

Novedades en enfermedades autoinflamatorias

Juan I. Aróstegui
Servicio de Inmunología
Hospital Clínic-IDIBAPS
Barcelona

XI Congreso de la Sociedad Española de Reumatología Pediátrica
Sevilla, 26-28 Noviembre 2015

Personal Disclosures

NOVARTIS

sobi
SWEDISH ORPHAN BIOVITRUM

Research grants
Honorarium for lectures
Clinical trial participation


10º
CONGRESO DE LA SOCIEDAD ESPAÑOLA DE
REUMATOLOGÍA PEDIÁTRICA
SERPE 2013
GRANADA
14 al 16 de noviembre 2013


XI CONGRESO
de la sociedad española
de reumatología pediátrica
SERPE
SOCIEDAD ESPAÑOLA DE
REUMATOLOGÍA PEDIÁTRICA
SEVILLA
26-28
NOVIEMBRE

Enfermedades autoinflamatorias





1995 2000 2005 2010 2015

FMF

TRAPS
HIDS

FCAS
MWS

CINCA
Blau
PAPA

EOS

NALP12

DIRA
IL-10

DITRA

APLAID
PLAID
CARD14
CANDLE

DADA2
SAVI
NLRC4

Hz/Hc
TNRT1
COPA
LACC1

A20

Deficiencia de ADA2

Sd. SAVI / Interferonopatías

Enfermedad por mutaciones en gen *NLRC4*

Sd. hiperzincemia e hipercalprotectinemia

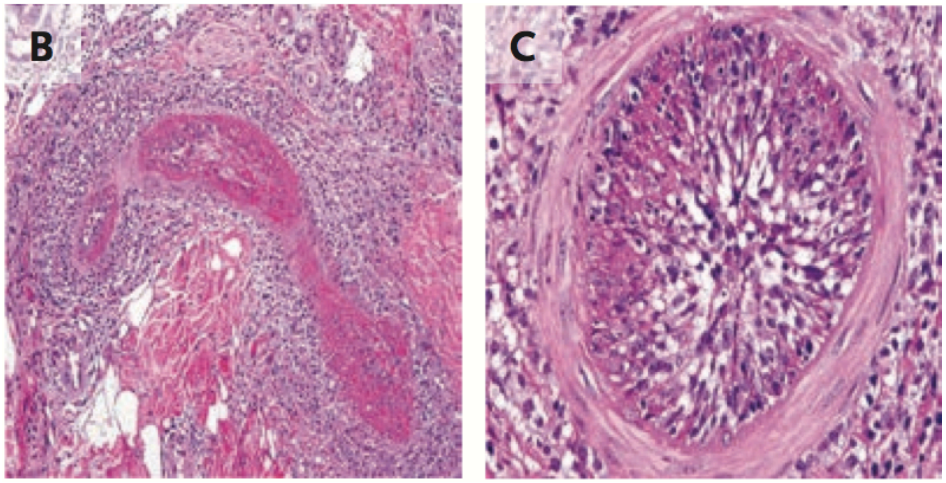
Deficiencia de ADA2

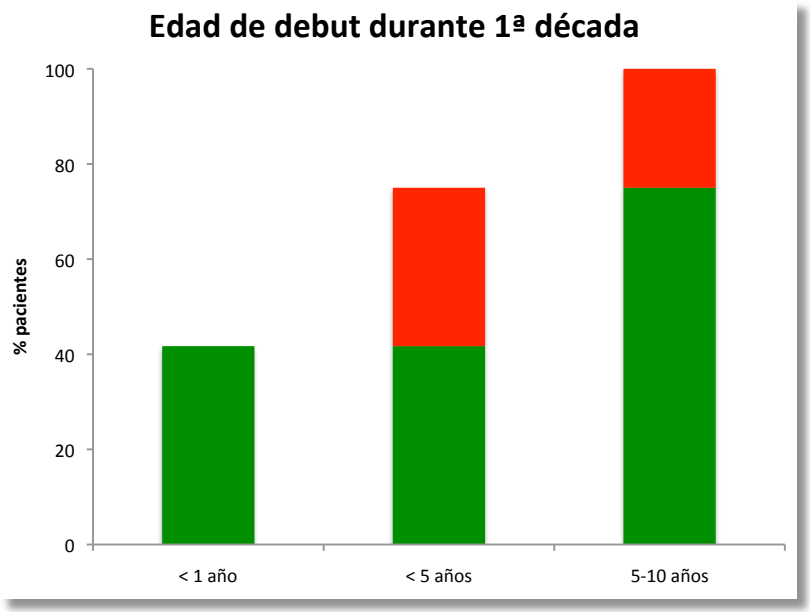
Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

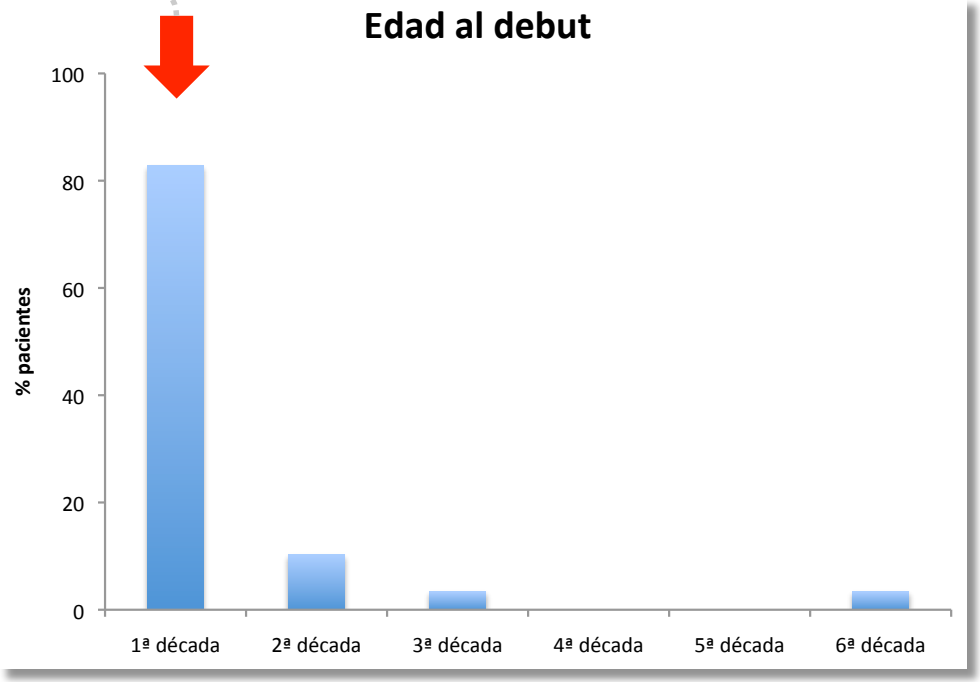
N Engl J Med 2014; 370:911-920

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

N Engl J Med 2014; 370:921-931



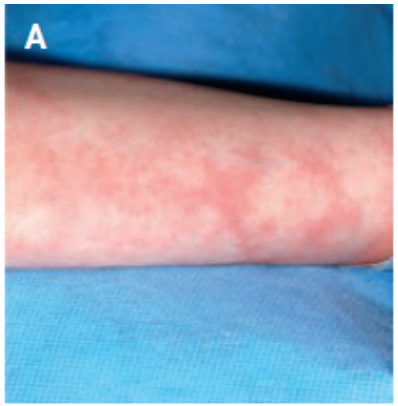




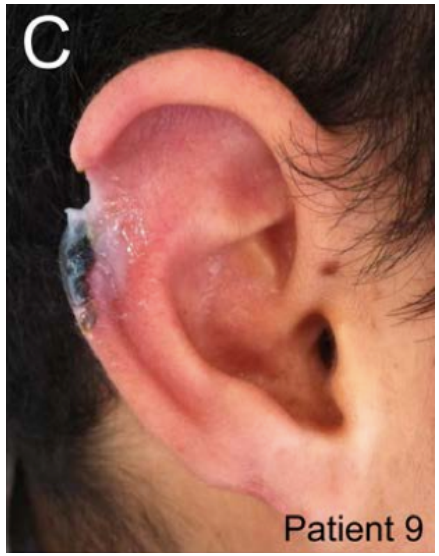


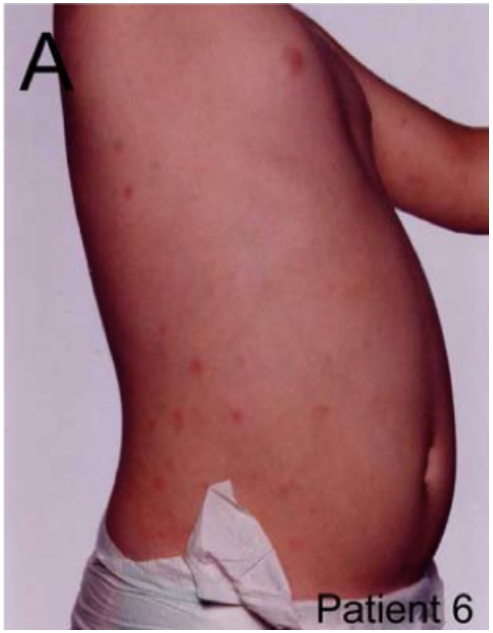
Diagnóstico diferencial con sd. hereditarios de fiebre periódica

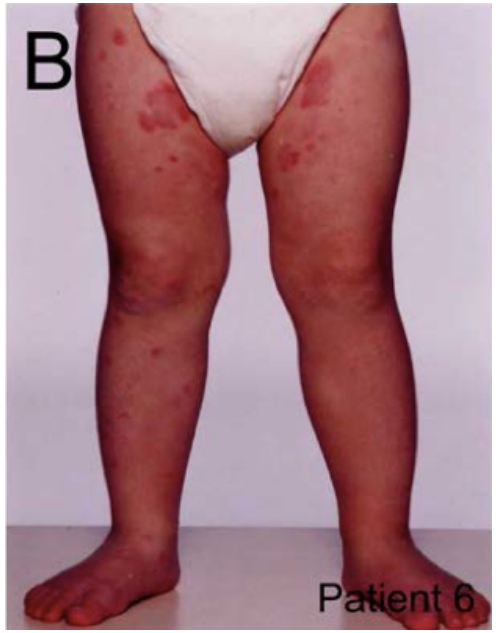
Livedo racemosa











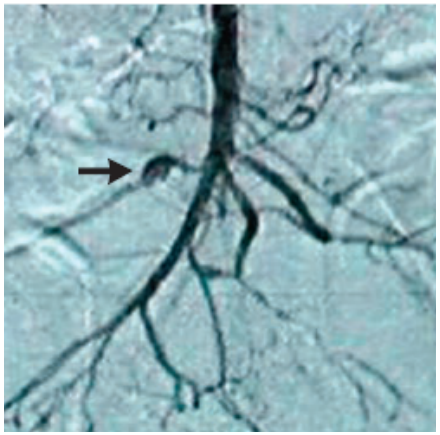


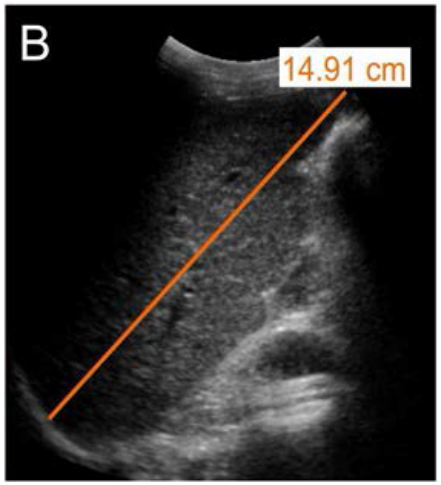
N Engl J Med 2014; 370:911-920
N Engl J Med 2014; 370:921-931

Aneurismas

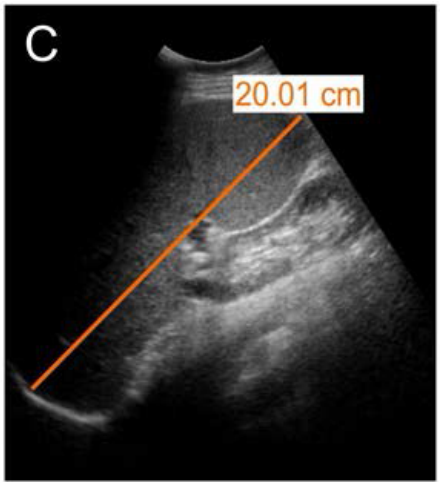
Renal, celíaca, mesentérica, cerebral, arteria retiniana, coronaria….



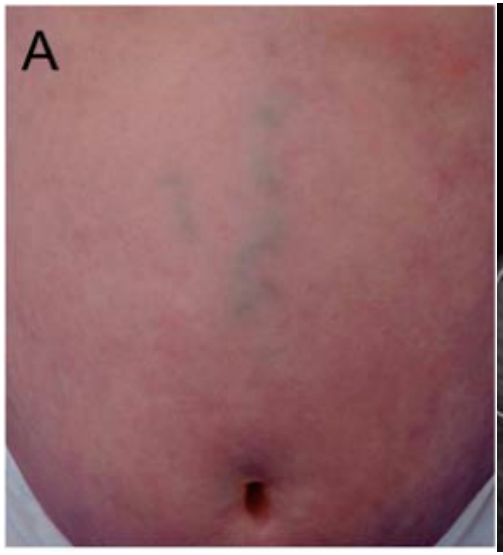


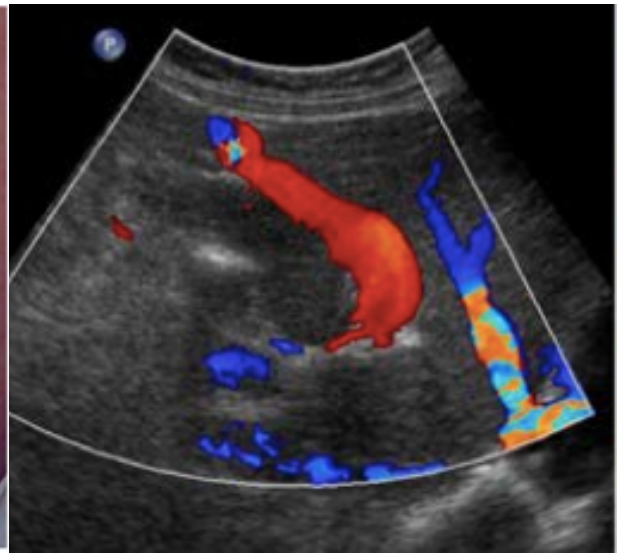


Hepatomegalia



Esplenomegalia



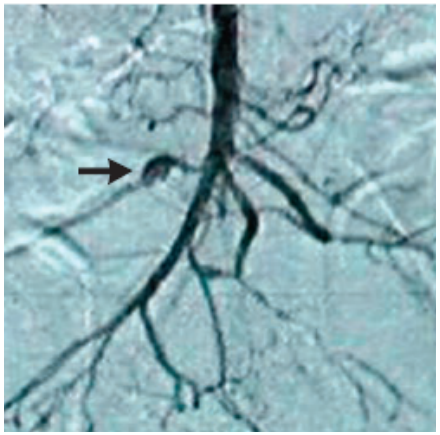


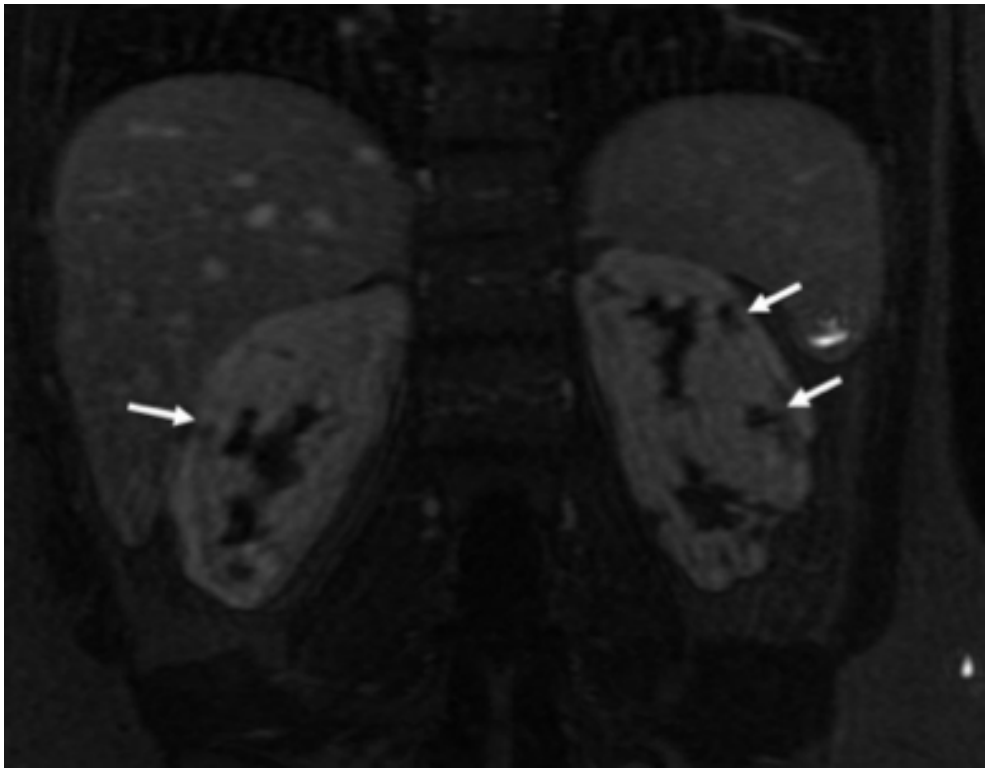
N Engl J Med 2014; 370:911-920

Aneurismas

Renal, celíaca, mesentérica, cerebral, arteria retiniana, coronaria….







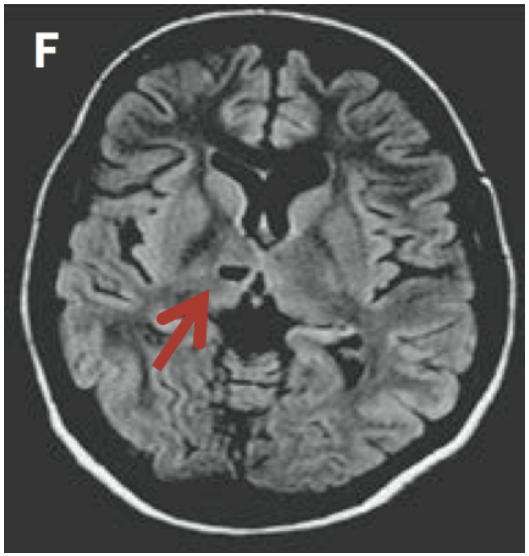
J Autoimmun 2014; 48-49: 84-89

Diagnóstico previo de PAN sistémica

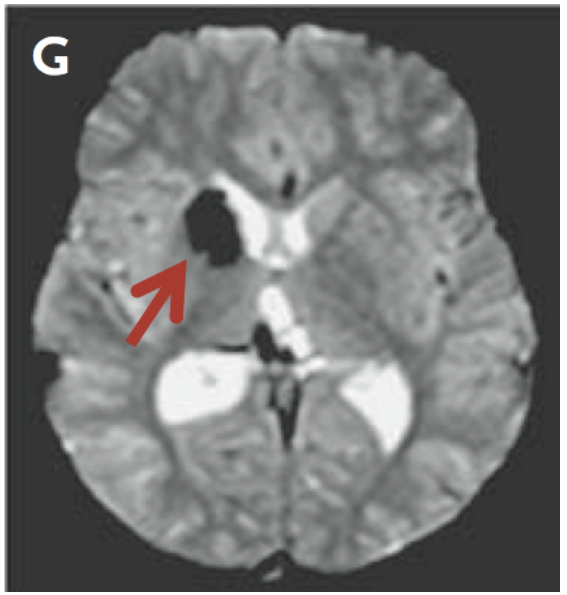
Infartos cerebrales recurrentes



Infartos isquémicos



Cavitaciones "lacune"



Infartos hemorrágicos

UNEXPLAINED EARLY-ONSET LACUNAR STROKE AND INFLAMMATORY SKIN LESIONS: CONSIDER ADA2 DEFICIENCY

Neurology 2015; 84: 2092-3

↑↑ Reactantes de fase aguda

Proteína C reactiva
SAA-1

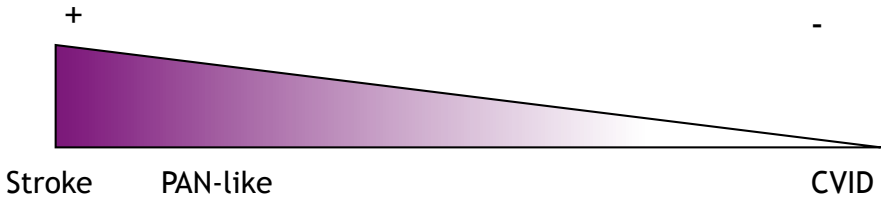
Citopenias

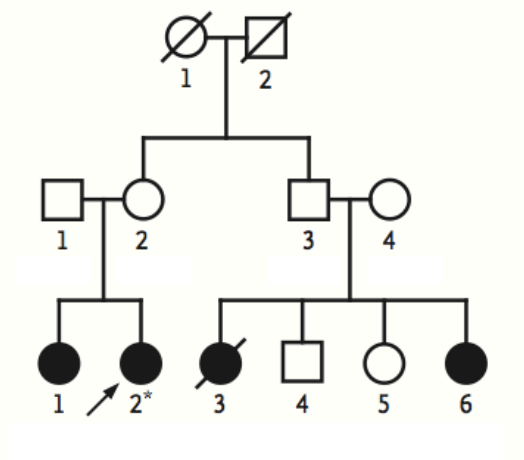
Pancitopenia
Leucopenias (linfopenia, neutropenia…)

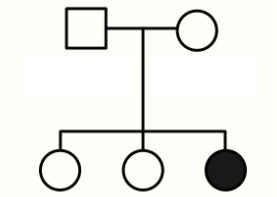


IgG (572-1474 mg/dL)	992	1090 (on IVIG)	1210 (on IVIG)	577	417
IgA (34-305 mg/dL)	62	15	35	50	57
IgM (32-208 mg/dL)	28	<6	14	22	13
IgE (0-90 IU/mL)	Not tested	141	4.4	Not tested	Not tested
IgD (<10mg/dL)	1	<1	1	Not tested	Not tested

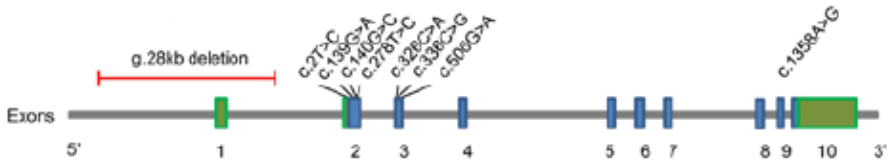
N Engl J Med 2014; 370:911-920





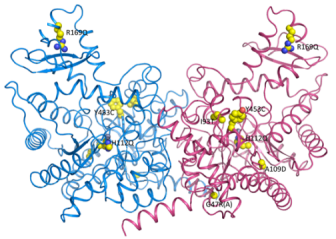


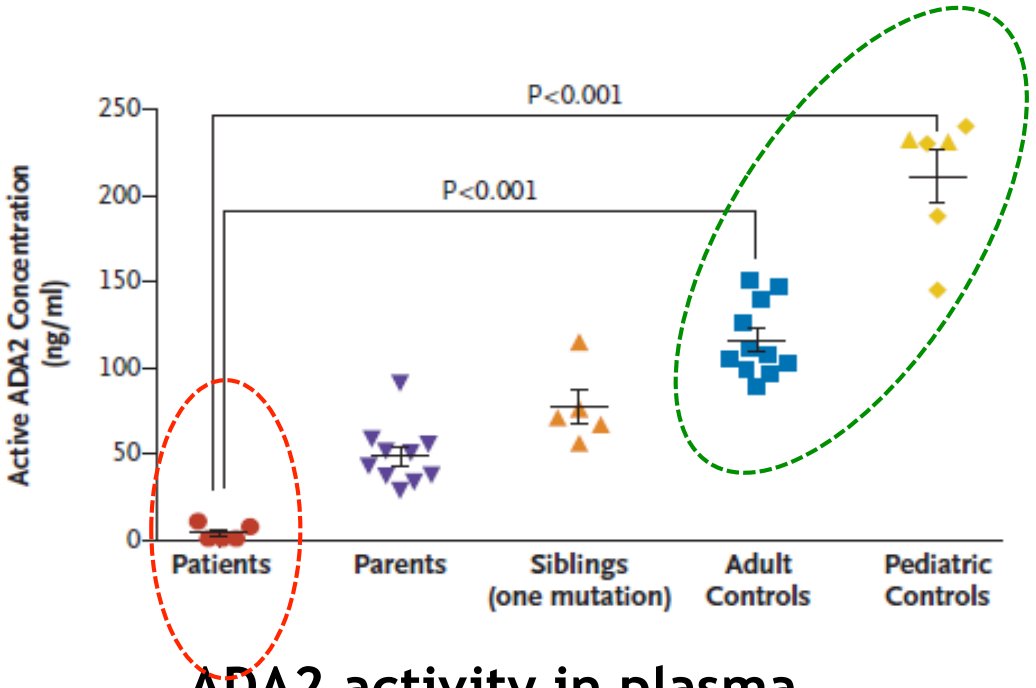
Herencia autosómica recesiva



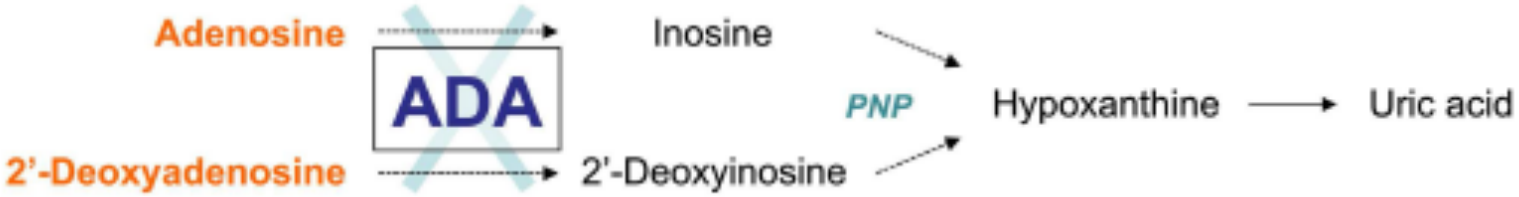
Gen *CECR1*

Proteína Adenosín deaminasa-2





ADA2 activity in plasma



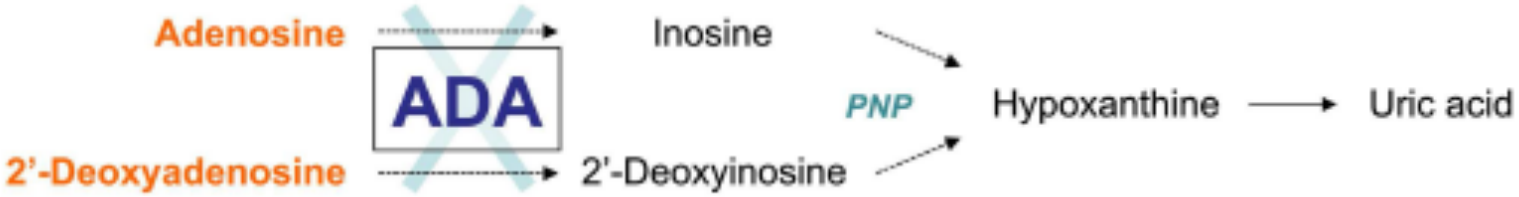
Isoenzimas humanos de adenosin deaminasa

ADA1 y **ADA2.**

	ADA-1
Localización	Intracelular
Función	Adenosina deaminasa (High affinity)
Deficiencia	SCID

Severe Combined Immunodeficiency





Isoenzimas humanos de adenosin deaminasa

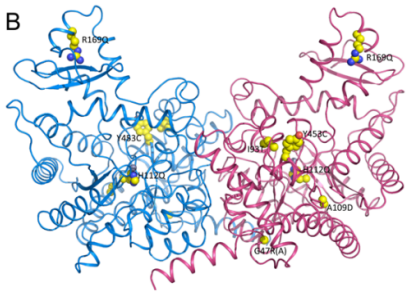
ADA1 y **ADA2.**

	ADA-1	ADA-2
Localización	Intracelular	Extracelular
Función	Adenosina deaminasa (High affinity)	1. Adenosina deaminasa (low affinity) 2. Growth factor 3. Diferenciación macrófagos
Deficiencia	SCID	Deficiencia ADA2









Localización extracelular



¿Plasma fresco?

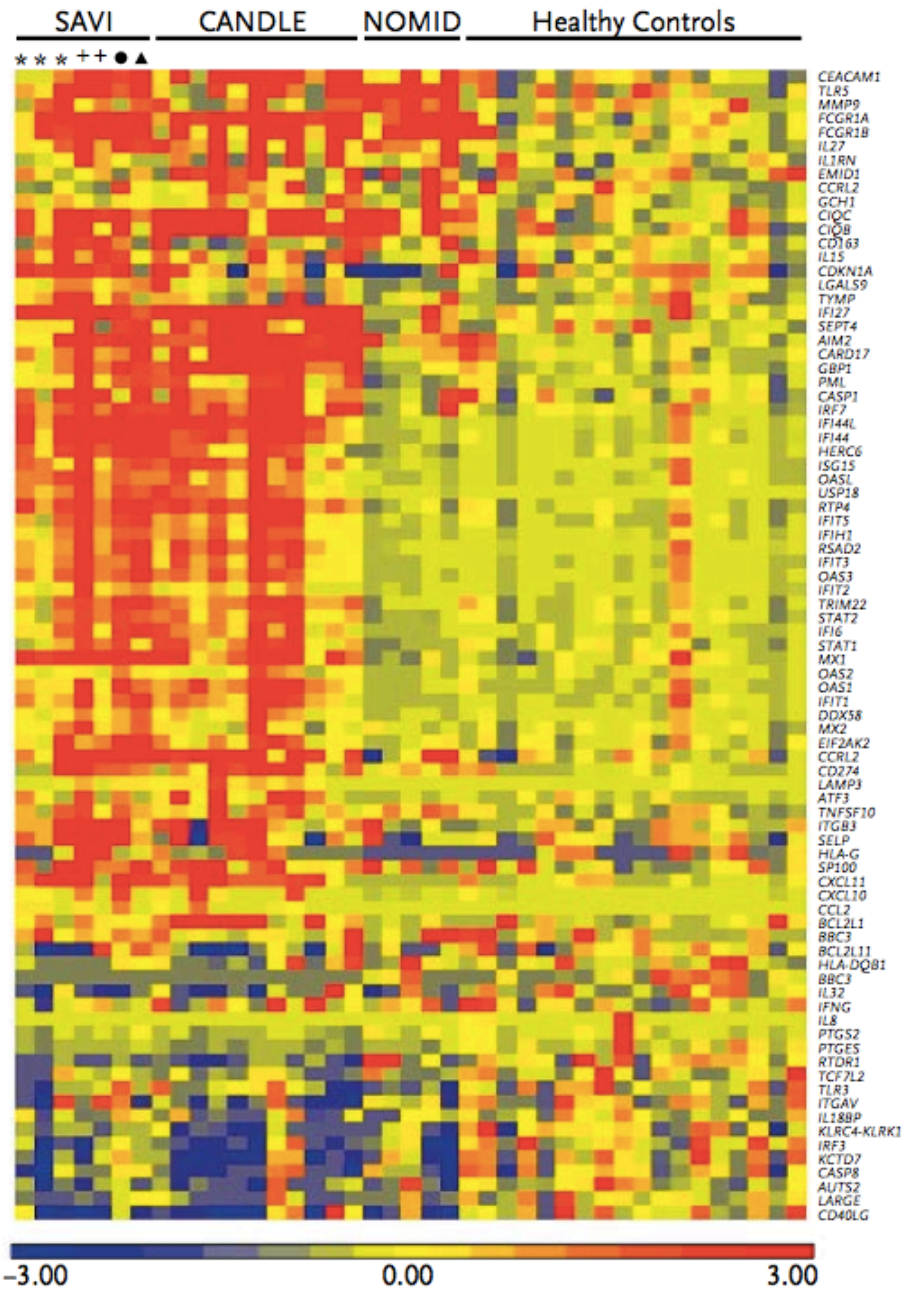
Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency

J Allergy Clin Immunol 2015; 135: 283-7

Deficiencia de ADA2

Sd. SAVI / Interferonopatías

Enfermedades autoinflamatorias



Monogénicas

Sd. Aicardi-Goutieres

Sd. CANDLE

Sd. SAVI

Poligénicas

LES

Activated STING in a Vascular and Pulmonary Syndrome

Y. Liu, A.A. Jesus, B. Marrero, D. Yang, S.E. Ramsey, G.A. Montealegre Sanchez, K. Tenbrock, H. Wittkowski, O.Y. Jones, H.S. Kuehn, C.-C.R. Lee, M.A. DiMattia, E.W. Cowen, B. Gonzalez, I. Palmer, J.J. DiGiovanna, A. Biancotto, H. Kim, W.L. Tsai, A.M. Trier, Y. Huang, D.L. Stone, S. Hill, H.J. Kim, C. St. Hilaire, S. Gurprasad, N. Plass, D. Chapelle, I. Horkayne-Szakaly, D. Foell, A. Barysenka, F. Candotti, S.M. Holland, J.D. Hughes, H. Mehmet, A.C. Issekutz, M. Raffeld, J. McElwee, J.R. Fontana, C.P. Minniti, S. Moir, D.L. Kastner, M. Gadina, A.C. Steven, P.T. Wingfield, S.R. Brooks, S.D. Rosenzweig, T.A. Fleisher, Z. Deng, M. Boehm, A.S. Paller, and R. Goldbach-Mansky

N Engl J Med 2014; 371: 507-18

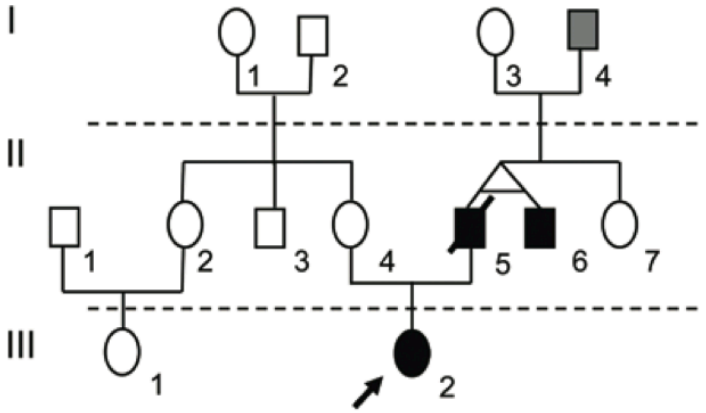
SAVI

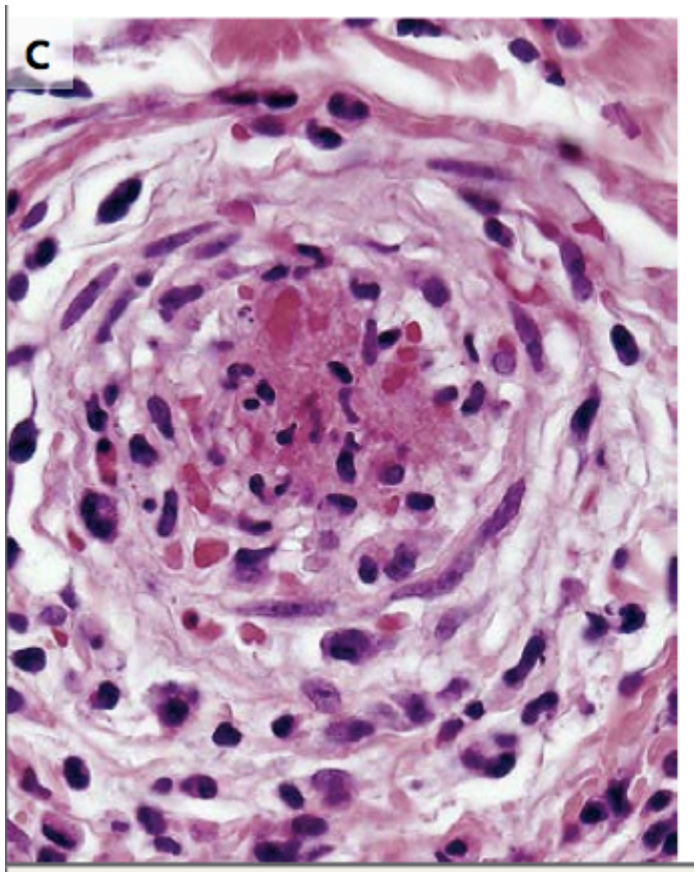
STING-associated vasculopathy with onset in infancy

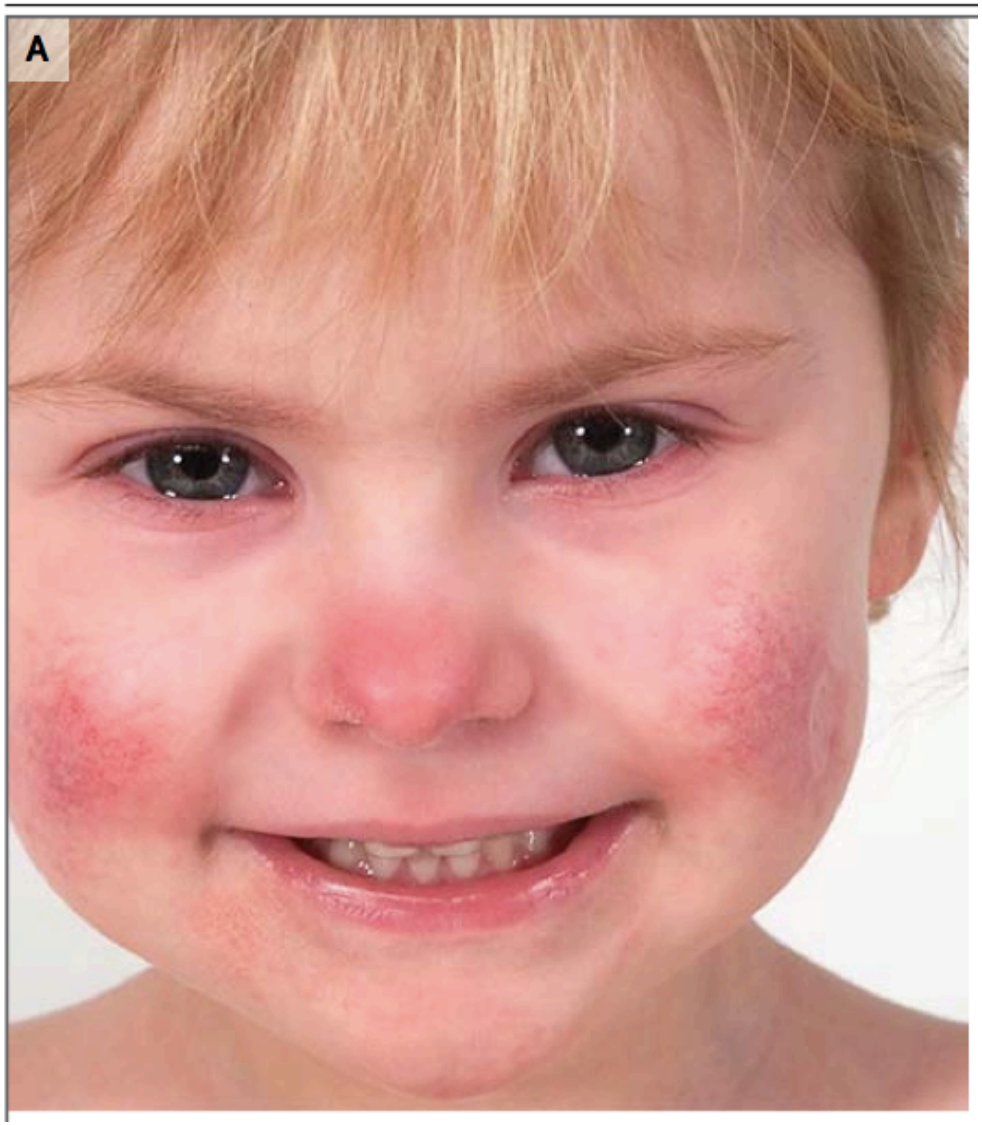
Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations

J Clin Invest 2014; 124: 5516-20

Familial chilblain lupus



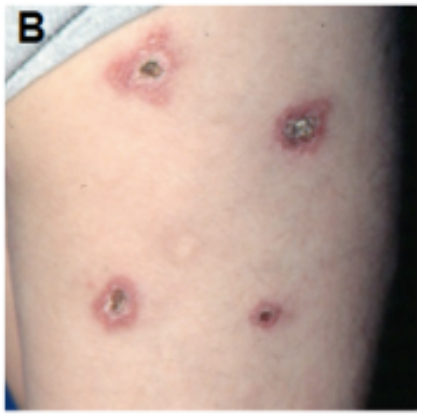




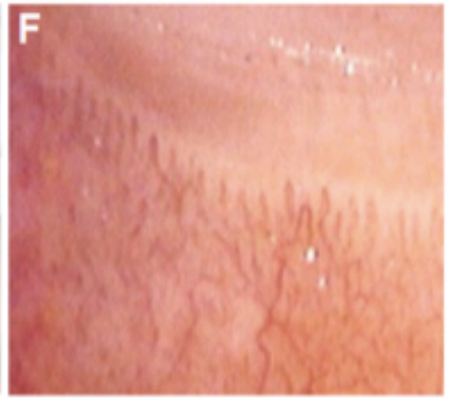
N Engl J Med 2014; 371: 507-18

Enfermedades autoinflamatorias









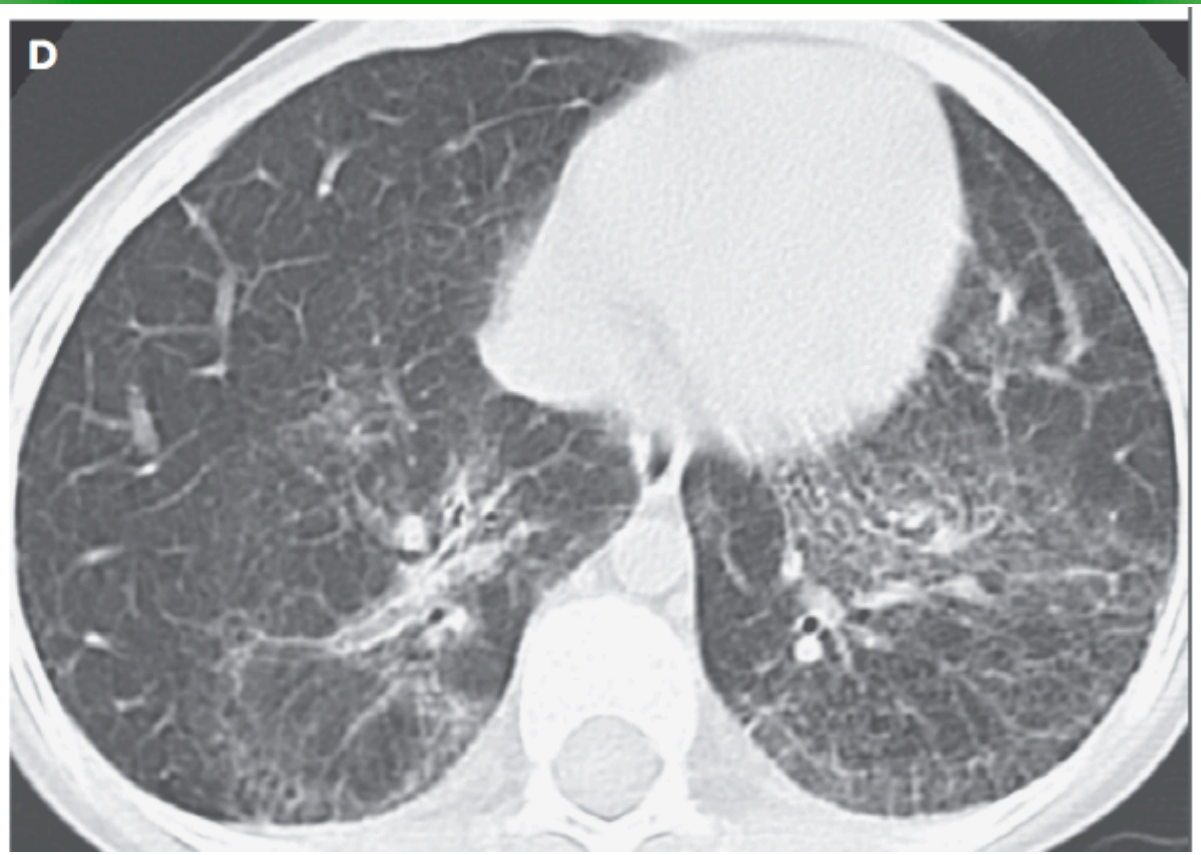


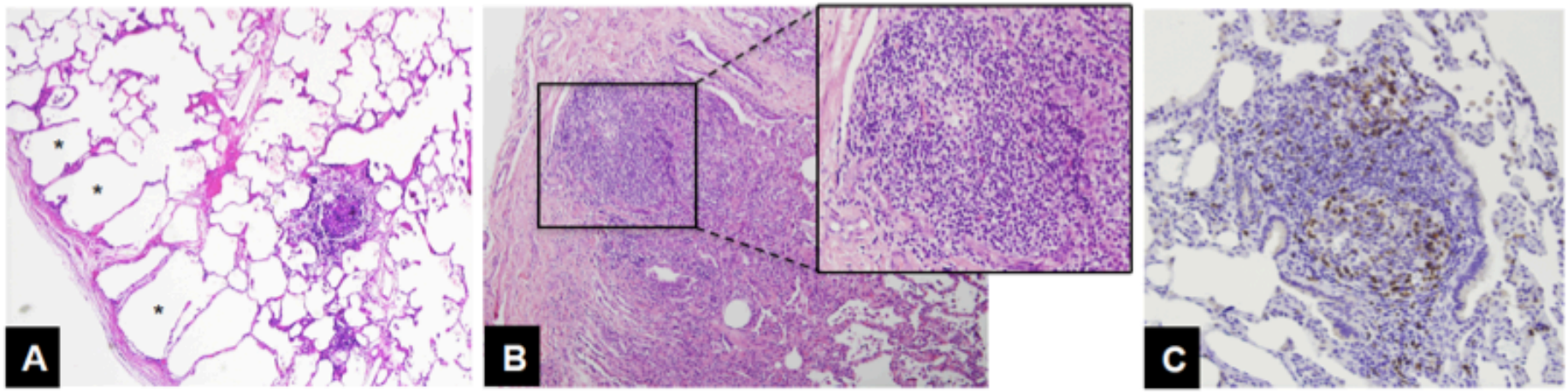




N Engl J Med 2014; 371: 507-18

Enfermedades autoinflamatorias



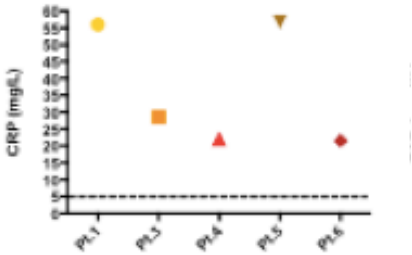


N Engl J Med 2014; 371: 507-18

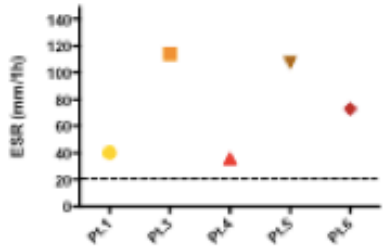
Enfermedades autoinflamatorias

Bioquímica

PCR

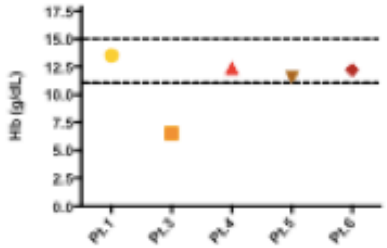


VSG

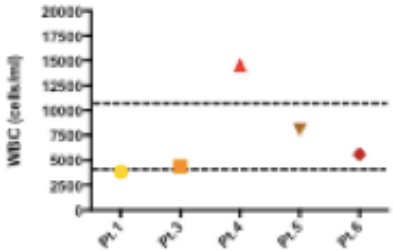


Hemograma

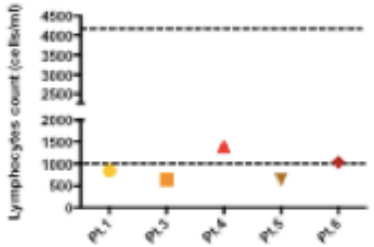
Hb



WBC



Linfocitos



Inmunología

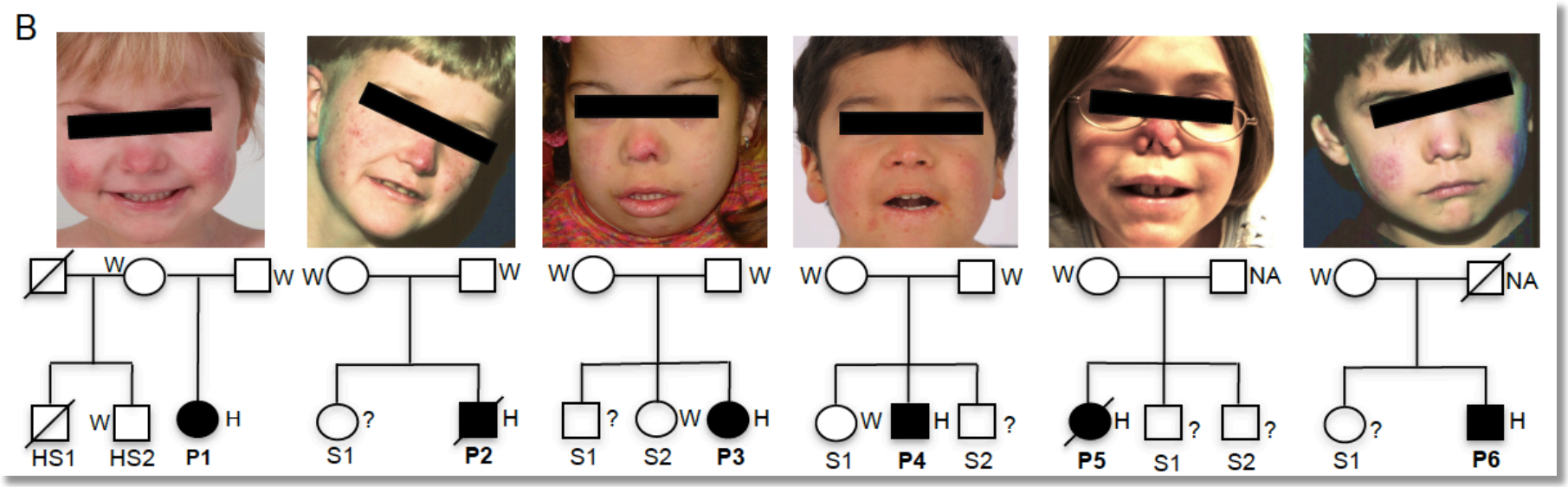
Autoanticuerpos circulantes diversos

ANAs
ANCAs (p-ANCA y c-ANCA)
Anti-cardiolipina
Anti-B2GPI
Factor Reumatoide
Anti-CCP

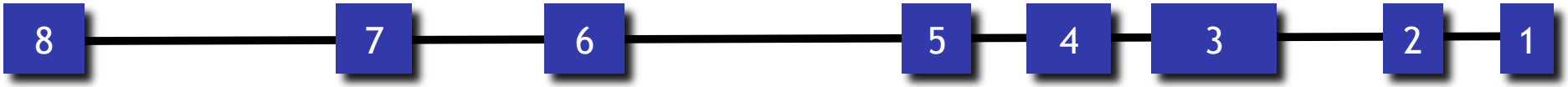
Títulos bajos

Títulos erráticos (se negativizan durante la evolución de la enfermedad)

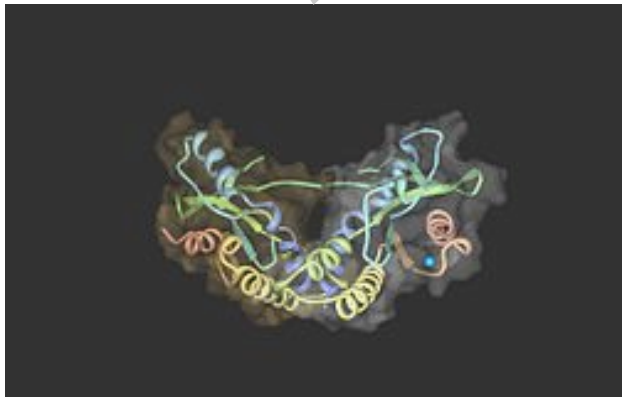
N Engl J Med 2014; 371: 507-18



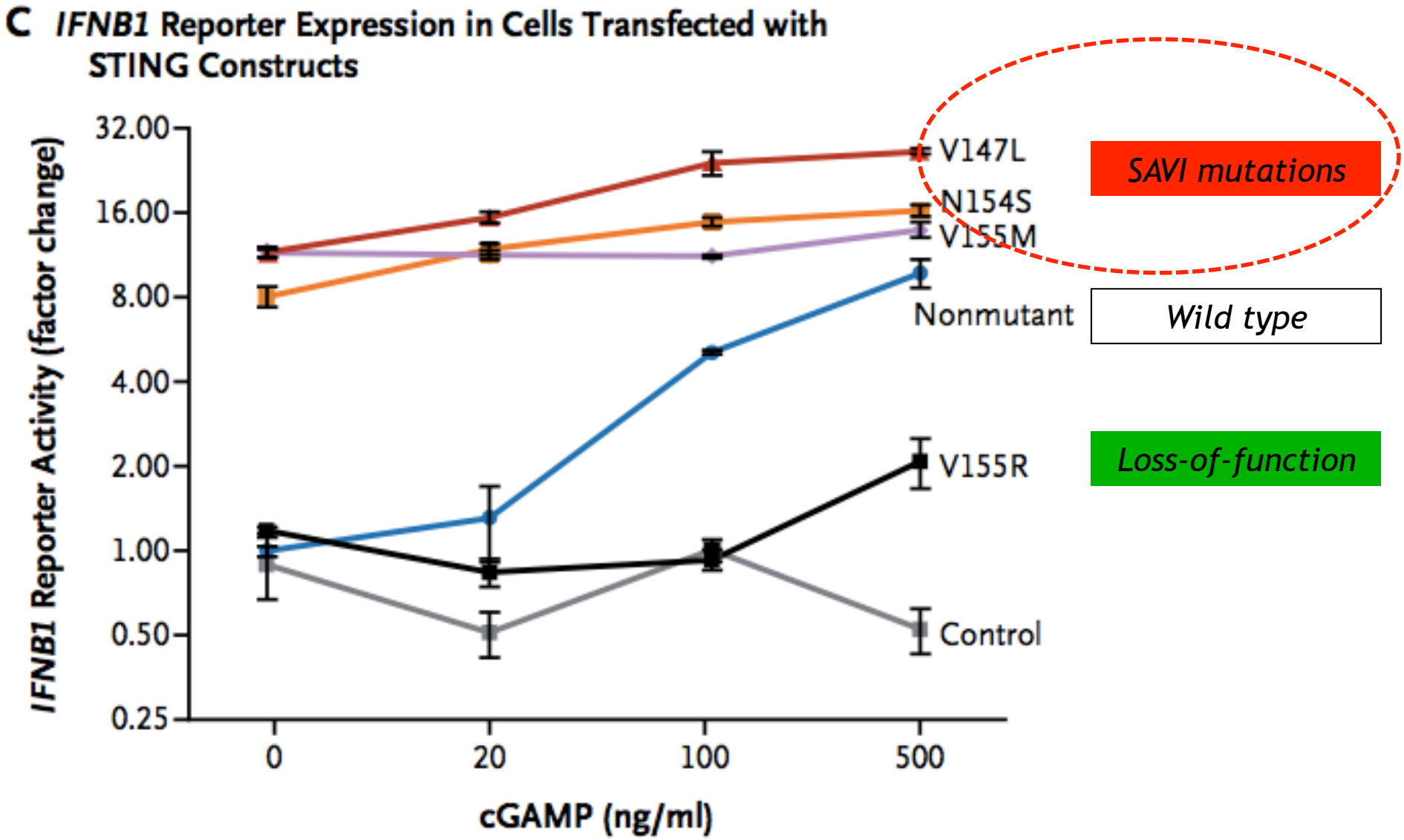
N Engl J Med 2014; 371: 507-18

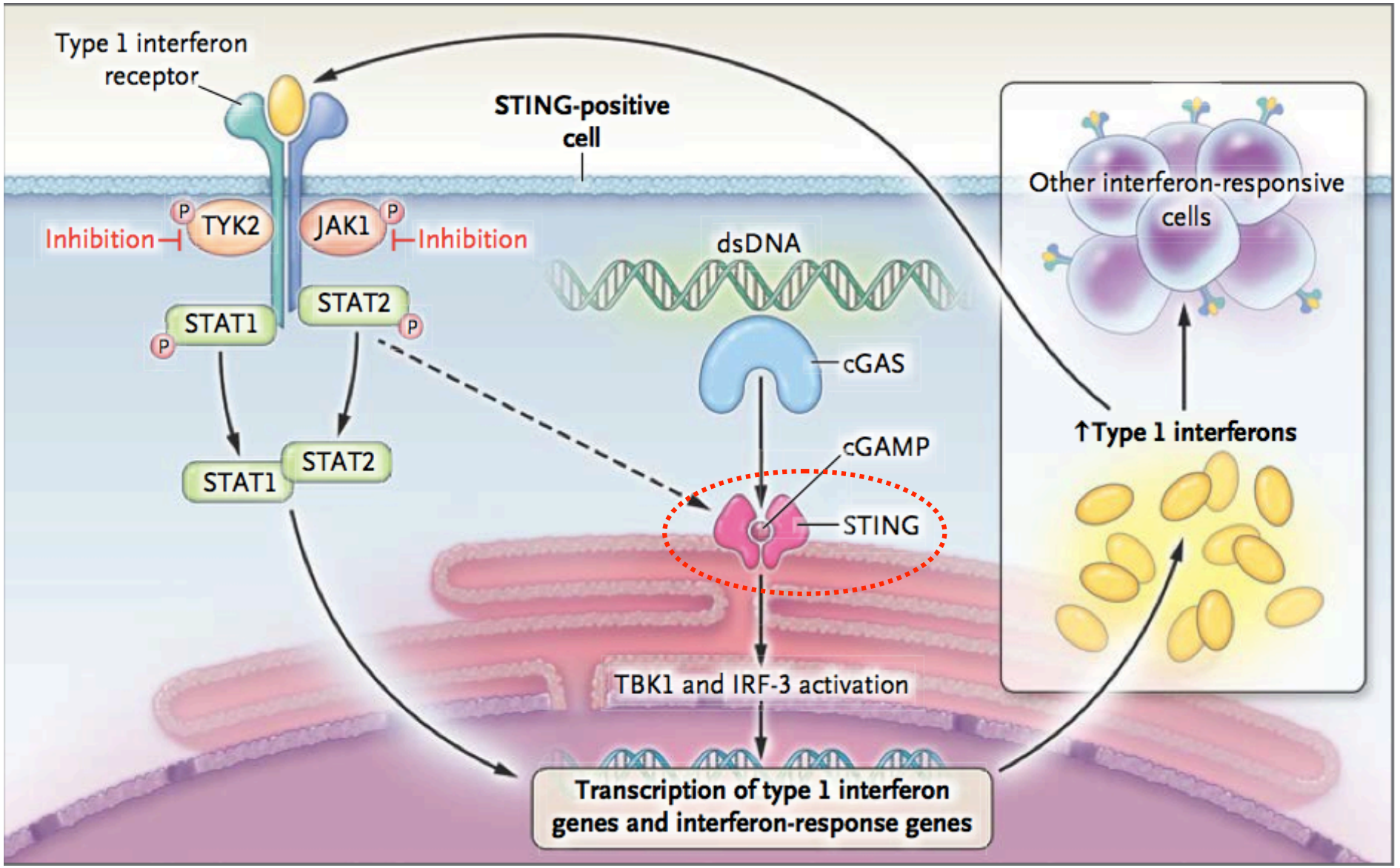


Gen TMEM173

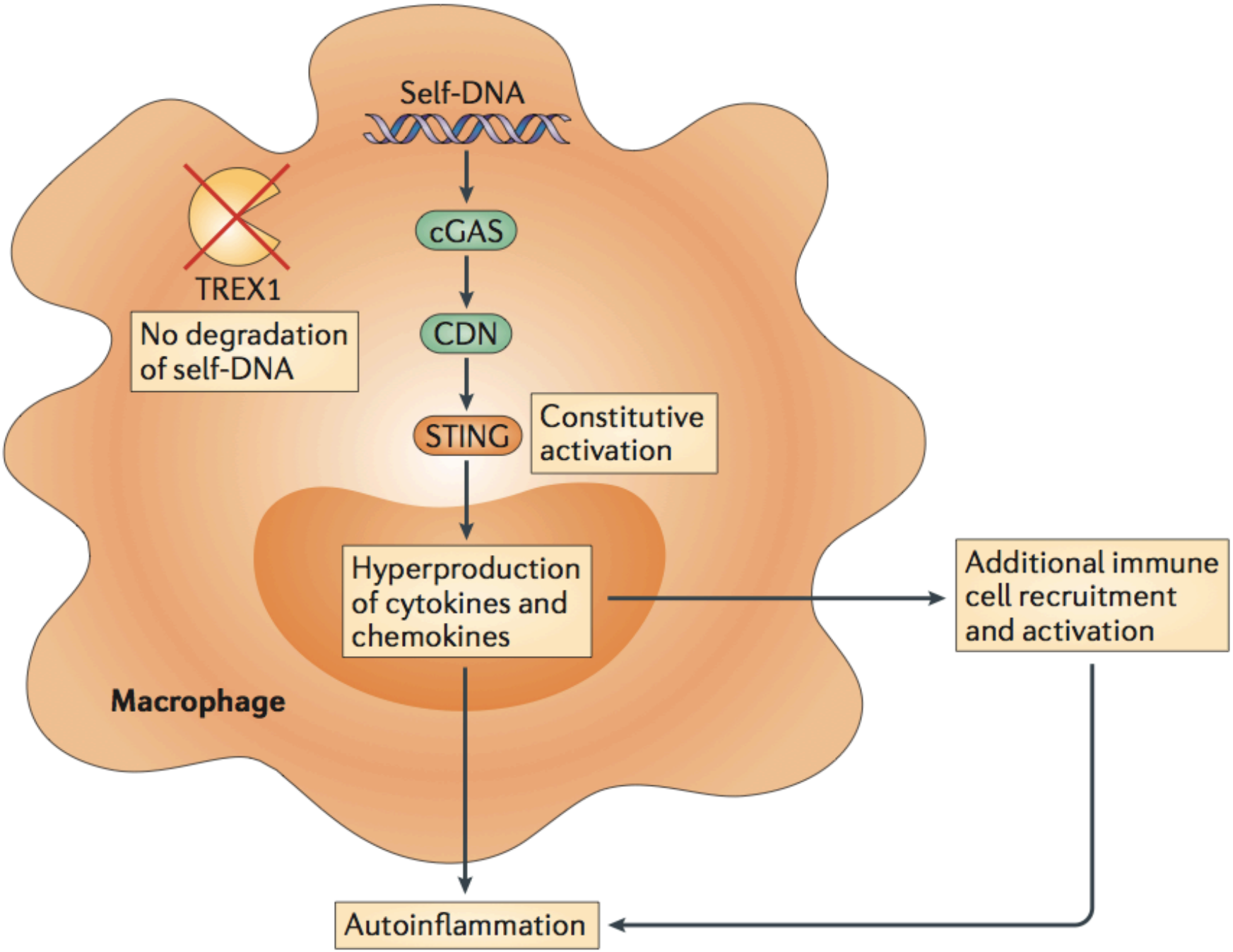


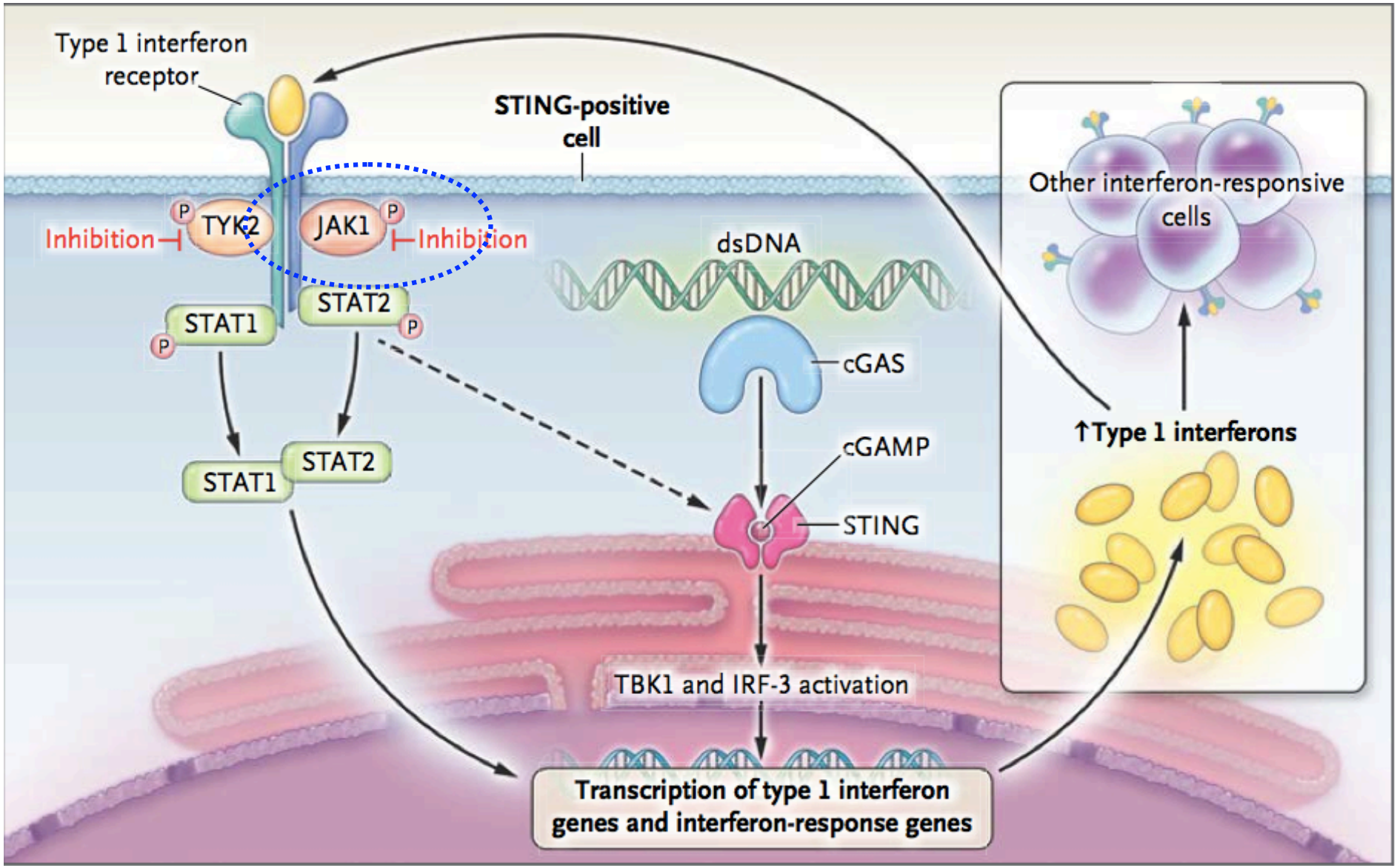
Proteína STING
(Stimulator of Interferon Genes)


C IFNB1 Reporter Expression in Cells Transfected with STING Constructs
IFNB1 Reporter Activity (factor change)
32.00
16.00
8.00
4.00
2.00
1.00
0.50
0.25
0
20
100
500
cGAMP (ng/ml)
V147L
N154S
V155M
Nonmutant
V155R
Control
SAVI mutations
Wild type
Loss-of-function



N Engl J Med 2014; 371: 507-18

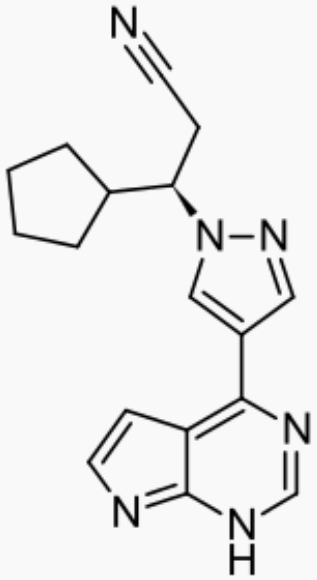

Self-DNA
cGAS
CDN
STING
Constitutive activation
TREX1
No degradation of self-DNA
Hyperproduction of cytokines and chemokines
Additional immune cell recruitment and activation
Macrophage
Autoinflammation



N Engl J Med 2014; 371: 507-18

Enfermedades autoinflamatorias

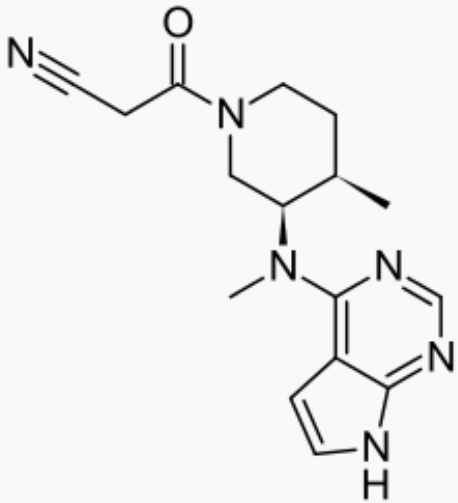
Ruxolitinib



Systematic (IUPAC) name

(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile

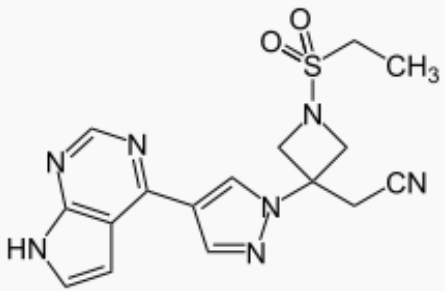
Tofacitinib



Systematic (IUPAC) name

3-[(3*R*,4*R*)-4-methyl-3-[methyl(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile

Baricitinib



Systematic (IUPAC) name

2-[1-ethylsulfonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetonitrile

Deficiencia de ADA2

Sd. SAVI / Interferonopatías

Enfermedad por mutaciones en gen *NLRC4*

An activating *NLRC4* inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome

Nat Genet 2014; 46: 1140-6

Mutation of *NLRC4* causes a syndrome of enterocolitis and autoinflammation

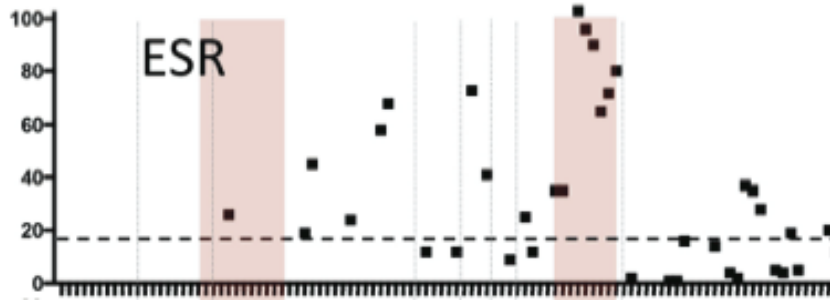
Nat Genet 2014; 46: 1135-9

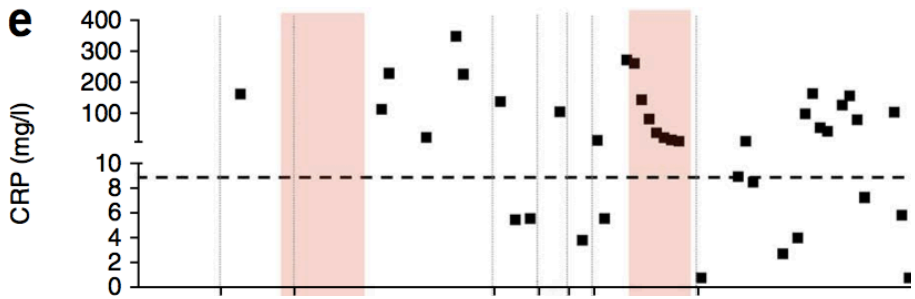
An inherited mutation in *NLRC4* causes autoinflammation in human and mice

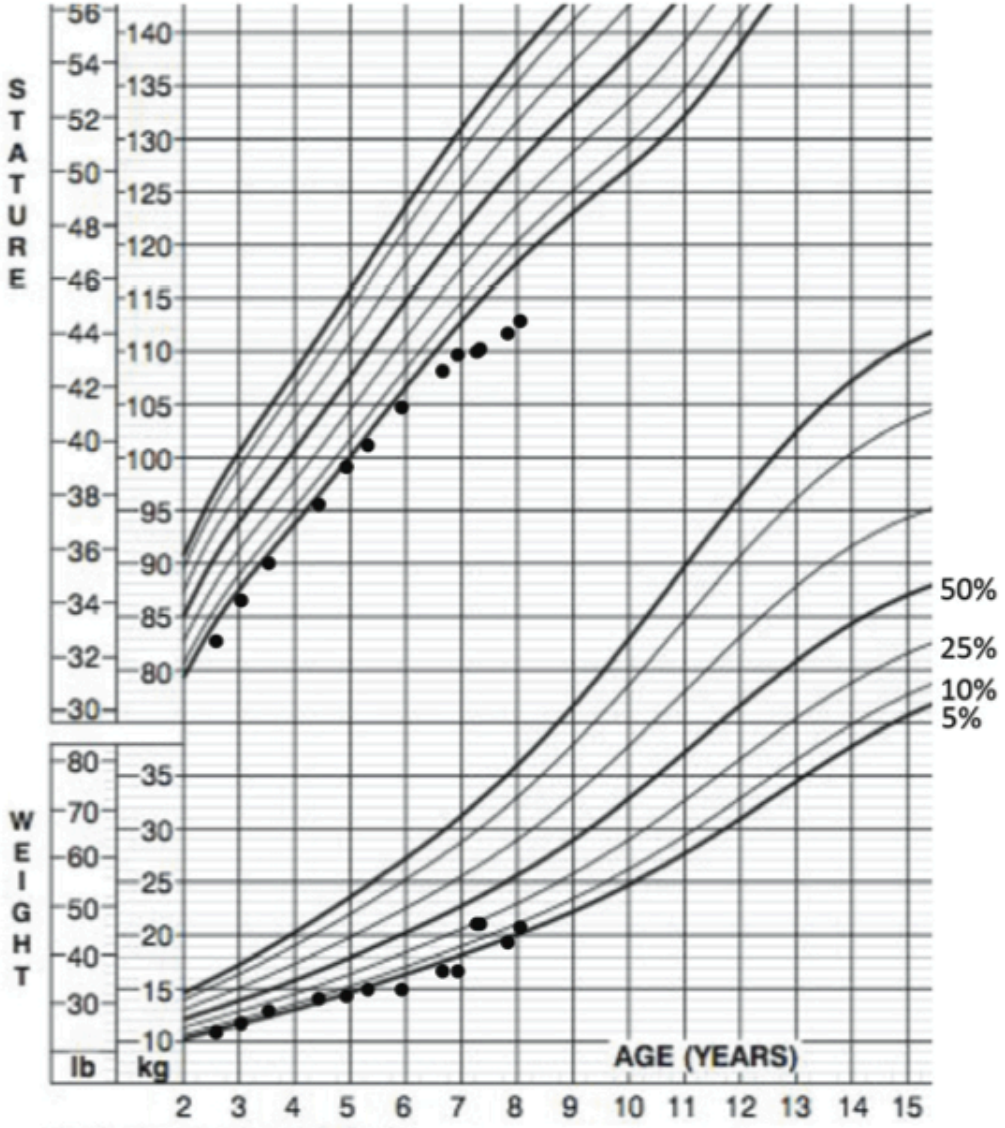
J Exp Med 2014; 211: 2385-96

Enfermedad inflamatoria

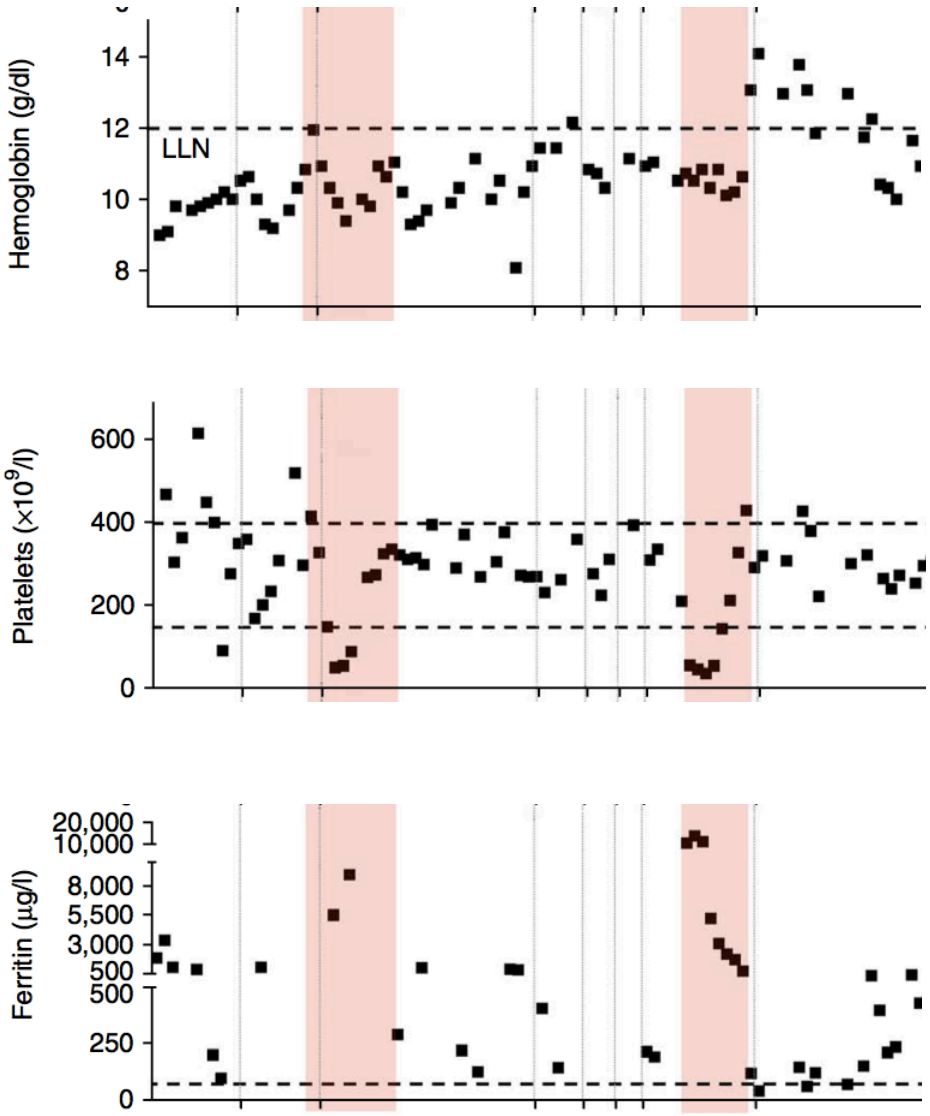


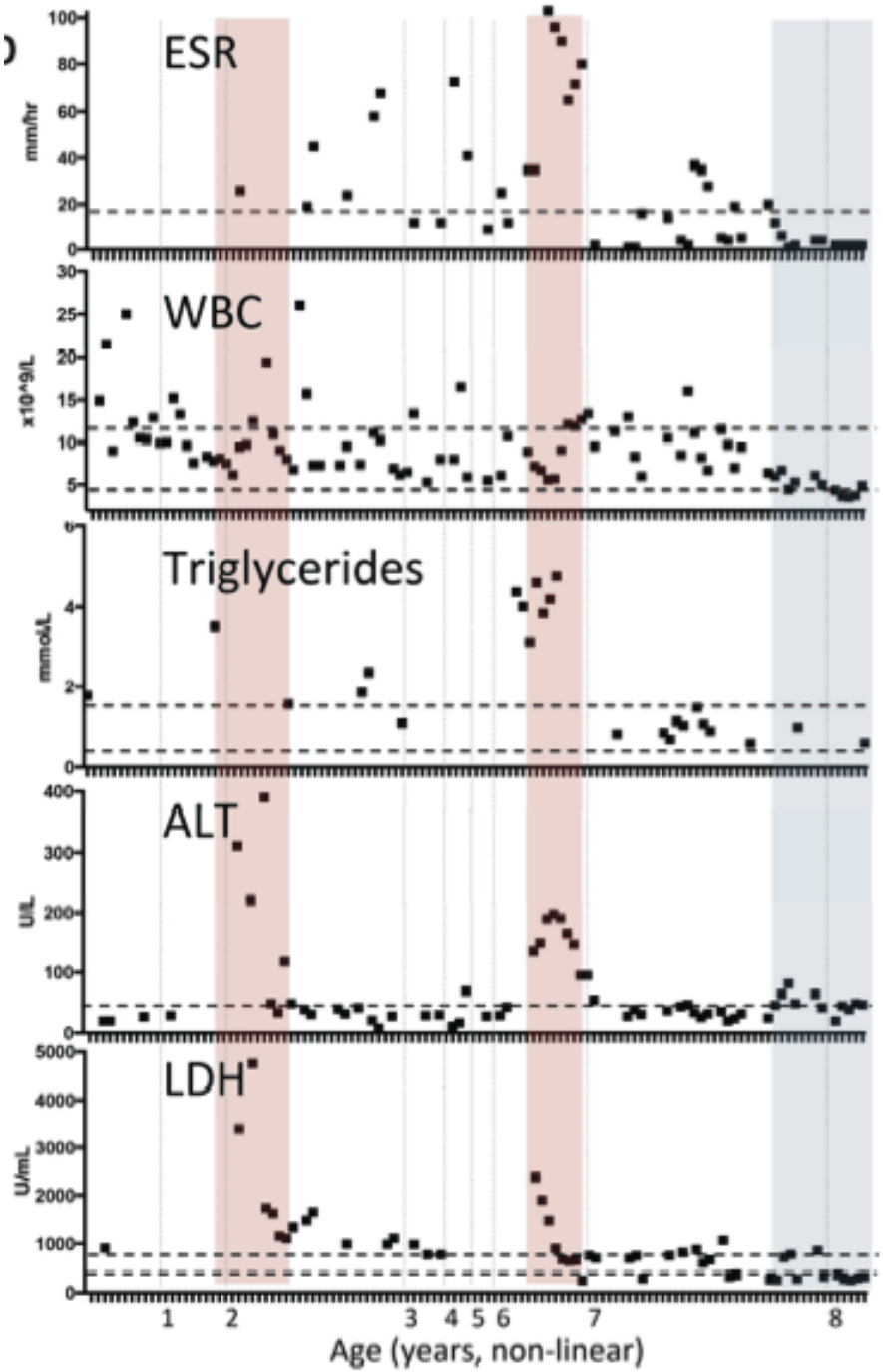






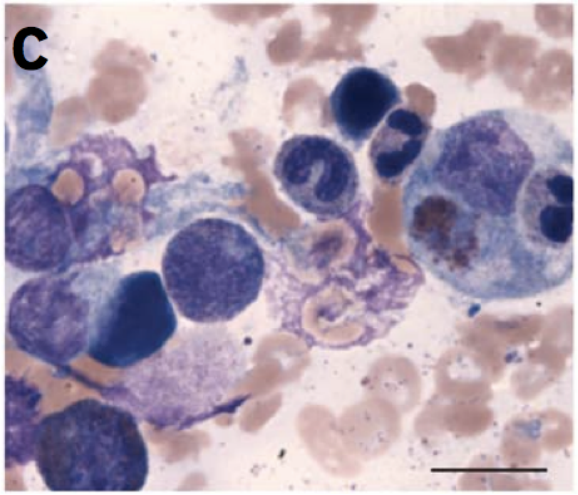
Episodios recurrentes de síndrome de activación macrofágica

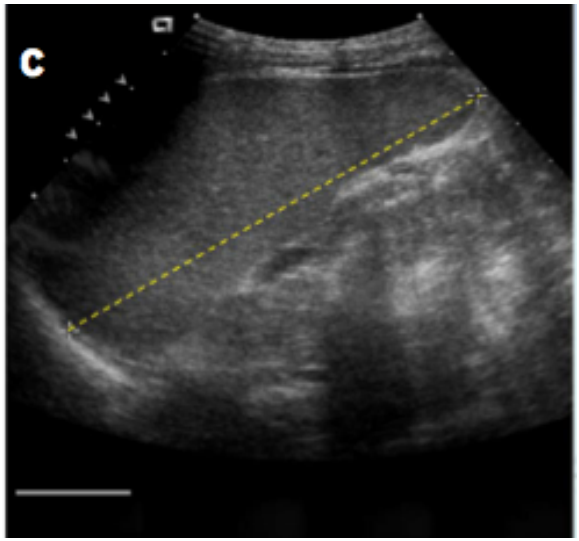




Nat Genet 2014; 46: 1140-6

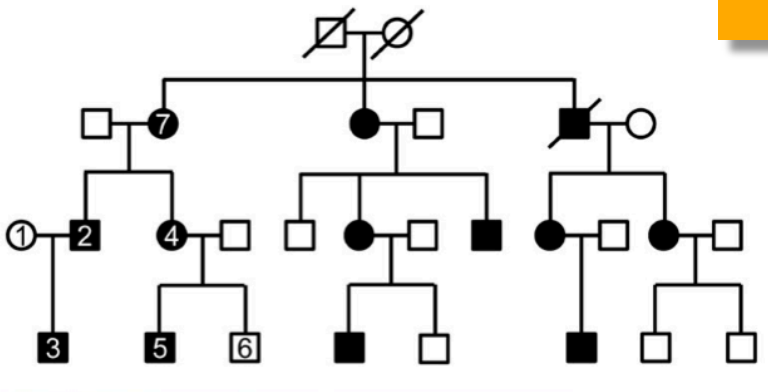
Episodios recurrentes de síndrome de activación macrofágica

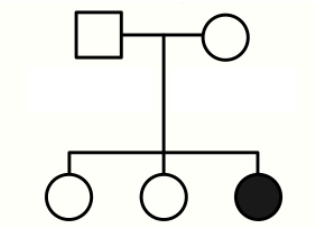




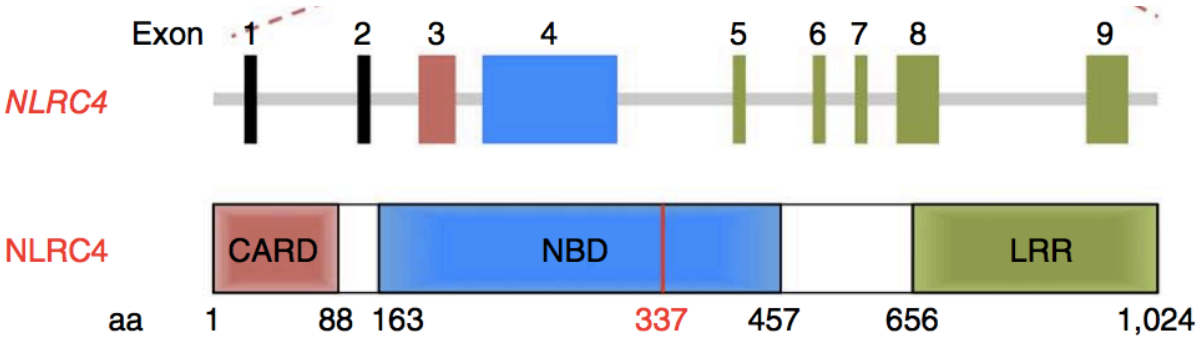
Nat Genet 2014; 46: 1140-6

Herencia autosómica dominante

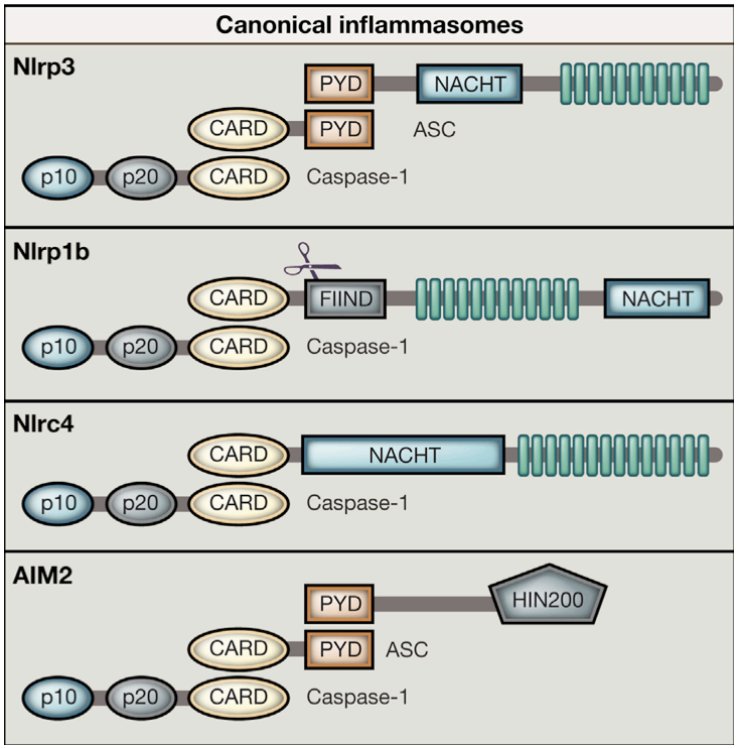








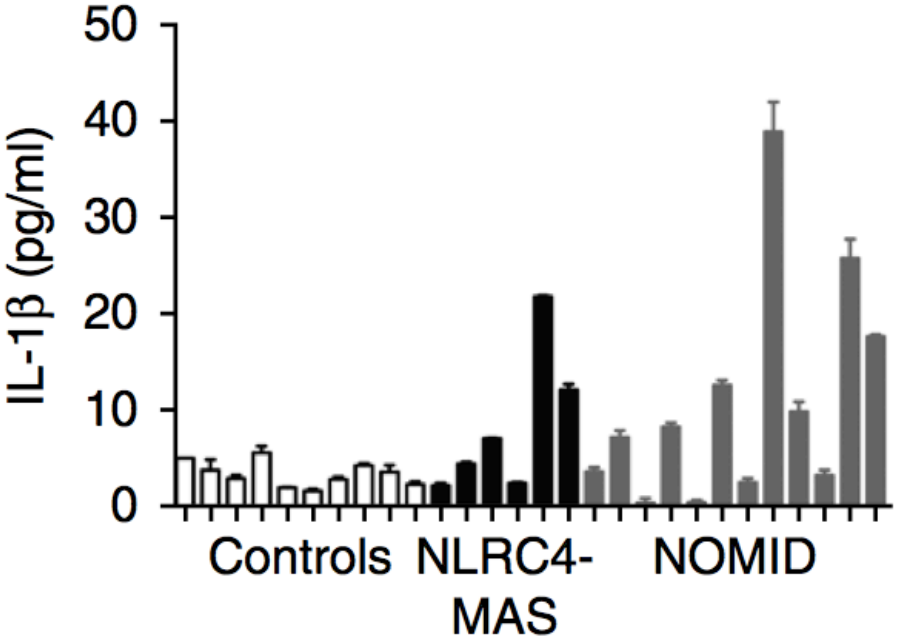
Enfermedades autoinflamatorias

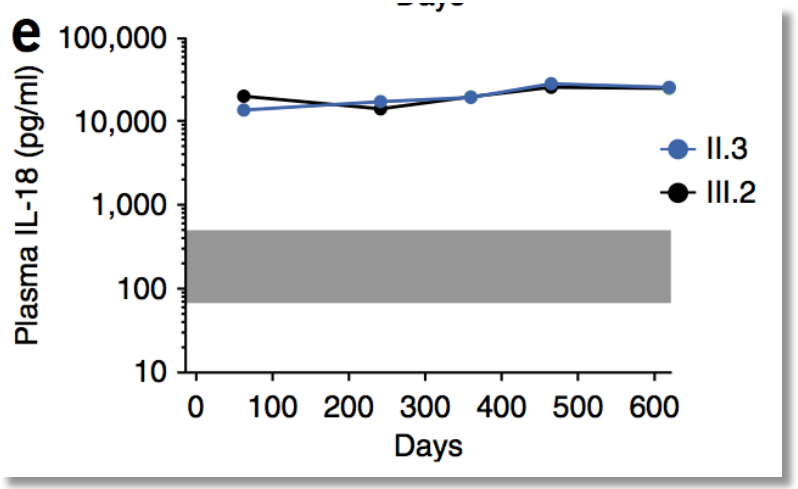


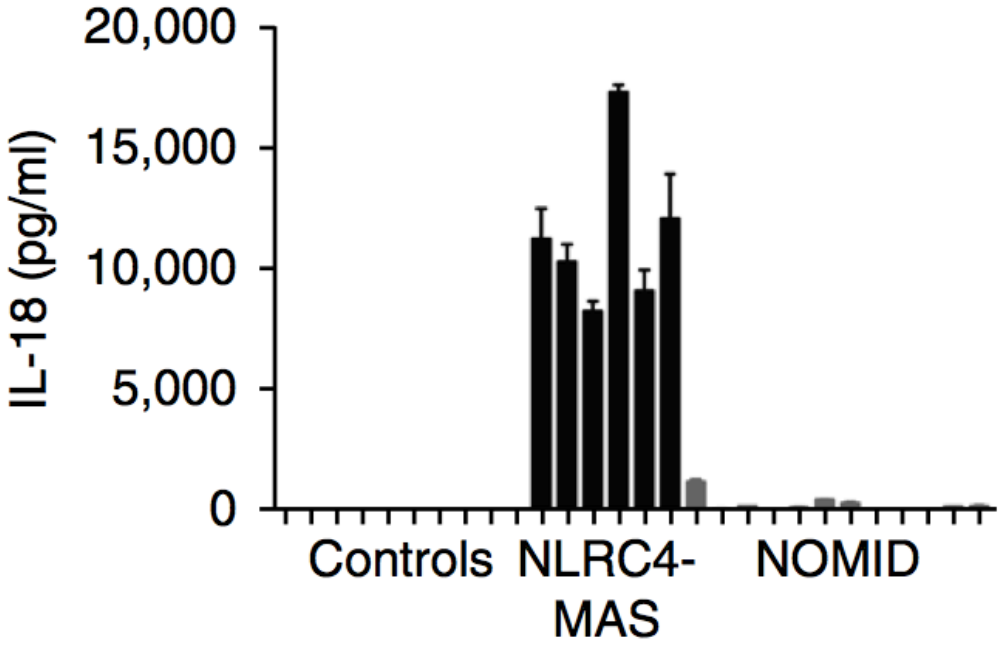
Cell 2014; 157: 1013-22



IL-1B **IL-18** IL-33

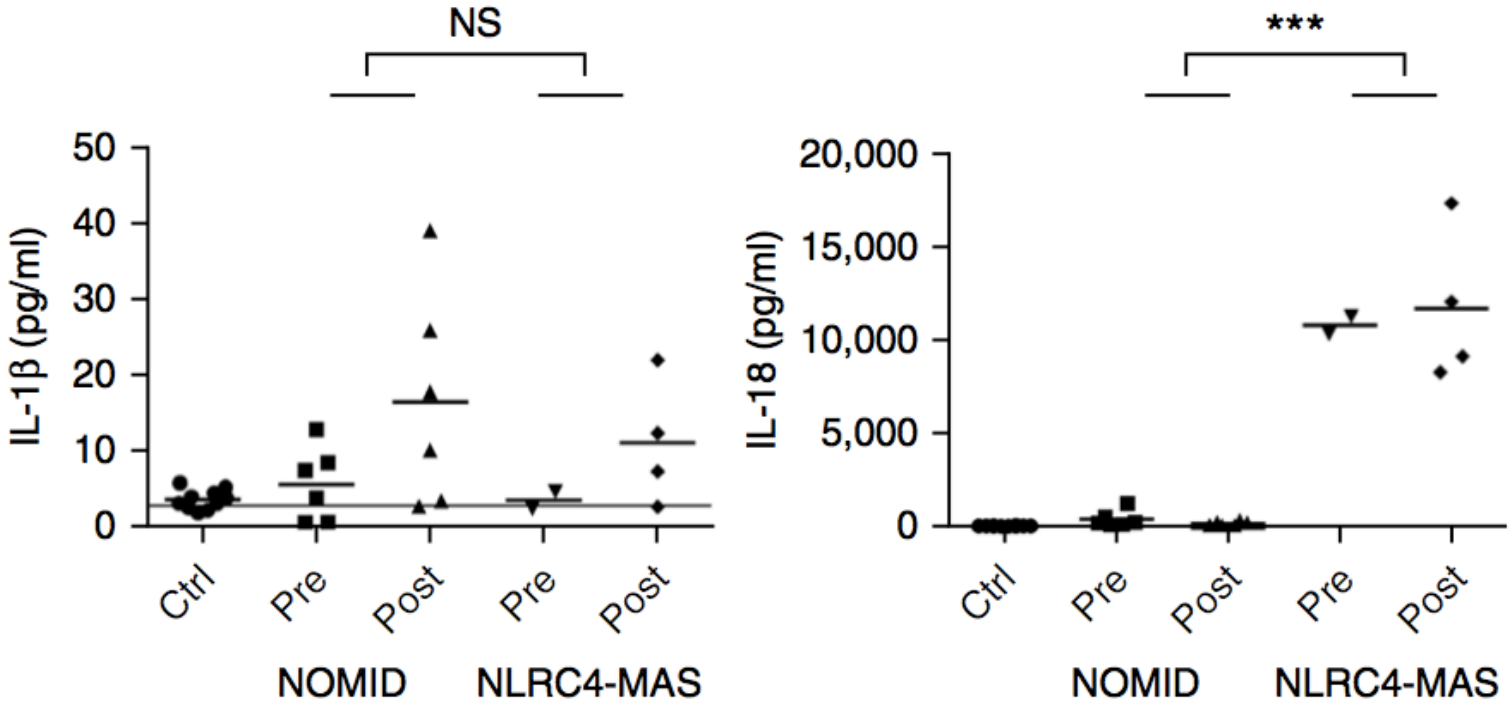

IL-1β (pg/ml)
50
40
30
20
10
0
Controls
NLRC4-MAS
NOMID


e
Plasma IL-18 (pg/ml)
100,000
10,000
1,000
100
10
0
100
200
300
400
500
600
Days
II.3
III.2


IL-18 (pg/ml)
20,000
15,000
10,000
5,000
0
Controls
NLRC4-MAS
NOMID

Kineret™
Anakinra
hrIL-1Ra





Deficiencia de ADA2

Sd. SAVI / Interferonopatías

Enfermedad por mutaciones en gen *NLRC4*

Sd. hiperzincemia e hipercalprotectinemia

Hyperzincemia with systemic inflammation: A heritable disorder of calprotectin metabolism with rheumatic manifestations?

Yoshiaki Saito, MD, Kayoko Saito, MD, Yukiko Hirano, MD, Kiyoko Ikeya, MD, Haruko Suzuki, MD, Keiko Shishikura, MD, Sumie Manno, PhD, Yuichi Takakuwa, PhD, Kiyoshi Nakagawa, PhD, Aiko Iwasa, PhD, Satoshi Fujikawa, MD, Makoto Moriya, MD, Nobuyuki Mizoguchi, MD, Barbara E. Golden, MD, and Makiko Osawa, MD

J Pediatr 2002; 140: 267-9

Hyperzincaemia and hypercalprotectinaemia: a new disorder of zinc metabolism

Barry Sampson, Magne K Fagerhol, Cord Sunderkötter, Barbara E Golden, Peter Richmond, Nigel Klein, Ilya Z Kovar, John H Beattie, Beata Wolska-Kusnierz, Yoshiaki Saito, Johannes Roth

Lancet 2002; 360: 1742-45

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J Pediatr 2002; 140: 267-9

	Age (y)	Sex	Onset	Arthritis	Stunted growth	Hepato-splenomegaly
Patient	14	M	Neonate	+	+	+
Mother	35	F	9 y	+	–	+
Hambidge et al[3]	18	M	Infancy	+	—	—
Sampson et al,[4] Richmond et al[6]	11	M	Neonate	–	+	+

+, Present; –, absent; —, not mentioned; *NS*, not studied.

J Pediatr 2002; 140: 267-9

Hyperzincaemia and hypercalprotectinaemia: a new disorder of zinc metabolism

Barry Sampson, Magne K Fagerhol, Cord Sunderkötter, Barbara E Golden, Peter Richmond, Nigel Klein, Ilya Z Kovar, John H Beattie, Beata Wolska-Kusnierz, Yoshiaki Saito, Johannes Roth

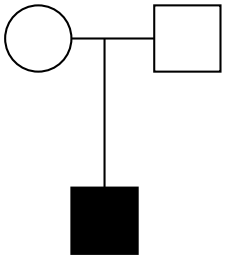
Lancet 2002; 360: 1742-45

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	18	9	14	35	21
Sex	M	F	M	F	M
Growth failure	<3rd percentile	<3rd percentile	<3rd percentile	Normal	Normal
Hepatosplenomegaly	Yes	Yes	Yes	Yes	Yes
Dermatological symptoms	Vasculitis	None	None	Vasculitis, eczema	Vasculitis, furuncules ulcers
Rheumatic symptoms	Arthritis	Arthritis	Arthritis	Arthritis, uveitis	Arthritis
Plasma C-reactive protein (mg/L)†	41–143	100–200	22	17	45–146
Haemoglobin (g/L)	80	90	109	125	80
Total white-cell counts (10^9 cells/mL)	2·0	3·7–5·0	1·5	5·0	3·8
Monocytes	0		1·9%	1·9%	4·3%
Plasma zinc (µmol/L)‡	180–200	82–96	160–200	175	77
Plasma calprotectin (g/L)§	6·5	1·4, 2·55	9	6·1	1·5

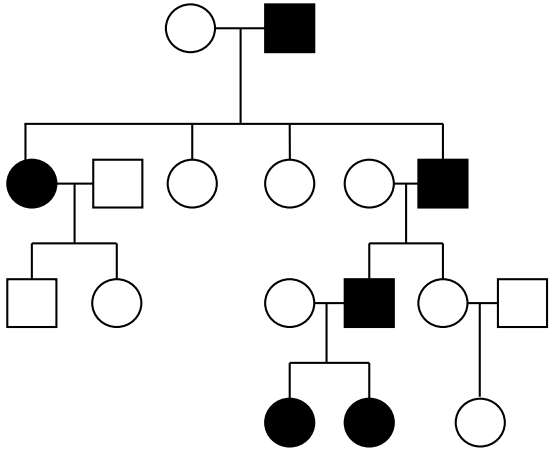
*Data from patient identified by Hambridge and colleagues.[4] †Reference <10 mg/L. ‡Reference 10–18 µmol/L. §Reference <1 mg/L.

Lancet 2002; 360: 1742-45

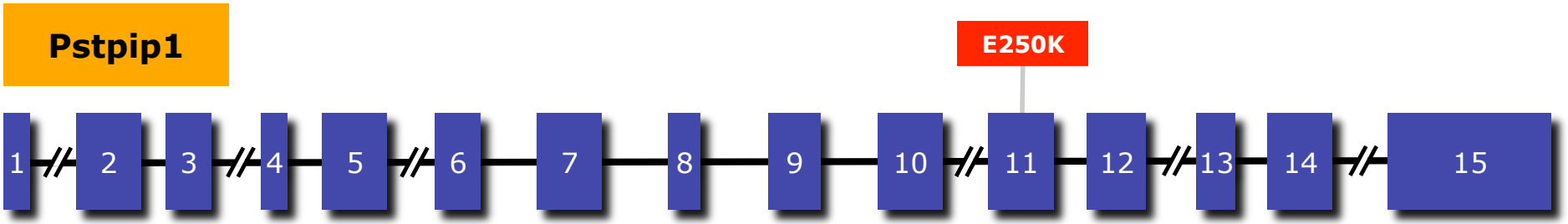
Zn **Calprotectin**



CASOS ESPORÁDICOS



CASOS FAMILIARES



A New Autosomal Dominant Disorder of Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne: PAPA Syndrome

Mayo Clin Proc 1997; 72: 611



Hum Mol Genet 2002; 11: 961



Cortesía Dra. Calvo - Hospital La Fe



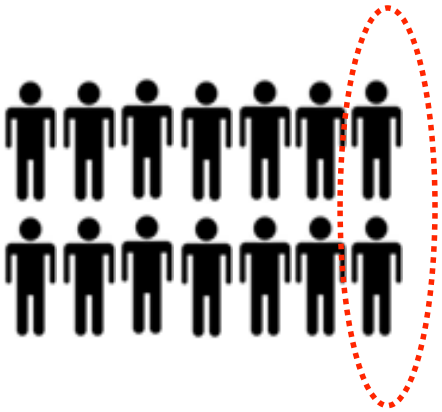
Ped Dermatol 2005; 22: 262



Single amino acid charge switch defines clinically distinct proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)–associated inflammatory diseases

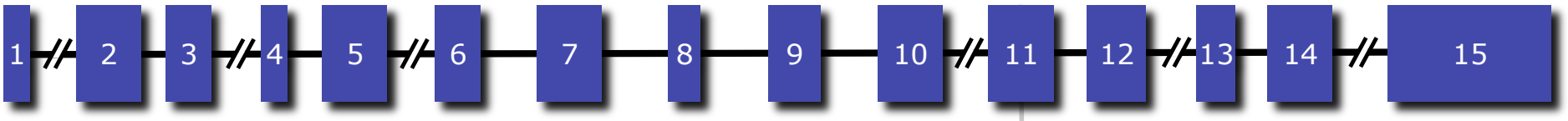
J Allergy Clin Immunol 2015; 136: 1337-45

Hz/ Hc



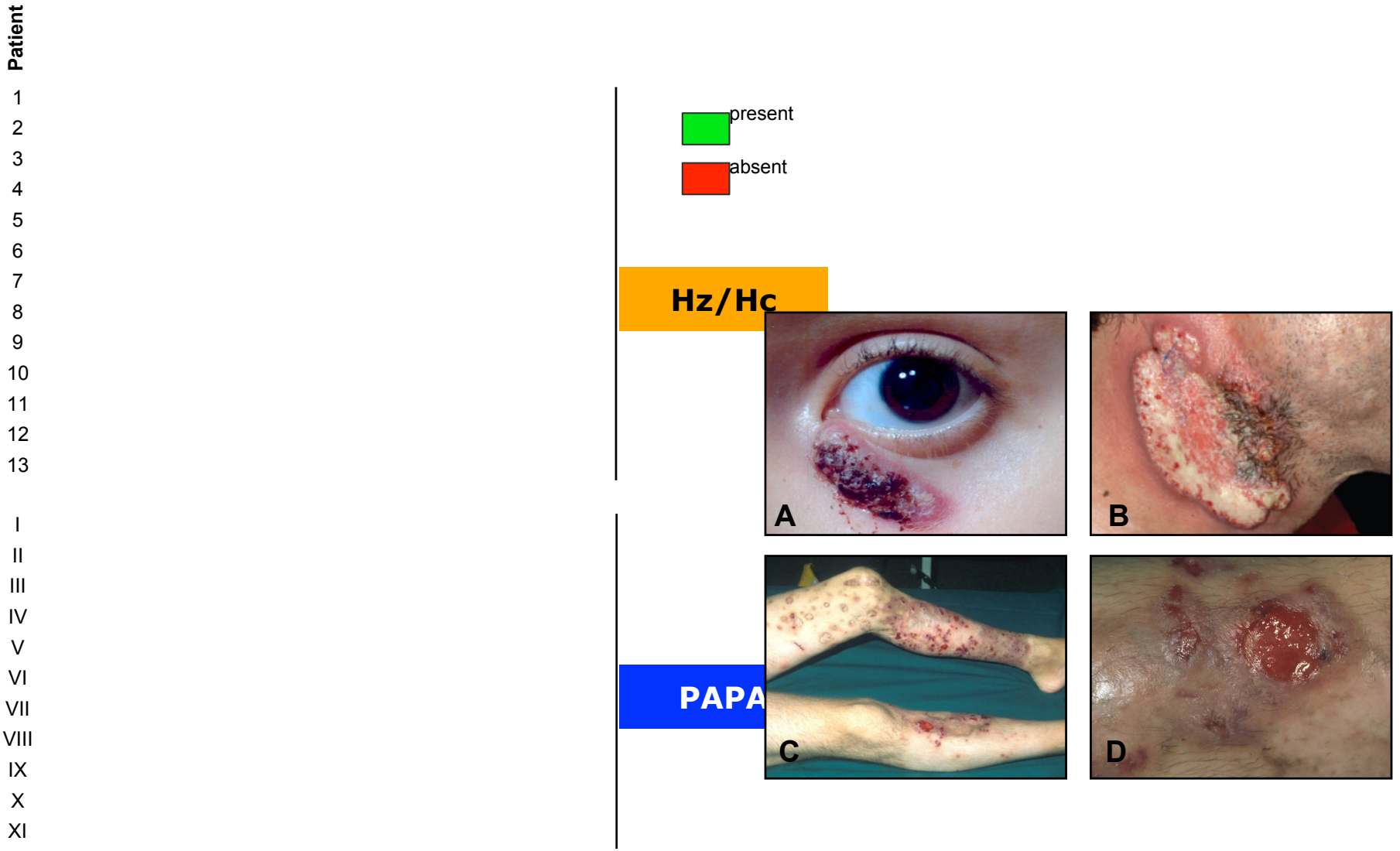


Pstpip1

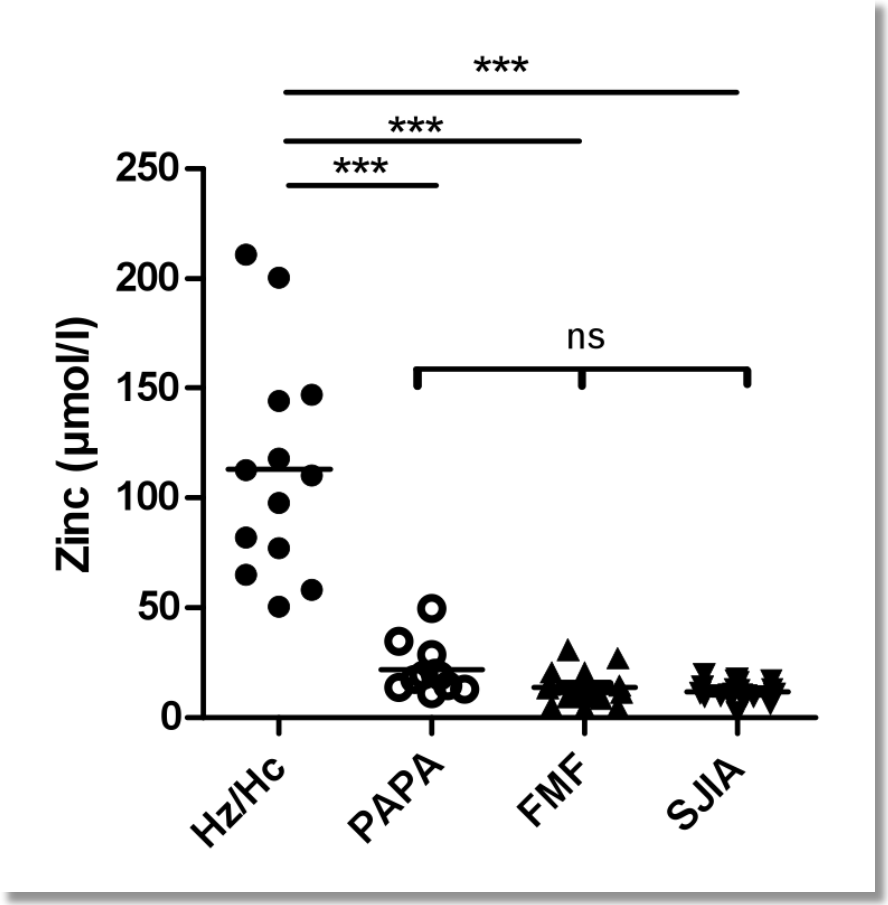


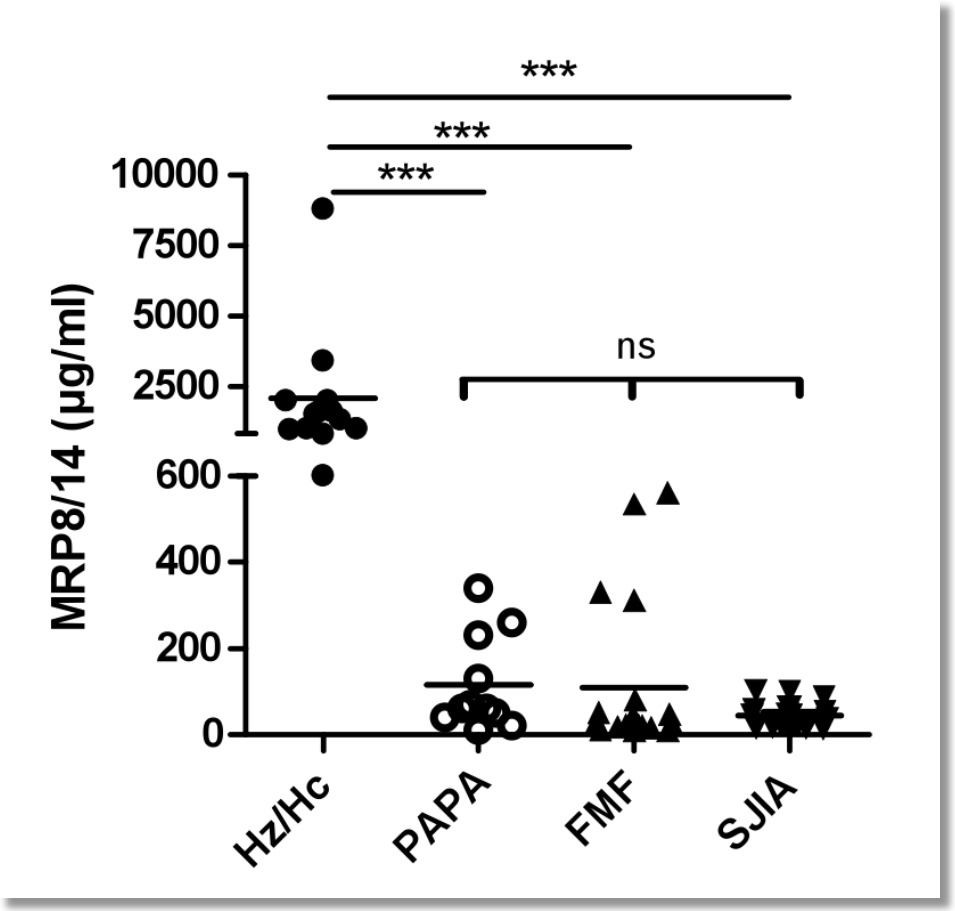
E250K **n: 13**

E257K **n: 1**



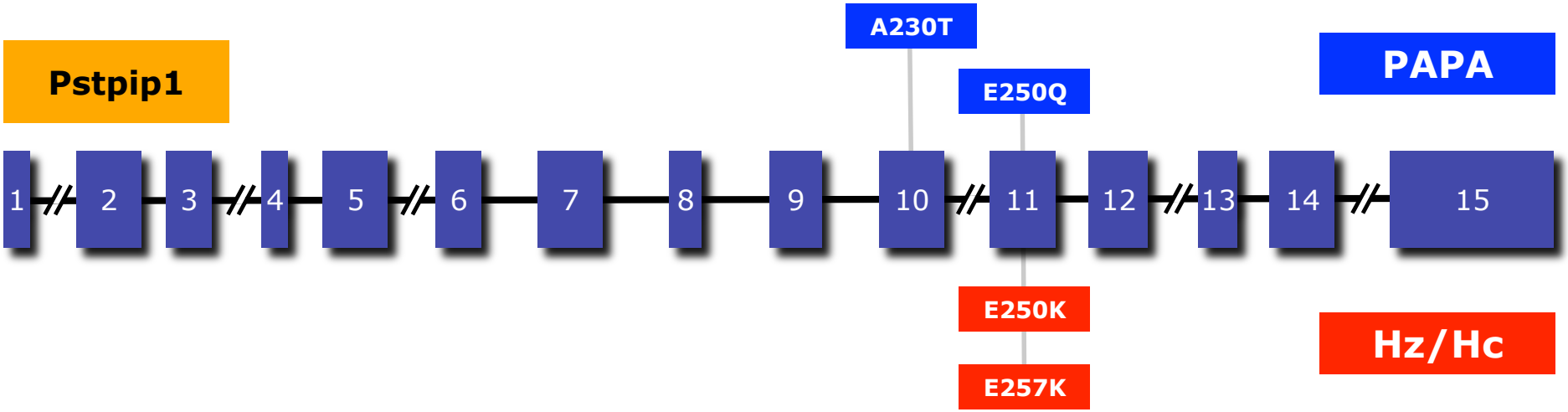
J Allergy Clin Immunol 2015; 136: 1337-45


***
***
***
250
200
150
100
50
0
Zinc (µmol/l)
ns
Hz/Hc
PAPA
FMF
SJIA


***
***
***
10000
7500
5000
2500
600
400
200
0
MRP8/14 (µg/ml)
ns
Hz/Hc
PAPA
FMF
SJIA

Hz/ Hc

Fisiopatología



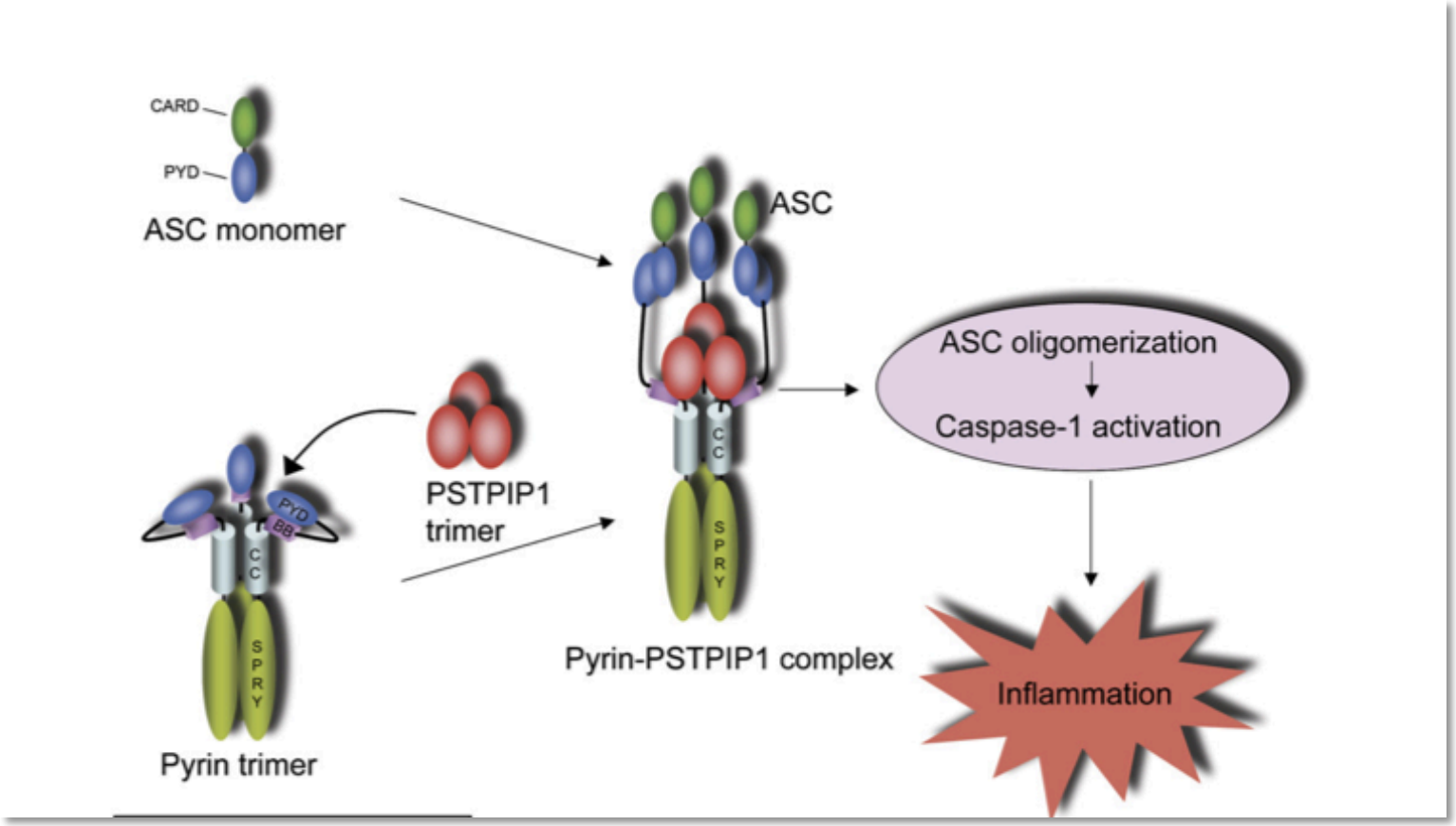
Hz/ Hc

PAPA-like disease
No FMF phenotype

Autosomal dominant inheritance
p.S242R *MEFV* mutation

Pyrin-inflammasome disease

Fisiopatología



Hz/ Hc

Tratamiento

Anakinra for flares of pyogenic arthritis in PAPA syndrome

Rheumatology 2005; 44: 406

Dramatic Improvement of Pyoderma Gangrenosum with Infliximab in a Patient with PAPA Syndrome

Pediatric Dermatology 2005; 22: 262

ABNORMAL PRODUCTION OF THE TUMOR NECROSIS FACTOR INHIBITOR ETANERCEPT AND CLINICAL EFFICACY OF TUMOR IN A PATIENT WITH PAPA SYNDROME

J Pediatr 2004; 145: 851


¡¡Gracias!!