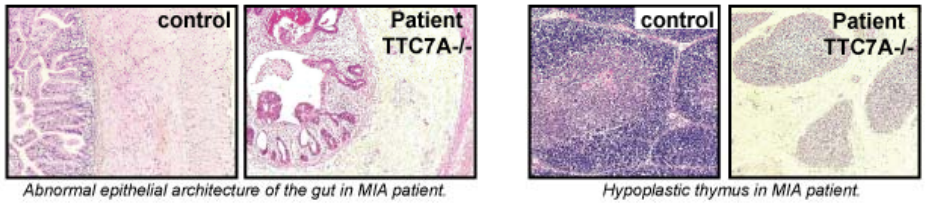
Defecto en TTC7A

Manifestación inicial

Whole-exome sequencing identifies tetratricopeptide repeat domain 7A (*TTC7A*) mutations for combined immunodeficiency with intestinal atresias

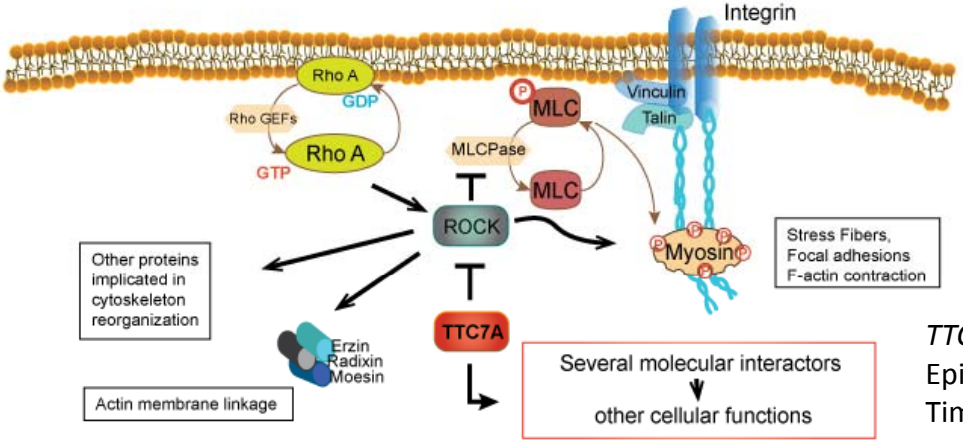
Rui Chen, PhD,[a*] Silvia Giliani, PhD,[b*] Gaetana Lanzi, PhD,[b] George I. Mias, PhD,[a] Silvia Lonardi, BS,[c] Kerry Dobbs, BS,[d] John Manis, MD,[e] Hogune Im, PhD,[a] Jennifer E. Gallagher, PhD,[a‡] Douglas H. Phanstiel, PhD,[a] Ghia Euskirchen, PhD,[a] Philippe Lacroute, PhD,[a] Keith Bettinger, MS,[a] Daniele Moratto, PhD,[b] Katja Weinacht, MD,[f] Davide Montin, MD,[g] Eleonora Gallo, MD,[g] Giovanna Mangili, MD,[h] Fulvio Porta, MD,[i] Lucia D. Notarangelo, MD,[i] Stefania Pedretti, MD,[h] Waleed Al-Herz, MD,[j] Wasmi Alfahdli, MD,[k] Anne Marie Comeau, PhD,[l] Russell S. Traister, MD, PhD,[m] Sung-Yun Pai, MD,[n] Graziella Carella, PhD,[o] Fabio Facchetti, MD,[c] Kari C. Nadeau, MD, PhD,[p] Michael Snyder, PhD,[a] and Luigi D. Notarangelo, MD[d,q] *Stanford, Calif, Brescia, Torino, and Bergamo, Italy, Boston and Worcester, Mass, Kuwait City, Kuwait, and Pittsburgh, Pa*

J ALLERGY CLIN IMMUNOL
■■■ 2013



Abnormal epithelial architecture of the gut in MIA patient.

Hypoplastic thymus in MIA patient.



Atresia intestinal Múltiple
ID Combinada
5 pacientes WES
3 pacientes Sanger

Variantes bialélicas deletéreas en 8 ptes

TTC7A
Epitelio tímico
Timocitos

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

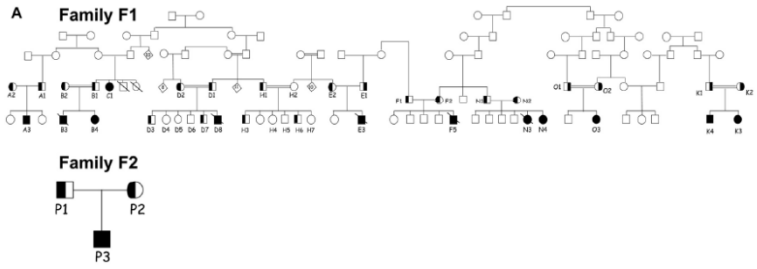
Defecto en TTC7A

Immune deficiency–related enteropathy-lymphocytopenia-alopecia syndrome results from tetratricopeptide repeat domain 7A deficiency

Roxane Lemoine, PhD,[a,b,c] Jana Pachlopnik-Schmid, MD, PhD,[a,b,c,‡] Henner F. Farin, PhD,[d*] Amélie Bigorgne, PhD,[a,b,c*] Marianne Debré, MD,[c] Fernando Sepulveda, PhD,[a,b,c] Sébastien Héritier, MD,[c] Julie Lemale, MD,[e] Cécile Talbotec, MD,[f] Frédéric Rieux-Laucat, PhD,[a,b,c] Frank Ruemmele, MD,[f] Alain Morali, MD,[g] Pascal Cathebras, MD,[h] Patrick Nitschke, PhD,[b] Christine Bole-Feysot, PhD,[b] Stéphane Blanche, MD,[a,b] Nicole Brousse, MD,[b,i] Capucine Picard, MD, PhD,[b,c,j] Hans Clevers, MD, PhD,[d] Alain Fischer, MD, PhD,[a,b,c,k] and Geneviève de Saint Basile, MD, PhD[a,b,c,j]

Paris and Saint Etienne, France, and Utrecht, The Netherlands

J Allergy Clin Immunolo 2014



Here we show that an early-onset IBD associated with progressive immune deficiency and eventually alopecia, as observed in 14 patients from 2 unrelated families, results from biallelic missense mutations in *TTC7A*. TTC7A deficiency causes inappropriate activation of RhoA-dependent effectors regulating cytoskeletal dynamics. This activation alters cell polarization,

TTC7A mutations disrupt intestinal epithelial apicobasal polarity
Amélie E. Bigorgne,Henner F. Farin,Roxane Lemoine, Nizar Mahlaoui, Nathalie Lambert, Marine Gil, Ansgar Schulz, Pierre Philippet, Patrick Schlesser, Tore G. Abrahamsen,Knut Oymar, E. Graham Davies, Christian Lycke Ellingsen, Emmanuelle Leteurtre,1 Brigitte Moreau-Massart, Dominique Berrebi, Christine Bole-Feysot,Patrick Nischke,Nicole Brousse, Alain Fischer,Hans Clevers,and Geneviève de Saint Basile

The Journal of Clinical Investigation http://www.jci.org Volume 124 Number 1 January 2014

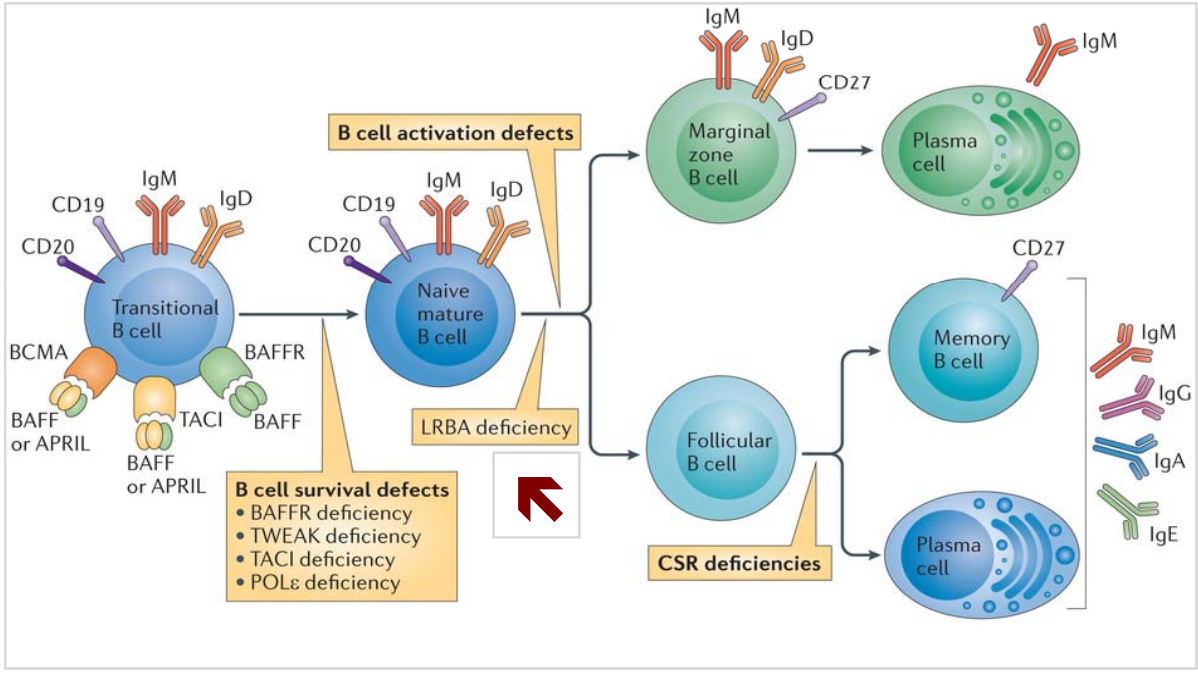
Hypomorphic mutation in TTC7A causes combined immunodeficiency with mild structural intestinal defects
Stavroula Woutsas, Caner Aytekin, Elisabeth Salzer, Cecilia Domínguez Conde, Sema Apaydin, Herbert Pichler, Nima Memaran-Dadgar, Ferda Ozbay Hosnut, Elisabeth Förster-Waldl, Susanne Matthes, Wolf-Dietrich Huber, Thomas Lion, Wolfgang Holter, Ivan Bilic, and Kaan Boztugcorresponding

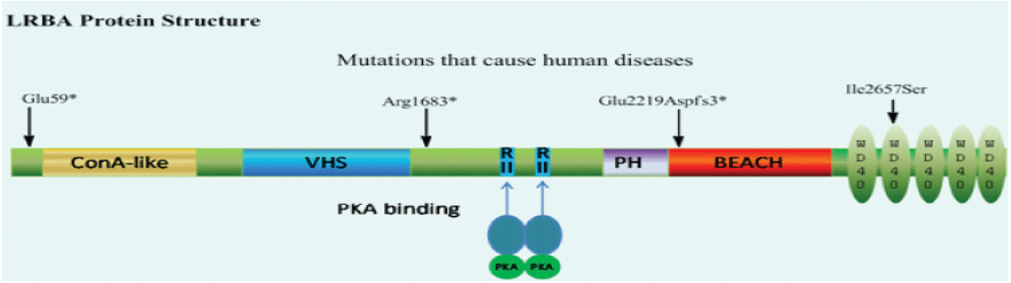
Blood. 2015 March 5; 125(10): 1674–1676.

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en LRBA

Manifestación inicial - evolutiva





LRBA: LPS-responsive beige-like anchor

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

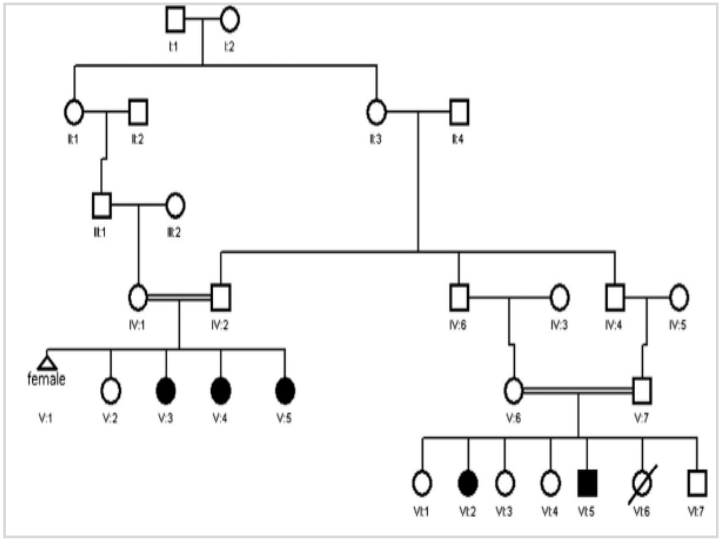
Defecto en LRBA

Manifestación inicial - evolutiva

LPS-responsive beige-like anchor (*LRBA*) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency

Abdullah Alangari, MD[a,*], Abdulrahman Alsultan, MD[a,*], Nouran Adly, BSc[b,*], Michel J. Massaad, PhD[d], Iram Shakir Kiani, MD[c], Abdulrahman Aljebreen, MD[c], Emad Raddaoui, MD[d], Abdul-Kareem Almomen, MD[c], Saleh Al-Muhsen, MD[a], Raif S. Geha, MD[e], and Fowzan S. Alkuraya, MD[a,b,f]

J Allergy Clin Immunol 2012; 130(2): 481-8.e2.



Presentación clínica

5 miembros afectados (consanguíneos)

Fenotipo CVID, desregulación inmune, o ambos.

- **Diarrea crónica: Enf. Inflamatoria Intestinal**
- Citopenias AI
- Enf. linfoproliferativa inducida por *EBV*

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en LRBA

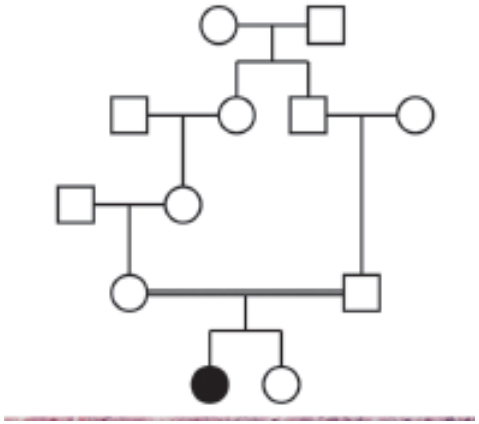
Manifestación inicial - evolutiva

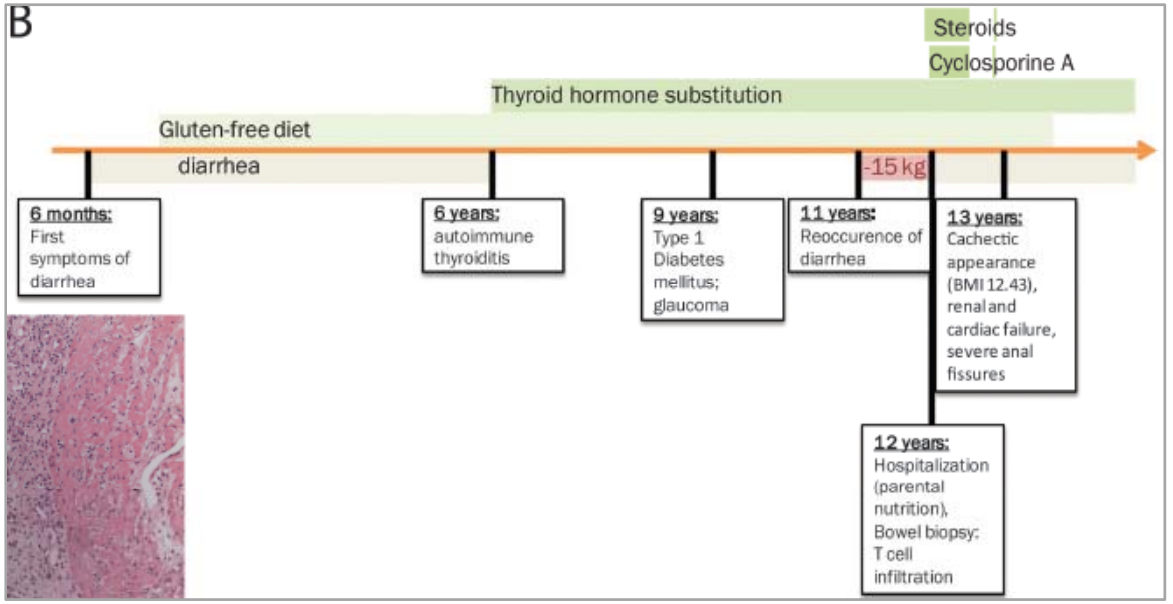
ORIGINAL ARTICLE

Atypical Manifestation of LRBA Deficiency with Predominant IBD-like Phenotype

Nina Kathrin Serwas, MSc, Aydan Kansu, MD,† Elisangela Santos-Valente, MD,* Zarife Kuloğlu, MD,† Arzu Demir, MD,† Aytaç Yaman, MD,† Laura Yaneth Gamez Diaz, MSc,‡ Reha Artan, MD,§ Ersin Sayar, MD,‖ Arzu Ensari, MD,¶ Bodo Grimbacher, MD,‡ and Kaan Boztug, MD*,***

Inflamm Bowel Dis • Volume 21, Number 1, January 2015





LRBA: LPS-responsive beige-like anchor

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en LRBA

Metodología diagnóstica

- Valoración de la ***expresión de LRBA*** intracitoplasmática

en células mononucleares estimuladas *in vitro* con PHA 72 hs,

Valorado mediante citometría de flujo

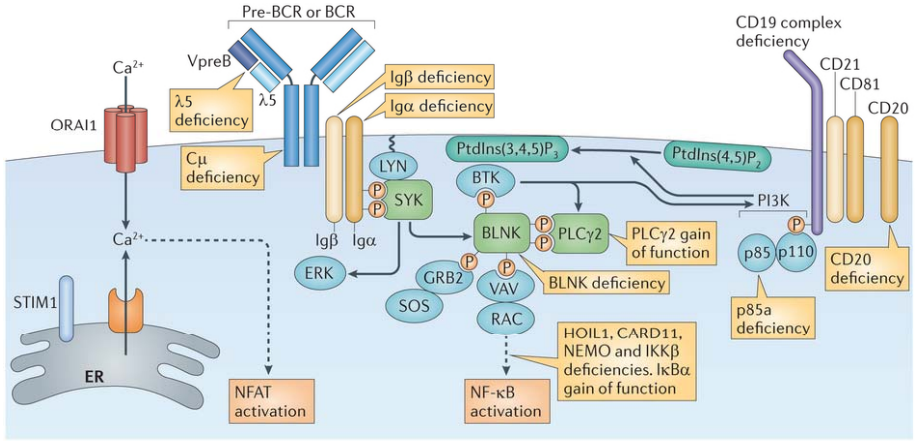
ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

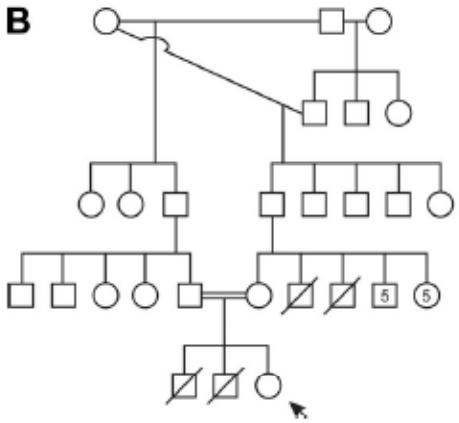
Defecto en PI3K (p85α) **Manifestación inicial - evolutiva**

Agammaglobulinemia and absent B lineage cells in a patient lacking the p85α subunit of PI3K

Mary Ellen Conley,[1,2] A. Kerry Dobbs,[2] Anita M. Quintana,[2] Amma Bosompem,[2] Yong-Dong Wang,[3] Elaine Coustan-Smith,[4] Amber M. Smith,[2,5] Elena E. Perez,[6] and Peter J. Murray[2,5]

2012 J. Exp. Med. Vol. 209 No. 3 463-470





was evaluated for immunodeficiency at 3.5 mo of age because of neutropenia (absolute neutrophil count of 0), interstitial pneumonia, and gastroenteritis. The family history was

pathic arthritis. At 17 yr of age, she was recognized to have recurrent *Campylobacter* bacteremia and inflammatory bowel disease that has been recalcitrant to therapy. Complete

PI3K: Phosphoinositide 3 kinase

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en PI3K (p85α)

Metodología diagnóstica

- Valoración la producción de IFNγ estimulando Células mononucleares con LPS.
- Alteraciones en los subset de linfocitos B (B transicionales)
- Alteración en los subset de linfopcitos T (CD4RA)

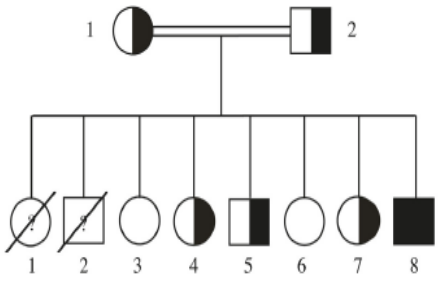
ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

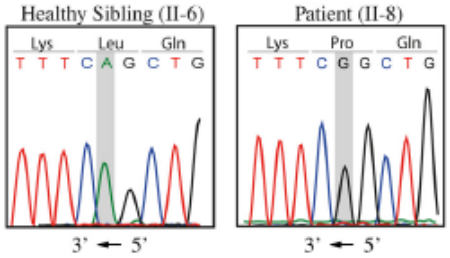
Defecto en IL-21

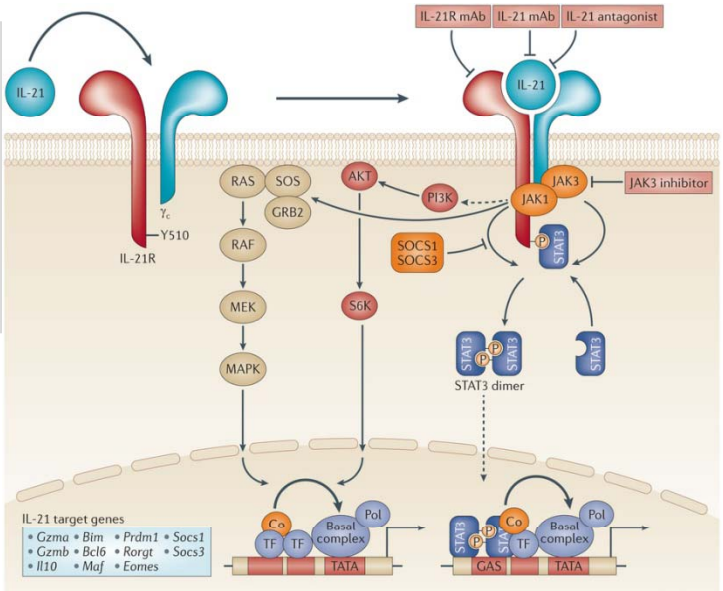
Early-onset inflammatory bowel disease and common variable immunodeficiency–like disease caused by IL-21 deficiency

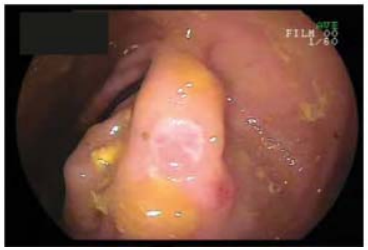
Elisabeth Salzer, MD,[a] Aydan Kansu, MD,[b] Heiko Sic, PhD,[c] Peter Májek, PhD,[a] Aydan Ikincioğullari, MD,[d] Figen E. Dogu, MD,[d] Nina Kathrin Prengemann, MSc,[a] Elisangela Santos-Valente, MD, MSc,[a] Winfried F. Pickl, PhD,[e] Ivan Bilic, PhD,[a] Sol A Ban,[a] Zarife Kuloğlu, MD,[b] Arzu Meltem Demir, MD,[b] Arzu Ensari, MD,[f] Jacques Colinge, PhD,[a] Marta Rizzi, PhD,[c] Hermann Eibel, PhD,[c] and Kaan Boztug, MD[a,g] *Vienna, Austria, Ankara, Turkey, and Freiburg, Germany*

J Allergy Clin Immunol 2014; 133: 1651-9

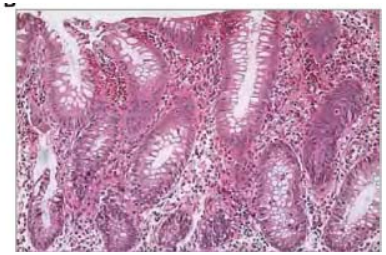








Colonoscopía



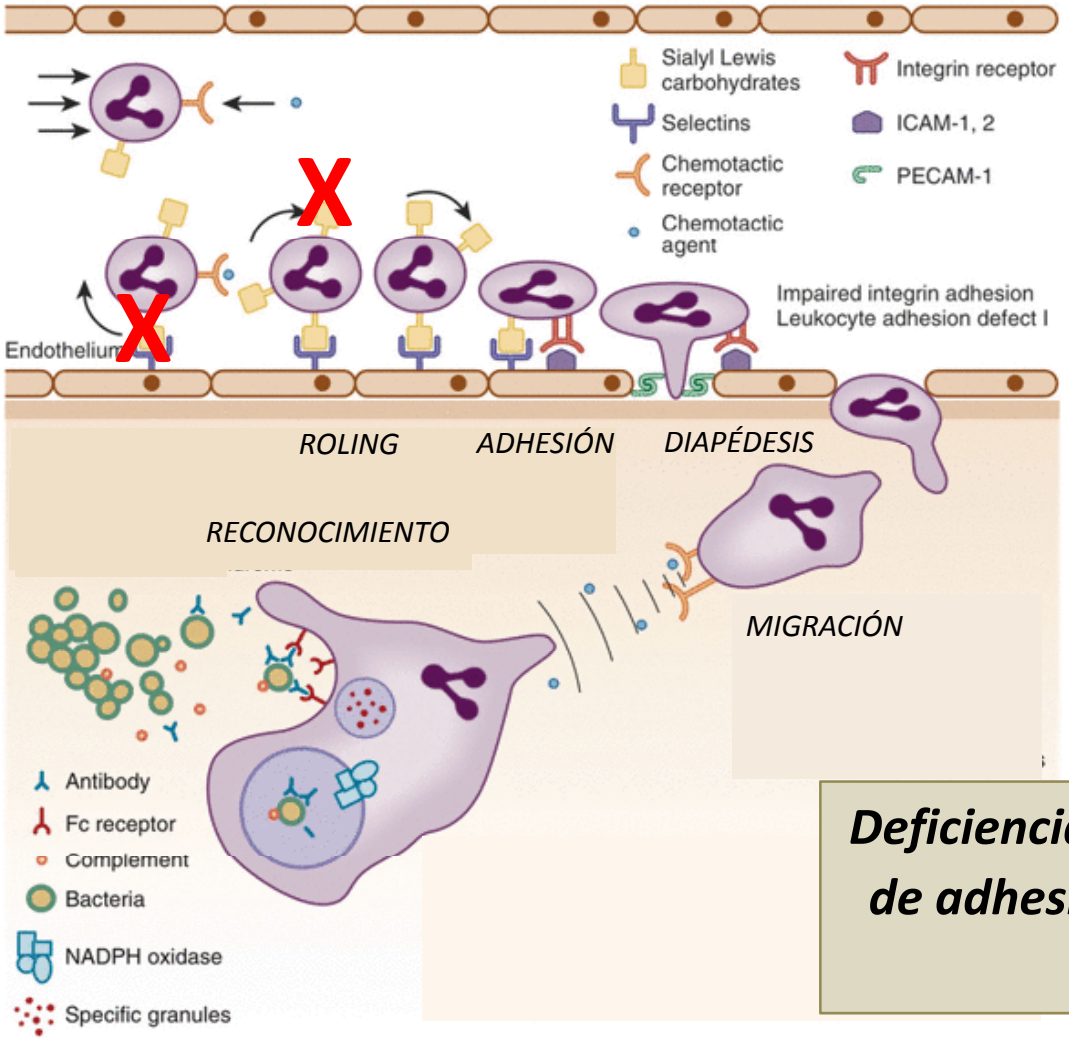
Histología: Enf Crohn like

Combining homozygosity mapping with exome sequencing, we uncovered IL-21 deficiency as a novel monogenetic cause of severe, early-onset IBD associated with a CVID-like primary immunodeficiency.

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defectos moléculas de adhesión

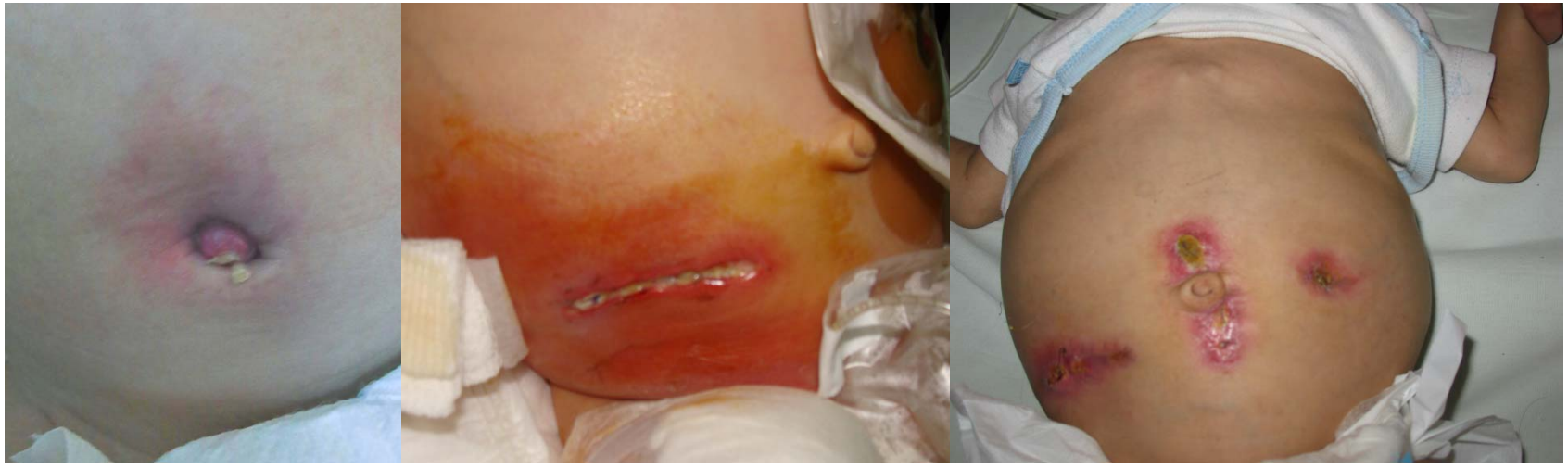
CIRCULACIÓN SANGUÍNEA



Deficiencias en moléculas de adhesión leucocitaria LAD

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defectos moléculas de adhesión



- Onfalorrexis tardía
- Onfalitis – Perionfalitis (Sin pus)
- **Enfermedad inflamatoria intestinal severa – refractaria**
- Mala cicatrización heridas quirúrgicas

Estudios:

- Neutrofila absoluta
- Deficiencia en CD18 (citometría de flujo)

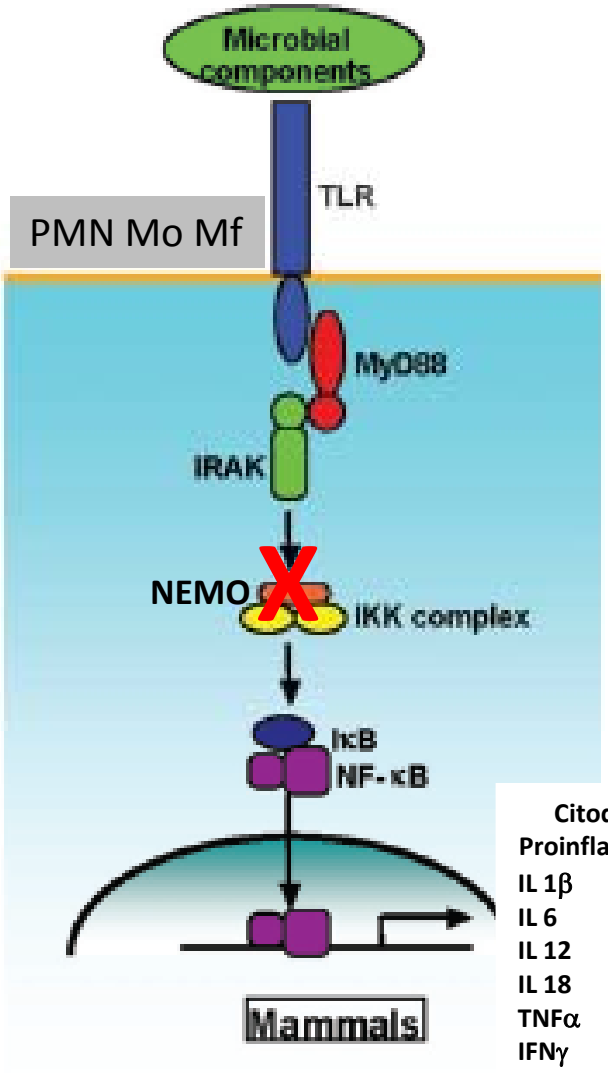
ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defectos moléculas de adhesión

	LAD 1	LAD 2	LAD 3
DEFECTO MOLECULAR	β_2 Integrinas CD18 (LFA1-Mac1-p150)	GDP – Fucose transporter (Fucocilación: SLeX: CD15)	Kindlin 3
GEN	*ITGB2*	*FUCT1*	*FERMT3*
FUNCIÓN	Adhesión Migración	Rolling	Activación β_{1-2-3} Integrinas (Adhesión – migración)
OTRAS MANIFESTACIONES	**Enfermedad inflamatoria intestinal**	Retraso mental Disforfias faciales	Hemorragias (Defecto plaquetario)
GRUPO SANGUÍNEO		Bombay	

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en NEMO



Citoquinas Proinflamatorias
IL 1β
IL 6
IL 12
IL 18
TNFα
IFNγ

Xq28

♦ **Mutaciones hipomórficas**

⇒ **DISPLASIA ECTODÉRMICA ANHIDRÓTICA LIGADA AL X (XL-EDA-ID)**

→ ***Displasia ectodérmica***
- Hipotricosis, dientes cónicos, hipodontia,
  Anhidrosis / hipodrosis por ausencia glándulas sudoríparas

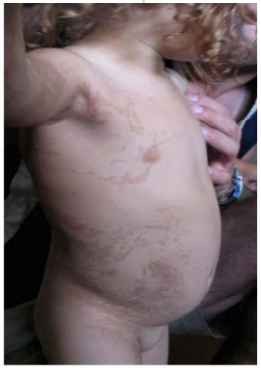
→ ***Inmunodeficiencia***
- Susceptibilidad a **infección por Micobacterias** L´X
- Susceptibilidad a infección por **Micobacterias y bacterias piógenas (*S pneumoniae*)**
- Susceptibilidad infección viral (Herpes, papiloma)

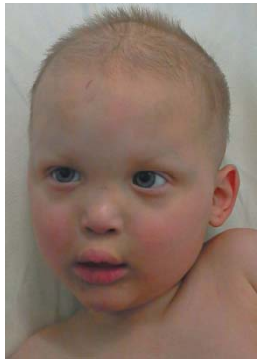
→ ***Linfedema + Osteopetrosis*** (OL-EDA-ID)

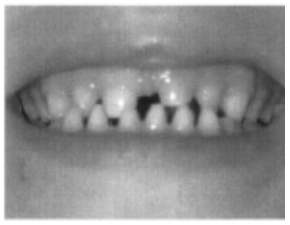
→ ***Enteropatía - Colitis***

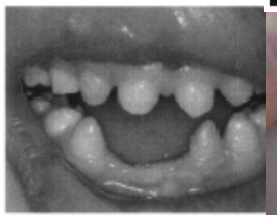
♦ **Mutaciones Amórficas/Nulas** (L´XD)

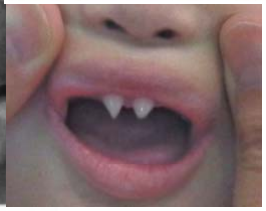
⇒ Varón: Muerte fetal
Mujer: Incontinencia pigmenti











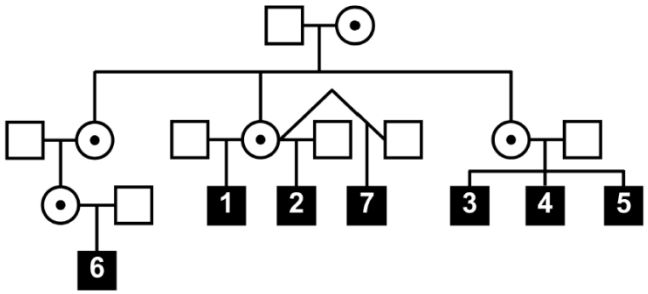
ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

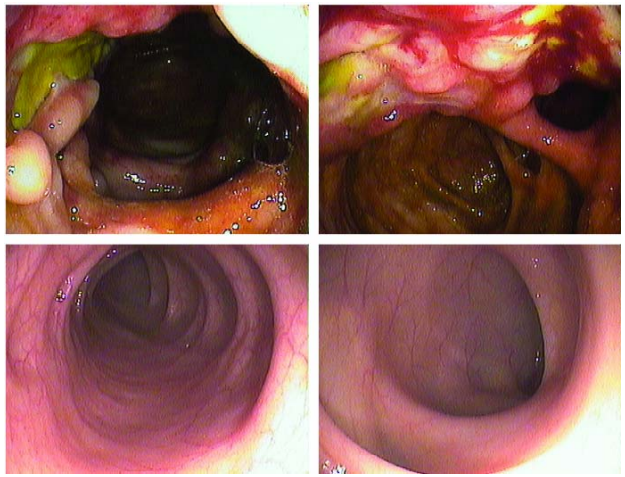
Defecto en NEMO

Persistent systemic inflammation and atypical enterocolitis in patients with NEMO syndrome

Laurence E. Cheng, MD, PhD[a,b], Bittoo Kanwar, MD[a,d], Haig Tcheurekdjian, MD[a,b,d,e], James P. Grenert, MD, PhD[c], Mica Muskat, RN, NP[a], Melvin B. Heyman, MD, MPH[a], Joseph M. McCune, MD, PhD[b,d], and Diane W. Wara, MD[a]

Clin Immunol. 2009 July ; 132(1): 124–131.

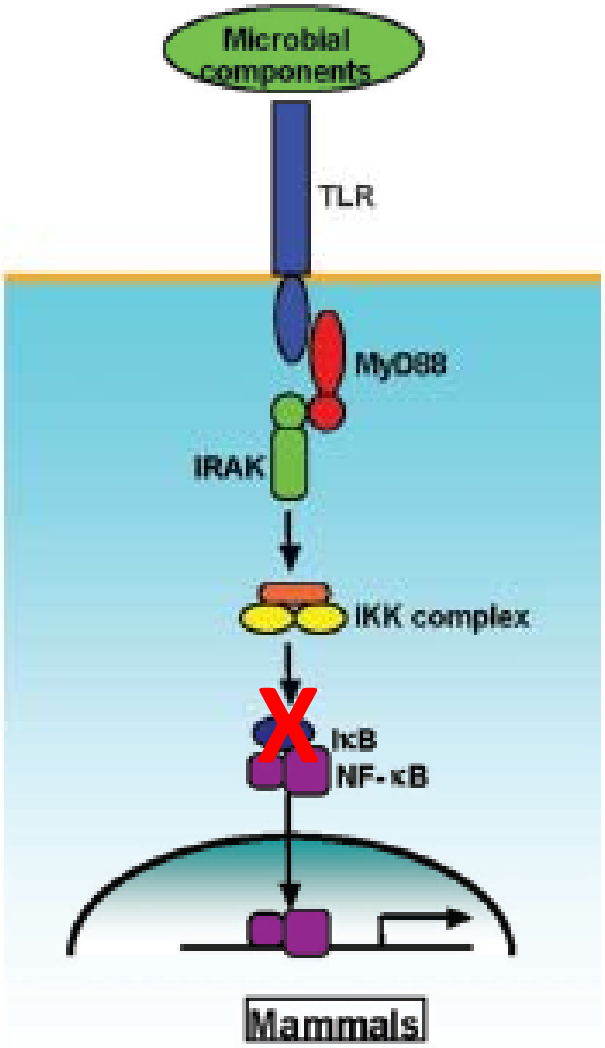




Paciente 3
Macroscopía e histología
Pre y pos tratamiento

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en IKBα

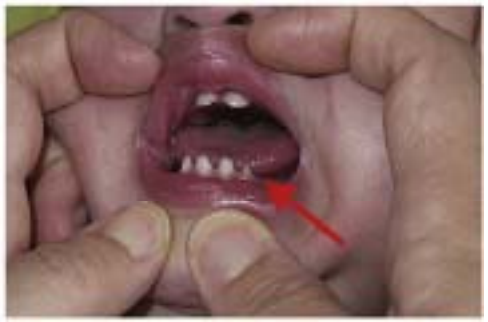


J ALLERGY CLIN IMMUNOL
FEBRUARY 2012

A rapid screening method to detect autosomal-dominant ectodermal dysplasia with immune deficiency syndrome

A patient presented to us with autosomal-dominant anhidrotic ectodermal dysplasia with immune deficiency syndrome (EDA-ID). By using a rapid flow cytometric screening system, we detected a novel mutation of the *IKBA* gene in the patient.

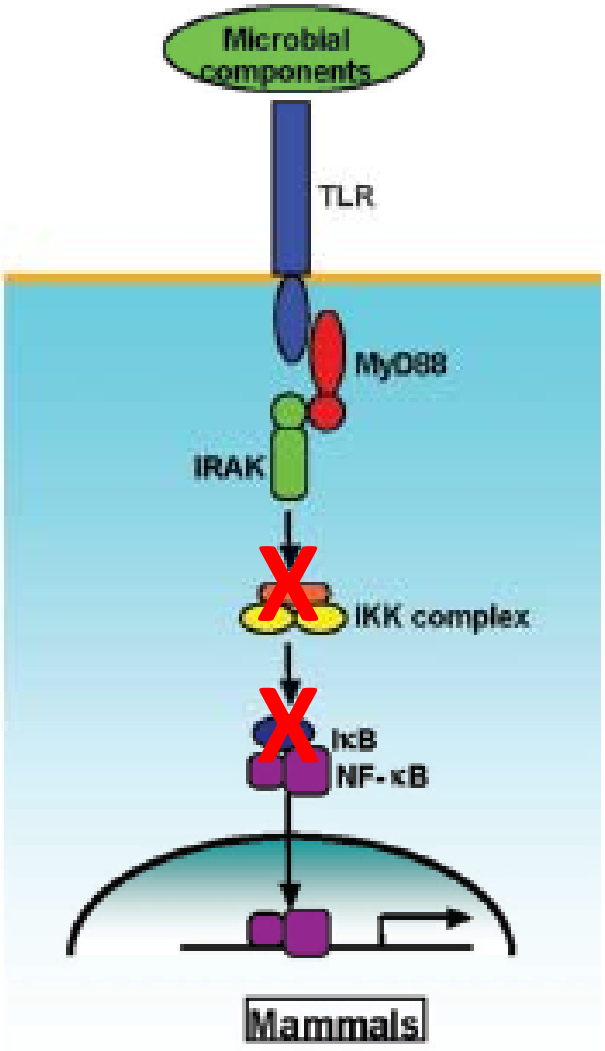
Hidenori Ohnishi, MD, PhD[a]
Rie Miyata, MD, PhD[b]
Tomonori Suzuki, MD[b]
Touichiro Nose, MD[b]
Kazuo Kubota, MD[a]
Zenichiro Kato, MD, PhD[a]
Hideo Kaneko, MD, PhD[a,c]
Naomi Kondo, MD, PhD[a]



ten been reported in XL-EDA-ID patients. The mechanism of the onset of inflammatory bowel disease with EDA-ID remains unknown, but our AD-EDA-ID patient also showed symptoms of inflammatory bowel disease.

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en IKBα



CLINICAL MICROBIOLOGY REVIEWS, July 2011, p. 490–497
0893-8512/11/$12.00 doi:10.1128/CMR.00001-11

Vol. 24, No. 3

Infectious Diseases in Patients with IRAK-4, MyD88, NEMO, or IκBα Deficiency

Capucine Picard,[1,2,3]* Jean-Laurent Casanova,[2,3,4,5] and Anne Puel[2,3]

TABLE 5. Clinical and biological phenotypes of IRAK-4, MyD88, NEMO, and IκBα deficiencies

Phenotype	Presence of phenotype for deficiency[b]			
	IRAK-4	MyD88	NEMO	IκBα
Pyogenic bacterial infection	+	+	+	+
Severe viral infection	−		+	
Environmental mycobacterial infection	+/−	−	+	−
Opportunistic infections	−	−	+	+
EDA	−	−	+ or −[a]	+
Colitis	−	−	+	+
Hypogammaglobulinemia	−	−	+	+
Specific protidic antibody defect	−	−	+	+
Specific polysaccharide antibody defect	+/−	ND	+	+
Low T-cell proliferation in response to anti-CD3	−		+/−	+
No IL-6 production by whole blood after activation with IL-1 or TLR agonists (except TLR3)	+	+	+/−	+
No IL-10 production by whole blood after activation with TNF-α	−	−	+	+

[a] Ten percent of NEMO-deficient patient have no EDA phenotype.
[b] −, absent; +, present; +/−, present in some patients.

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

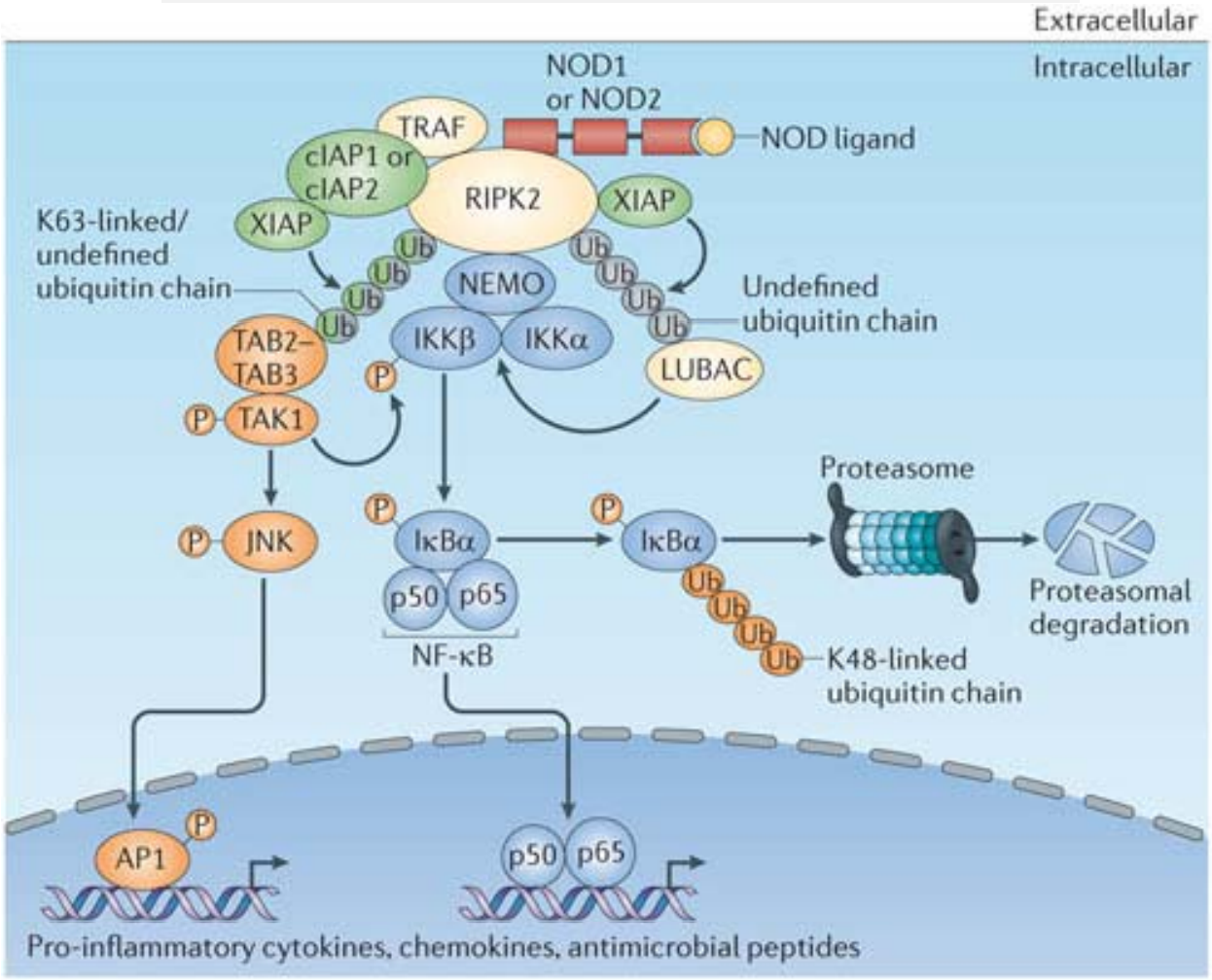
Defecto en NEMO

Metodología diagnóstica

- Valoración la producción de IL 10 estimulando Células mononucleares con TNFα
- Expresión proteína NEMO por citometría de flujo
- Secuenciación génica (NEMO, Ikβα)

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

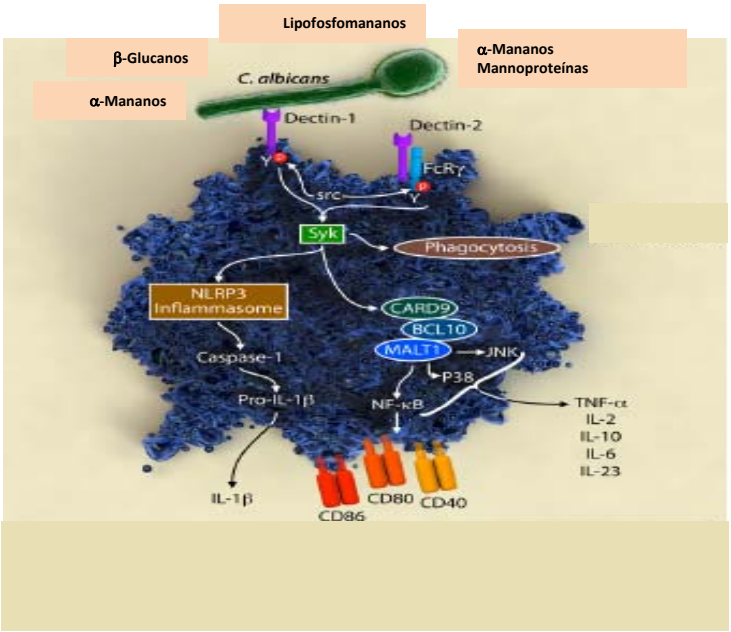
Defecto en XIAP – NEMO – IL10 – NOD - IKβα



Nature Reviews | Immunology

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Defecto en CARD9



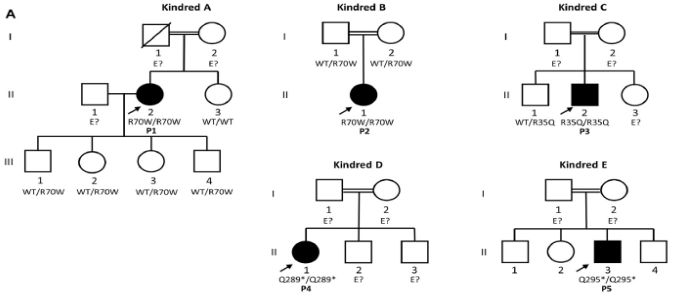
Immune deficiencies, infection, and systemic immune disorders

Inherited CARD9 deficiency in otherwise healthy children and adults with *Candida* species–induced meningoencephalitis, colitis, or both

Fanny Lanternier, MD, PhD,[a,b,c] Seyed Alireza Mahdaviani, MD,[d] Elisa Barbati, PhD,[a,b] Hélène Chaussade, MD,[e] Yatrika Koumar, MD,[f] Romain Levy, MD, MSc,[a,b] Blandine Denis, MD,[b,c] Anne-Sophie Brunel, MD,[f] Sophie Martin, MD,[g] Michèle Loop, MD,[h] Julie Peeters, MD,[g] Ariel de Selys, MD,[h] Jean Vanclaire, MD,[h] Christiane Vermylen, MD, PhD,[i] Marie-Cécile Nassogne, MD, PhD,[j] Olga Chatzis, MD, PhD,[g] Luyan Liu, PhD,[a,b] Mélanie Migaud, MSc,[a,b] Vincent Pedergnana, PhD,[a,b] Guillaume Desoubeaux, MD, PhD,[k] Gregory Jouvion, PhD,[l] Fabrice Chretien, MD, PhD,[l,m] Ilad Alavi Darazam, MD,[n] Alejandro A. Schäffer, PhD,[o] Mihai G. Netea, MD, PhD,[p] Jean J. De Bruycker, MD,[q] Louis Bernard, MD, PhD,[e] Jacques Reynes, MD, PhD,[f] Noureddine Amazrine, MD,[r] Laurent Abel, MD, PhD,[a,b,s] Dimitri Van der Linden, MD, PhD,[g]* Tom Harrison, MD, PhD,[t]* Capucine Picard, MD, PhD,[a,b,r,u,v]* Olivier Lortholary, MD, PhD,[b,c,w]* Davood Mansouri, MD, MPH,[n]* Jean-Laurent Casanova, MD, PhD,[a,b,s,v,x] and Anne Puel, PhD[a,b]

Paris, Tours, and Montpellier, France, Tehran, Iran, Brussels, Belgium, Bethesda, Md, Nijmegen, The Netherlands, Montreal, Quebec, Canada, Tangier, Morocco, New York, NY, and London, United Kingdom

J Allergy Clin Immunol 2015



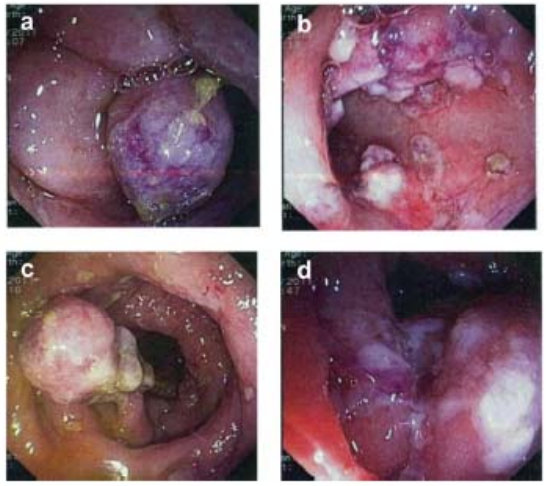


TABLE I. Characteristics of the 5 patients with invasive fungal infection and homozygous *CARD9* mutations

Patient ID	Age at onset (y)	Age at last follow-up (y)	Sex	Country of origin	Organ involvement	Associated CMC	Fungus	Status	*CARD9* mutation
P1	39	42	F	Turkey	CNS	Yes	*C albicans*	Alive	R70W/R70W
P2	7	8	F	Turkey	CNS	Yes	*C albicans*	Alive	R70W/R70W
P3	17	28	M	Iran	CNS, sinus, digestive tract	No	*C glabrata*	Alive	R35Q/R35Q
P4	37	37	F	Morocco	CNS	Yes	*C albicans*	Alive	Q289*/Q289*
P5	26	34	M	Pakistan	Digestive tract	No	*C albicans*	Alive	Q295*/Q295*

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Inmunodeficiencia Común Variable

Manifestación evolutiva

Moore *et al. World Allergy Organization Journal* 2015, **8**(Suppl 1):A267
http://www.waojournal.org/content/8/S1/A267

WAO journal
WORLD ALLERGY ORGANIZATION

MEETING ABSTRACT Open Access

Common variable immunodeficiency misdiagnosed as Crohn Disease

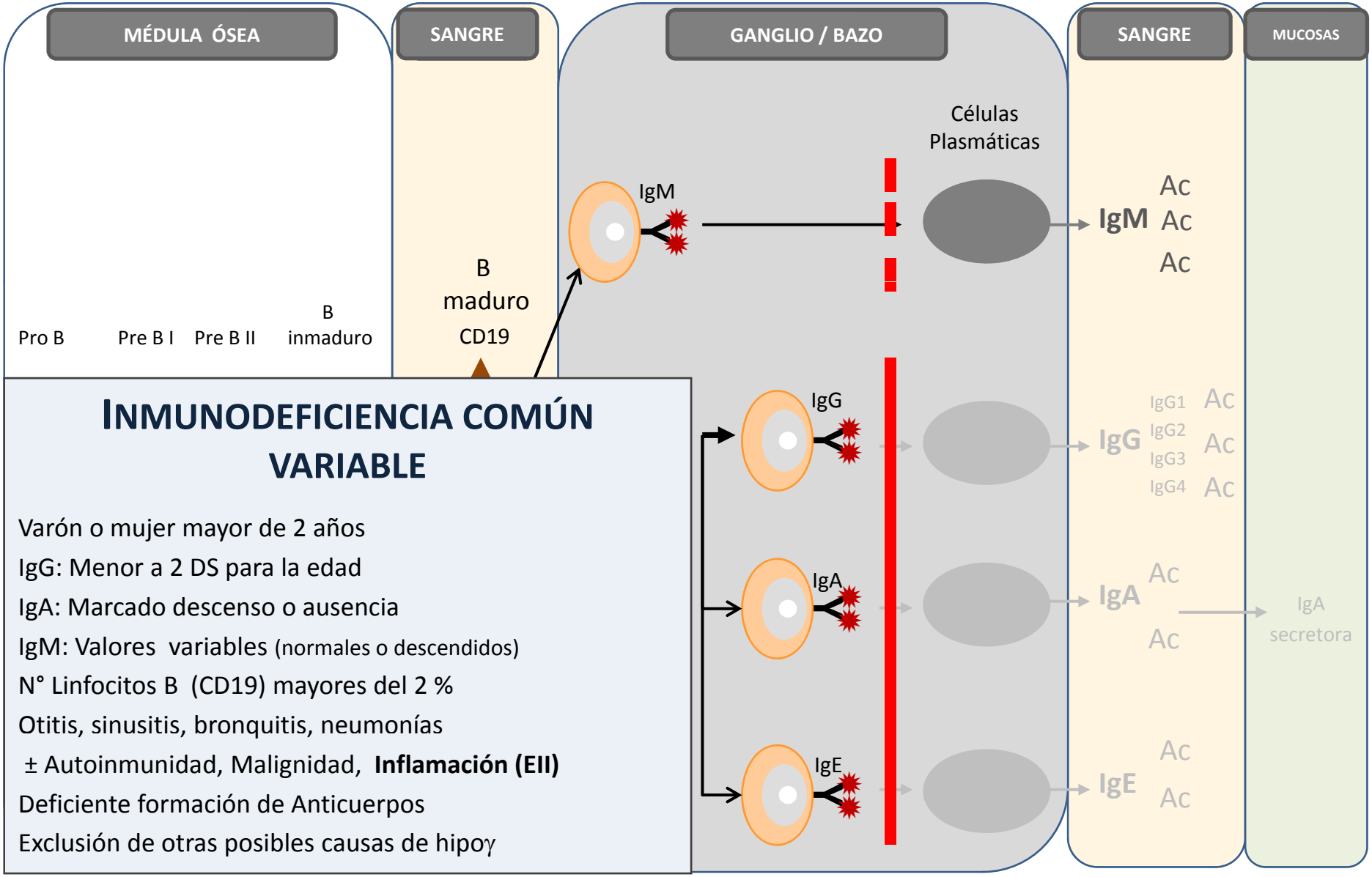
Daniella Moore[1*], Fabiane Dias[1], Eliane Esberard[1], Jorge Mugayar[1], Marcia Costa[1], Simone Pestana[2], Jose Laerte Boechat[1], Rossana Rabelo[2], Amanda Seba[3]

From 3rd WAO International Scientific Conference (WISC) 2014
Rio de Janeiro, Brazil. 6-9 December 2014

Criterio diagnóstico

Mayor de 4 años de edad

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia



INMUNODEFICIENCIA COMÚN VARIABLE

Varón o mujer mayor de 2 años
IgG: Menor a 2 DS para la edad
IgA: Marcado descenso o ausencia
IgM: Valores variables (normales o descendidos)
N° Linfocitos B (CD19) mayores del 2 %
Otitis, sinusitis, bronquitis, neumonías
± Autoinmunidad, Malignidad, **Inflamación (EII)**
Deficiente formación de Anticuerpos
Exclusión de otras posibles causas de hipoγ

ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Inmunodeficiencia Común Variable

Manifestación evolutiva

Niño/a > 6 m

Infecciones De la vía aérea

Conjuntivitis
OMA
Sinusitis
Bronquitis
Neumonía

St pneumoniae
H influenzae
Moraxella catarralis
St aureus
Mycoplasma pneumoniae

Otras infecciones

Bacteriemias
Meningoencefalitis
Sepsis

St pneumoniae
H influenzae
St aureus

Giardiasis

INFLAMACIÓN

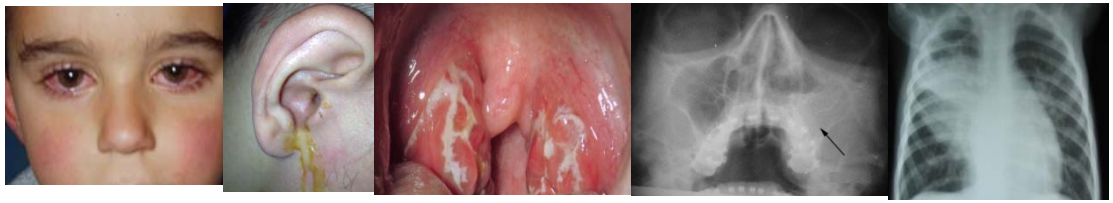
Artritis / ARJ
Enf. Infl Intestinal
Enf Infl Pulmonar

AUTOINMUNIDAD

Citopenias hemáticas
Enfermedad Celíaca
Vitiligo – Alopecía totalis

MALIGNIDAD

Leucemias
Linfomas
Carcinomas



ENFERMEDAD INTESTINAL INFLAMATORIA
Patogenia

Inmunodeficiencia Combinada- Defecto en Artemis

J Clin Immunol (2010) 30:314–320
DOI 10.1007/s10875-009-9349-x

Chronic Inflammatory Bowel Disease as Key Manifestation of Atypical ARTEMIS Deficiency

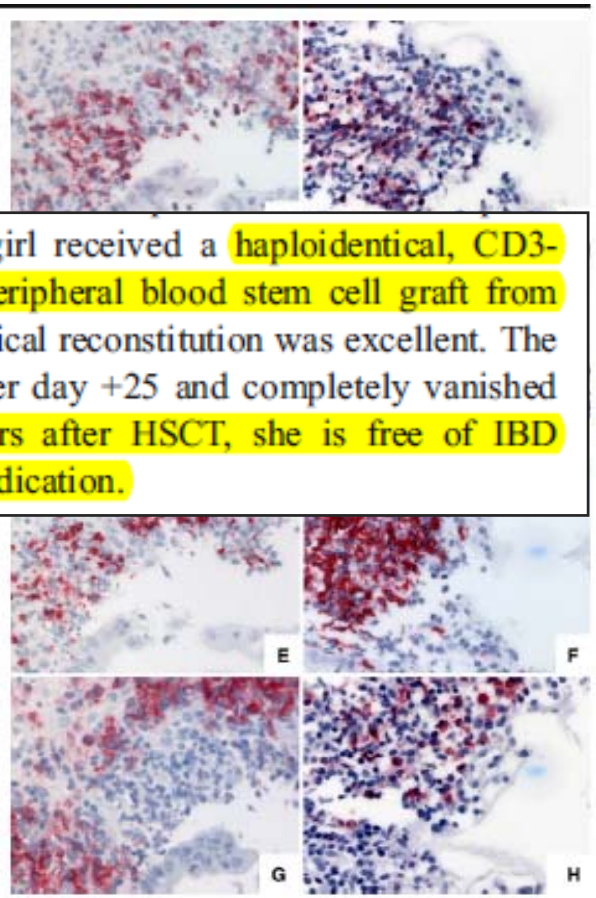
Jan Rohr · Ulrich Pannicke · Michaela Döring · Annette Schmitt-Graeff · Elisabeth Wiech · Andreas Busch · Carsten Speckmann · Ingo Müller · Peter Lang · Rupert Handgretinger · Paul Fisch · Klaus Schwarz · Stephan Ehl

We report a 6-year-old girl born to consanguineous Lebanese parents. Her history was uneventful until the age of 9 months, when she presented with recurrent diarrhea and weight loss. In addition to a persistently increased stool frequency, she experienced episodes of bloody diarrhea and fever every 2 months. Stool was

rotavirus, norovirus, and adenovirus. The girl was diagnosed with juvenile Crohn´s disease on the basis of intestinal biopsies showing patchy chronically active inflammation with superficial fissuring ulcerations. Her

Table I Lymphocyte Subpopulations

Cell population	Patient	Normal values
Lymphocytes/µl	761	1,700–6,900
CD3+/µl	146	900–4,500
CD4+ CD3+/µl	56	500–2,400
HLA-DR+of CD4+ (%)	24	3–11
CD62L+CD45RA+of CD4+ (%)	0.9	50–85
CD8+ CD3+/µl	15	300–1,600



tation (HSCT). The girl received a haploidentical, CD3- and CD19-depleted peripheral blood stem cell graft from her father. Immunological reconstitution was excellent. The diarrhea improved after day +25 and completely vanished eventually. Three years after HSCT, she is free of IBD symptoms without medication.

ENTEROCOLITIS AUTOINMUNE

IDP

Defecto en FOXP3

SÍNDROME IPEX
Manifestaciones

- ❑ **POLIENDOCRINOPATÍA** — **Diabetes mellitus Tipo 1 insulino dep** (< 1 año); **Tiroiditis**; **Hipoparatiroidismo**
- ❑ **DERMATOPATÍA** — **Eczema / eritrodermia**; **Dermatitis exfoliativa**; **Alopecía universal**
- ❑ **INFECCIONES** — **Sinopulmonares** (*Staphylococcus , Enterococcus*); **Digestivas**; **Sepsis**
- ❑ **AUTOINMUNIDAD** — **AHAI, PTI**; **GNF** (30 %); **Artritis,**

❑ **GASTROENTEROLÓGICAS (95 – 98 %)**

- ✓ **Diarrea acuosa ± muco / sangre** (más frecuente)
- ✓ **Atrofia vellositaria severa ≈ Celiaquía / Crohn**
- ✓ **Infiltrado linfocitario de mucosa intestinal**

❑ **HEPÁTICAS**

- ✓**Hepatitis AI (20 %)**
- ✓**Colangitis**

ENFERMEDAD INTESTINAL INFLAMATORIA

Enfermedad Monogénica - IDP

Center for Chronic Immunodeficiency
Universitats Klinikum Freiburg
Secuenciación de nueva generación
Paneles de genes candidatos (según fenotipo)

Panel para EII
53 genes candidatos con susceptibilidad a EII
Costo: 250 euros
Tiempo proceso: 1 a 4 meses

GENES CANDIDATOS – FENOTIPO EII			
ADAM17	CD40LG	NOD2	DEFB1
CYBA	CDX1	IL23R	DKC1
CYBB	CTLA4	ATG16L1	IKBKG
FOXP3	FUT2	IRGM	RTEL1
IL2RA	GATA2	IL17	TERC
IL10RA	GUCY2C	IL17RA	TERT
IL10RB	ICOS	P2RX7	TINF2
IL10	IKZF2	PLCG2	WRAP53
NCF1	IL1RL1	PTEN	IL23A
NCF2	IL4	TGFB2	IL33
NCF4	1L15	TGFB3	IRAK1
WASP	IL15RA	TGFB1	RORC
XIAP	STXBP2		SC2D1A
LRBA	TTC7A		

Defectos

Subunidades del Receptor del TGFβ: TGFRB1 – TGFRB2
Imflammatory Bowell Disease 2016, 22 (9): 2058 - 2062

P-197

Identification of a Homozygous Mutation in the ZBTB24 Gene in a Patient with Very Early Onset Inflammatory Bowel Disease

Maire Conrad[*], Noor Dawany[*], Kathleen Sullivan[†], Marcella Devoto[‡], Judith Kelsen[*]

[*]The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, [†]The Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; and, [‡]Division of Genetics and Department of Biostatistics and Epidemiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

Imflammatory Bowell Disease 2016 March, S68

Mutation in pyrin masquerading as primaryimmunodeficiency,
Clinical Immmunol 2016, 171,: 65- 66

Journal of Clinical Immunology
January 2017, Volume 37, Issue 1, pp 67–79
Targeted Sequencing and Immunological Analysis Reveal the Involvement of Primary Immunodeficiency Genes in Pediatric IBD: a Japanese Multicenter Study

5/35 pacientes pediatricos (< 16 años) con enfermedad monogénica
Secuenciación: WES y Paneles

IL10RA	2p	
XIAP	2p	➔ TCHP curado
CYBB	1 p	

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i24.5578

World J Gastroenterol 2016 June 28; 22(24): 5578-5588
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Comprehensive mutation screening for 10 genes in Chinese patients suffering very early onset inflammatory bowel disease

Yuan Xiao, Xin-Qiong Wang, Yi Yu, Yan Guo, Xu Xu, Ling Gong, Tong Zhou, Xiao-Qin Li, Chun-Di Xu

Identificacion 13 pacientes con VEO IBD
WES
Mutaciones en: 5 pacientes: IL10RA, IL10RB

Inflamatory Bowel Diseases abril 2017, 23 (4): 578- 590
Mutations in Interleukin-10 Receptor and Clinical Phenotypes in Patients **with Very Early Onset Inflammatory Bowel Disease:** A Chinese VEO-IBD Collaboration Group Survey
Huang, Zhiheng MD, PhD; Peng, Kaiyue MD; Li, Xiaoqin MD; Zhao, Ruiqin MD; You, Jieyu MD; Cheng, Xiuyong MD, PhD; Wang, Zhaoxia MD; Wang, Ying PhD; Wu, Bingbing PhD; Wang, Huijun PhD; Zeng, Huasong MD; Yu, Zhuowen; Zheng, Cuifang MD; Wang, Yuesheng MD; Huang, Ying MD
Secuenciación gen IL10RA-RB
32 Heterocigotas compuestos gen IL 10RA
9 homocigotas gen IL10RB
1 Homocigota en gen IL10RB

Takahashi et al. Genome Medicine (2017) 9:8
DOI 10.1186/s13073-016-0394-9

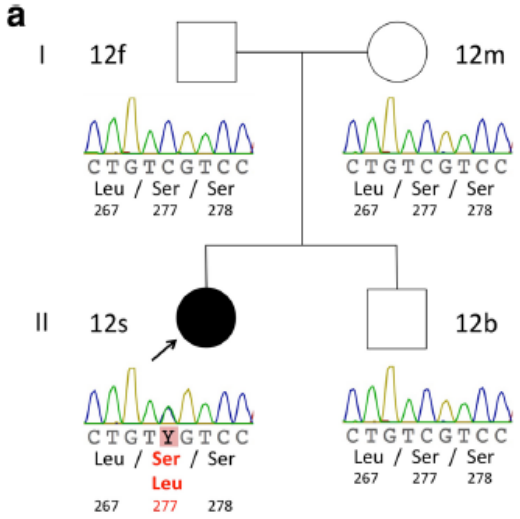
Genome Medicine

RESEARCH Open Access

De novo and rare mutations in the *HSPA1L* heat shock gene associated with inflammatory bowel disease

Shinichi Takahashi[1,2†], Gaia Andreoletti[3†], Rui Chen[1], Yoichi Munehira[4,5], Akshay Batra[6], Nadeem A. Afzal[6], R. Mark Beattie[6], Jonathan A. Bernstein[7], Sarah Ennis[3*] and Michael Snyder[1*]

Una familia
WES
Gen: HSP1L (heat shok 70 kDal protein 1 like)
asociada a HLA clase III (transporte intracelular)



IIMMUNODEFICIENCY POLIENDROCRONOPATHY AND ENTEROPATHY X LIKED
IPEX: FOXP3
IPEX like; CD25, LRBA, CTLA4, STAT5b, STAT 3 GOF

Journal Pediatr Gastroenterol March 2017, 64 (3): 378 - 384

Deficiency in Mucosa-associated Lymphoid Tissue Lymphoma Translocation 1: A Novel Cause of IPEX-Like Syndrome

Charbit-Henrion, Fabienne; Jeverica, Anja K.; Bègue, Bernadette; Markelj, Gasper; Parlato, Marianna; Avčin, Simona Lucija; Callebaut, Isabelle; Bras, Marc; Parisot, Mélanie; Jazbec, Janez; Homan, Matjaz; Ihan, Alojz; Rieux-Laucat, Frédéric; Stolzenberg, Marie-Claude; GENIUS Group; Ruemmele, Frank M.; Avčin, Tadej; Cerf-Bensussan, Nadine

WES
2 hermanos de una Familia
Mutación homocigota en MALT1