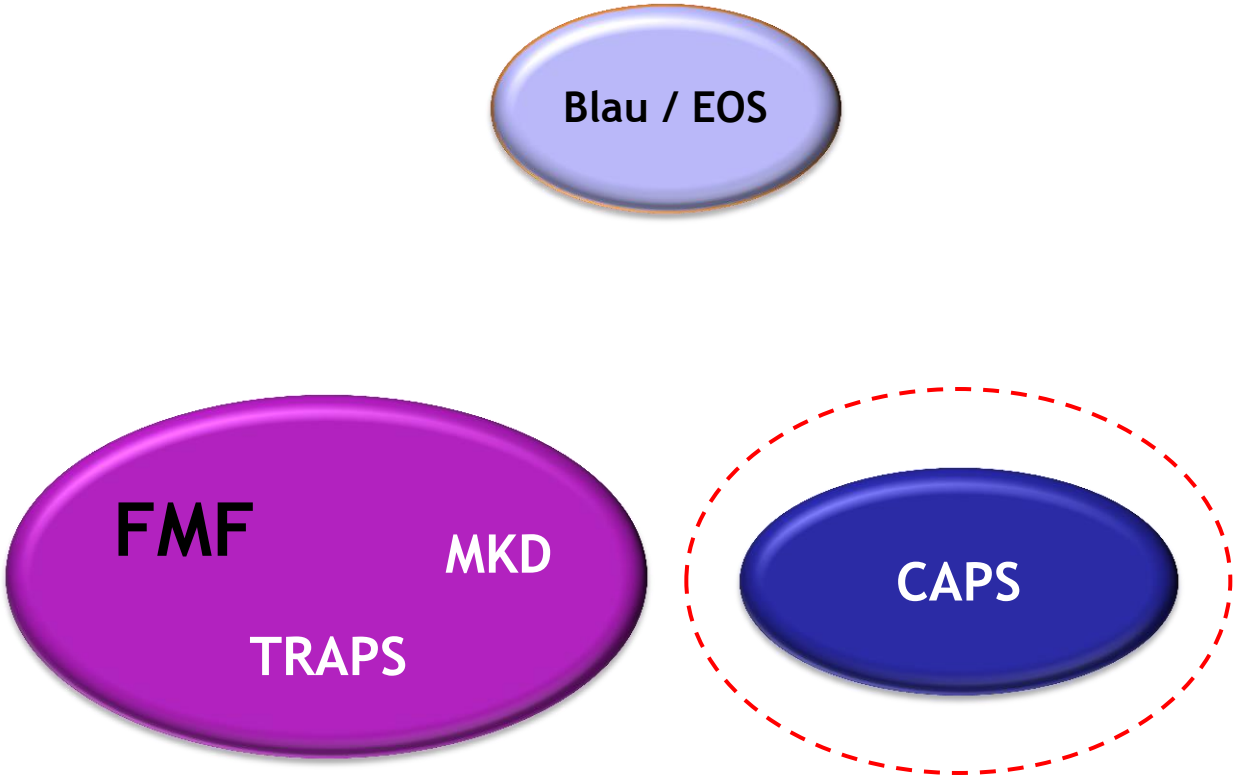
Novedades en enfermedades autoinflamatorias

Juan I. Aróstegui
Servicio de Inmunología
Hospital Clínic
Barcelona



10º Congreso de la Sociedad Española de Reumatología Pediátrica

Granada, 16 de noviembre de 2013



Mosaicismo somático en el gen *NLRP3*

CINCA-NOMID

Muckle-Wells syndrome

FCAS

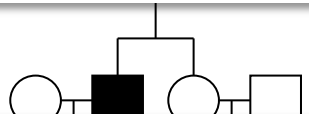


Geneviève de Saint Basile
Necker-Enfants Malades

Chronic Infantile Neurological Cutaneous and Articular Syndrome Is Caused by Mutations in *CIAS1*, a Gene Highly Expressed in Polymorphonuclear Cells and Chondrocytes

Jérôme Feldmann,[1] Anne-Marie Prieur,[2] Pierre Quartier,[2] Patrick Berquin,[4] Stéphanie Certain,[1] Elisabetta Cortis,[5] Dominique Teillac-Hamel,[3] Alain Fischer,[1,2] and Geneviève de Saint Basile[1]

Am J Hum Genet 2002; 71: 198-203



esporá

De Novo *CIAS1* Mutations, Cytokine Activation, and Evidence for Genetic Heterogeneity in Patients With Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

Ivona Aksentijevich,[1] Miroslawa Nowak,[1] Mustapha Mallah,[1] Jae Jin Chae,[1] Wendy T. Watford,[1] Sigrun R. Hofmann,[1] Leonard Stein,[2] Ricardo Russo,[3] Donald Goldsmith,[4] Peter Dent,[5] Helene F. Rosenberg,[6] Frances Austin,[1] Elaine F. Remmers,[1] James E. Balow, Jr.,[1] Sergio Rosenzweig,[6] Hirsh Komarow,[1] Nitza G. Shoham,[1] Geryl Wood,[1] Janet Jones,[1] Nadira Mangra,[1] Hector Carrero,[1] Barbara S. Adams,[7] Terry L. Moore,[8] Kenneth Schikler,[9] Hal Hoffman,[10] Daniel J. Lovell,[11] Robert Lipnick,[1] Karyl Barron,[6] John J. O'Shea,[1] Daniel L. Kastner,[1] and Raphaela Goldbach-Mansky[1]

Arthritis Rheum 2002; 46: 3340-3348



Raphaela Goldbach-Mansky
NIAMS-NIH

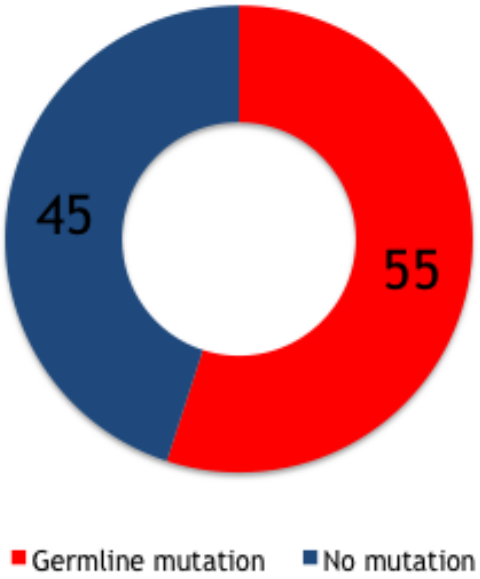
CINCA/NOMID

Análisis genético convencional
Secuenciación Sanger

NLRP3 negativo

NLRP3 positivo (Germline)

Otros genes? Relacionados con criopirina?



Somatic Mosaicism of *CIAS1* in a Patient With Chronic Infantile Neurologic, Cutaneous, Articular Syndrome

Megumu Saito, Akihiro Fujisawa, Ryuta Nishikomori, Naotomo Kambe, Mami Nakata-Hizume, Momoko Yoshimoto, Katsuyuki Ohmori, Ikuo Okafuji, Takakazu Yoshioka, Takashi Kusunoki, Yoshiki Miyachi, Toshio Heike, and Tatsutoshi Nakahata

Arthritis Rheum 2005; 52: 3579

A Somatic *NLRP3* Mutation as a Cause of a Sporadic Case of Chronic Infantile Neurologic, Cutaneous, Articular Syndrome/ Neonatal-Onset Multisystem Inflammatory Disease

Juan I. Aróstegui,[1] Mª Dolores Lopez Saldaña,[2] Mariona Pascal,[1] Daniel Clemente,[2] Marta Aymerich,[1] Francesc Balaguer,[3] Ajay Goel,[4] Concepción Fournier del Castillo,[2] Josefa Rius,[1] Susana Plaza,[1] Juan Carlos López Robledillo,[2] Manel Juan,[1] Mercedes Ibañez,[2] and Jordi Yagüe[1]

Arthritis Rheum 2010; 62: 1158

CINCA/NOMID

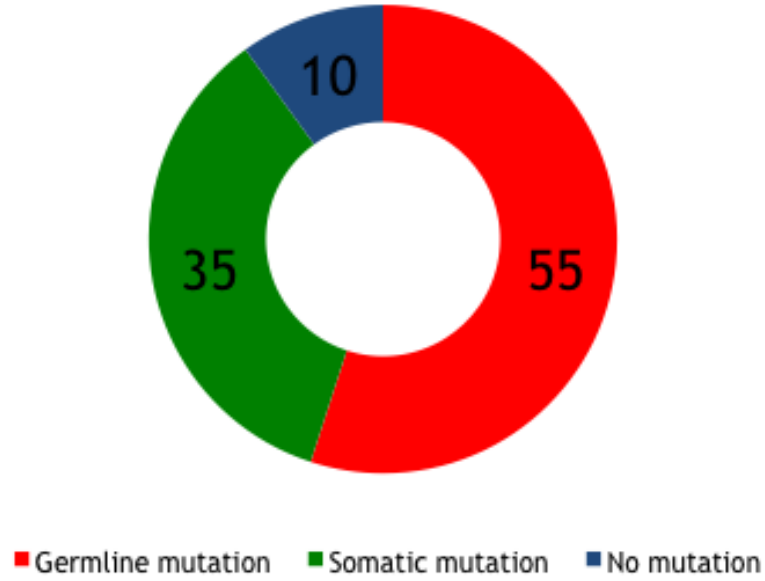
Análisis genético convencional
Secuenciación Sanger

NLRP3 negativo

NLRP3 positivo (Germline)

Búsqueda de mosaicismo somático en el gen *NLRP3*

~70% (18/26)



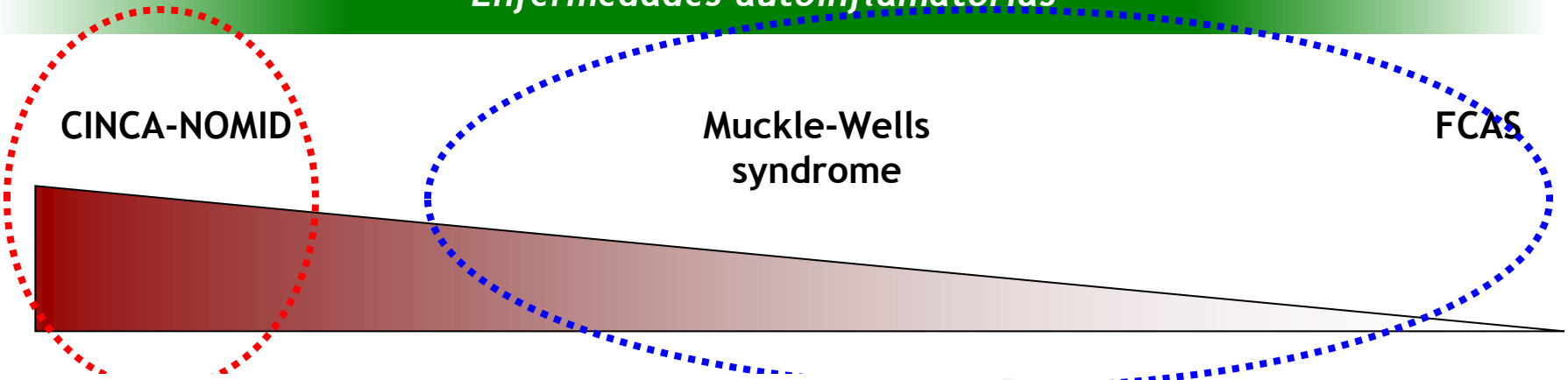
PCR cloning
Secuenciación clonas

High Incidence of *NLRP3* Somatic Mosaicism in Patients With Chronic Infantile Neurologic, Cutaneous, Articular Syndrome

Results of an International Multicenter Collaborative Study

Naoko Tanaka,[1] Kazushi Izawa,[1] Megumu K. Saito,[2] Mio Sakuma,[3] Koichi Oshima,[4] Osamu Ohara,[4] Ryuta Nishikomori,[1] Takeshi Morimoto,[3] Naotomo Kambe,[5] Raphaela Goldbach-Mansky,[6] Ivona Aksentijevich,[6] Geneviève de Saint Basile,[7] Bénédicte Neven,[8] Mariëlle van Gijn,[9] Joost Frenkel,[9] Juan I. Aróstegui,[10] Jordi Yagüe,[10] Rosa Merino,[11] Mercedes Ibañez,[12] Alessandra Pontillo,[13] Hidetoshi Takada,[14] Tomoyuki Imagawa,[15] Tomoki Kawai,[1] Takahiro Yasumi,[1] Tatsutoshi Nakahata,[2] and Toshio Heike[1]

Arthritis Rheum 2011; 63: 3625



Estudio multicéntrico sobre sd. Muckle-Wells Japón-España

≈10% de los candidatos son portadores de un grado variable de mosaicismo somático en el gen *NLRP3*

≈50% mutaciones del gen *NLRP3* son nuevas

Todas las mutaciones detectadas son del tipo *gain-of-function*

Excelentes respuestas clinicas y bioquímicas al bloqueo de IL-1

Posibles diferencias con pacientes portadores de mutaciones germinales del gen *NLRP3*
- Debut tardío de la enfermedad
- Debut tardío de la sordera neurosensorial
- Incidencia reducida de amiloidosis AA

Reino Unido
Great Ormond Street Hospital
National Amyloidosis Center

Italia

Turquía
USA

Somatic *NLRP3* mosaicism in Muckle-Wells syndrome.

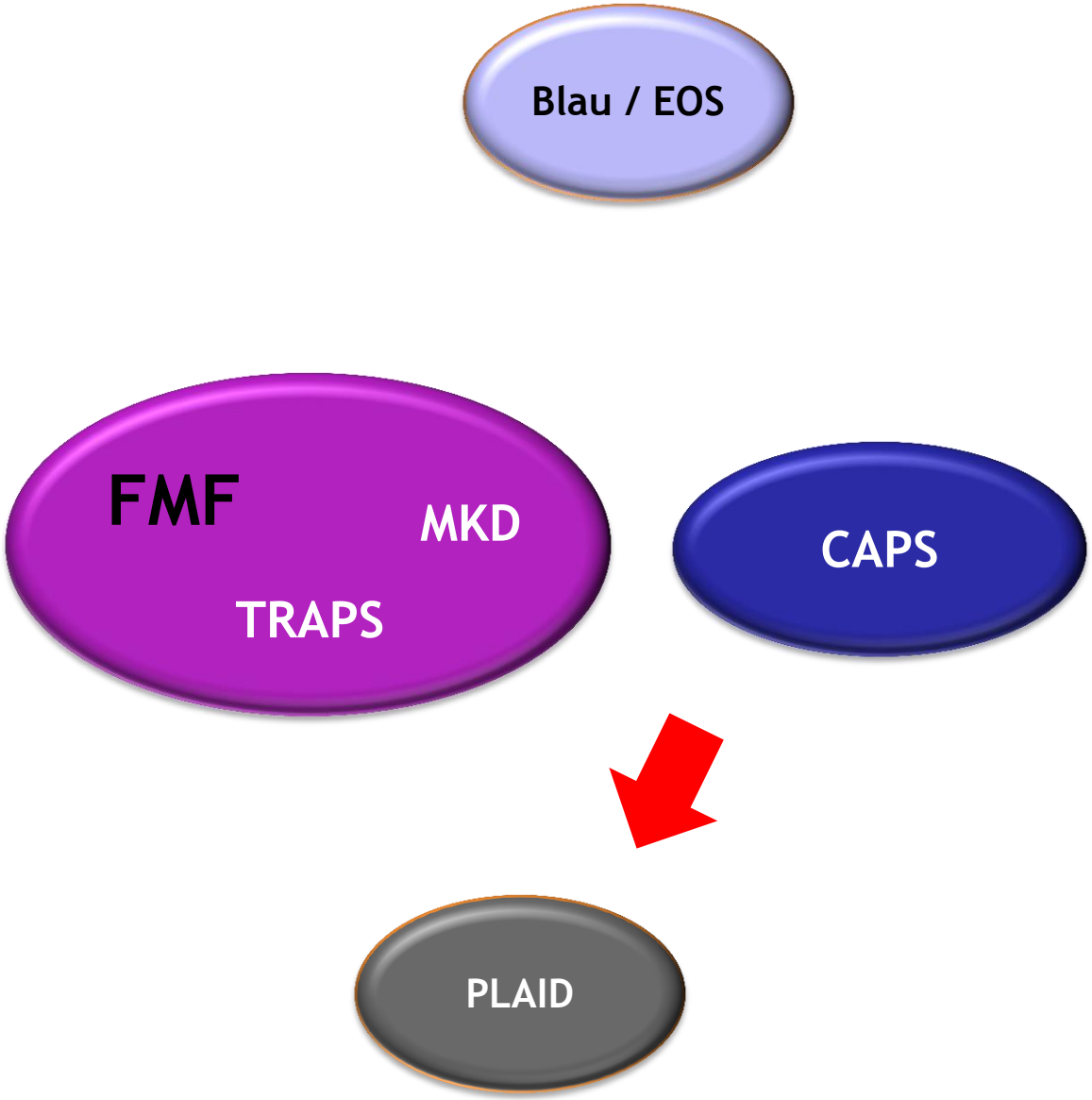
A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes

Authors

Kenji Nakagawa MD[1,*], Eva Gonzalez-Roca PhD[2,*], Alejandro Souto MD[3], Toshinao Kawai MD PhD[4], Hiroaki Umebayashi MD[5], Josep María Campistol MD PhD[6], Jeronima Cañellas MD[7], Syuji Takei MD[8], Norimoto Kobayashi MD PhD[9], Jose Luis Callejas-Rubio MD PhD[10], Norberto Ortego-Centeno MD PhD[10], Estíbaliz Ruiz-Ortiz PhD[2], Fina Rius AS[2], Jordi Anton MD PhD[11], Estibaliz Iglesias MD PhD[11], Santiago Jimenez-Treviño MD[12], Carmen Vargas MD PhD[13], Julian Fernandez-Martin MD PhD[14], Inmaculada Calvo MD PhD[15], José Hernández-Rodríguez MD PhD[16], María Mendez MD[17], María Teresa Dordal MD[18], Maria Basagaña MD, PhD[19], Segundo Bujan MD PhD[20], Masato Yashiro MD PhD[21], Tetsuo Kubota MD PhD[22], Ryuji Koike MD PhD[22], Naoko Akuta MD PhD[23], Kumiko Shimoyama MD PhD[24], Naomi Iwata MD[25], Megumu K. Saito MD PhD[26], Osamu Ohara PhD[27], Naotomo Kambe, MD PhD[28], Takahiro Yasumi MD PhD[1], Kazushi Izawa MD PhD[1], Tomoki Kawai, MD PhD[1], Toshio Heike MD PhD[1], Jordi Yagüe MD PhD[2], Ryuta Nishikomori MD PhD[1,*], Juan I. Aróstegui MD PhD[2,*].

Confidential - For Review

First revision - Annals of the Rheumatic Diseases


Blau / EOS
FMF
MKD
TRAPS
CAPS
PLAID

Cold Urticaria, Immunodeficiency, and Autoimmunity Related to *PLCG2* Deletions

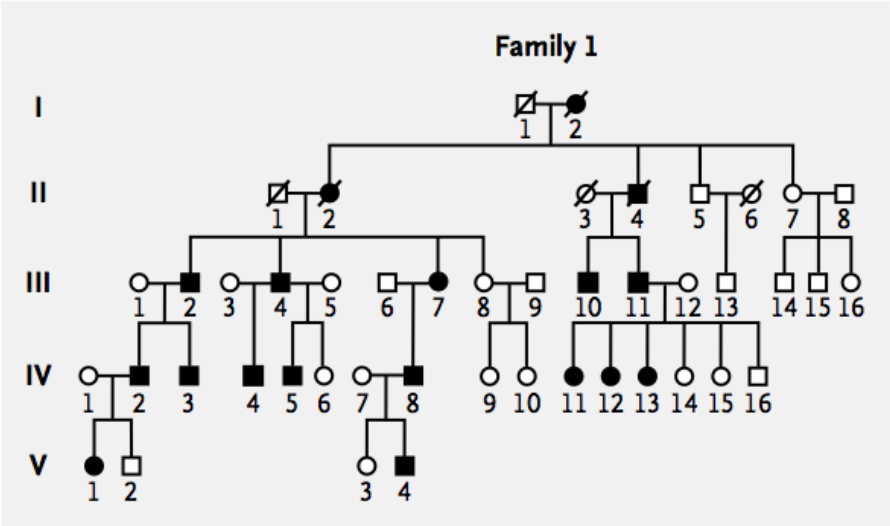
Michael J. Ombrello, M.D., Elaine F. Remmers, Ph.D., Guangping Sun, M.D., Alexandra F. Freeman, M.D., Shrimati Datta, Ph.D., Parizad Torabi-Parizi, M.D., Naeha Subramanian, Ph.D., Tom D. Bunney, Ph.D., Rhona W. Baxendale, Ph.D., Marta S. Martins, Ph.D., Neil Romberg, M.D., Hirsh Komarow, M.D., Ivona Aksentijevich, M.D., Hun Sik Kim, Ph.D., Jason Ho, Ph.D., Glenn Cruse, Ph.D., Mi-Yeon Jung, Ph.D., Alasdair M. Gilfillan, Ph.D., Dean D. Metcalfe, M.D., Celeste Nelson, C.R.N.P., Michelle O'Brien, B.S.N., Laura Wisch, M.S.N., Kelly Stone, M.D., Ph.D., Daniel C. Douek, M.D., Ph.D., Chhavi Gandhi, M.D., Alan A. Wanderer, M.D., Hane Lee, Ph.D., Stanley F. Nelson, M.D., Kevin V. Shianna, Ph.D., Elizabeth T. Cirulli, Ph.D., David B. Goldstein, Ph.D., Eric O. Long, Ph.D., Susan Moir, Ph.D., Eric Meffre, Ph.D., Steven M. Holland, M.D., Daniel L. Kastner, M.D., Ph.D., Matilda Katan, Ph.D., Hal M. Hoffman, M.D., and Joshua D. Milner, M.D.

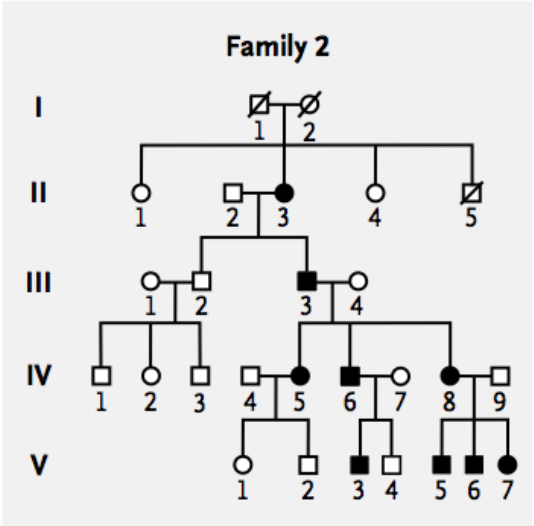
N Eng J Med 2012; 366: 330

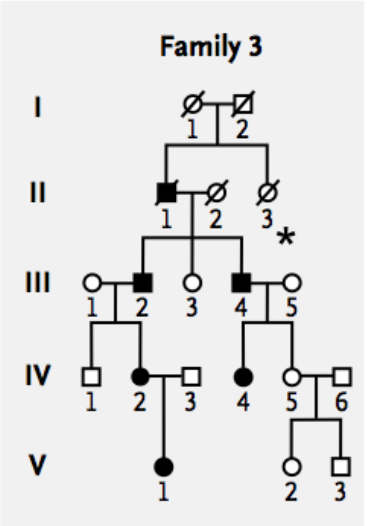
Familial atypical cold urticaria: Description of a new hereditary disease

Chhavi Gandhi, MD,[a] Chris Healy, MD,[b] Alan A. Wanderer, MD,[c] and Hal M. Hoffman, MD[a,d,e] *La Jolla, Calif, Madison, Wis, Bozeman, Mont, and San Diego, Calif*

J Allergy Clin Immunol 2009; 124: 1245





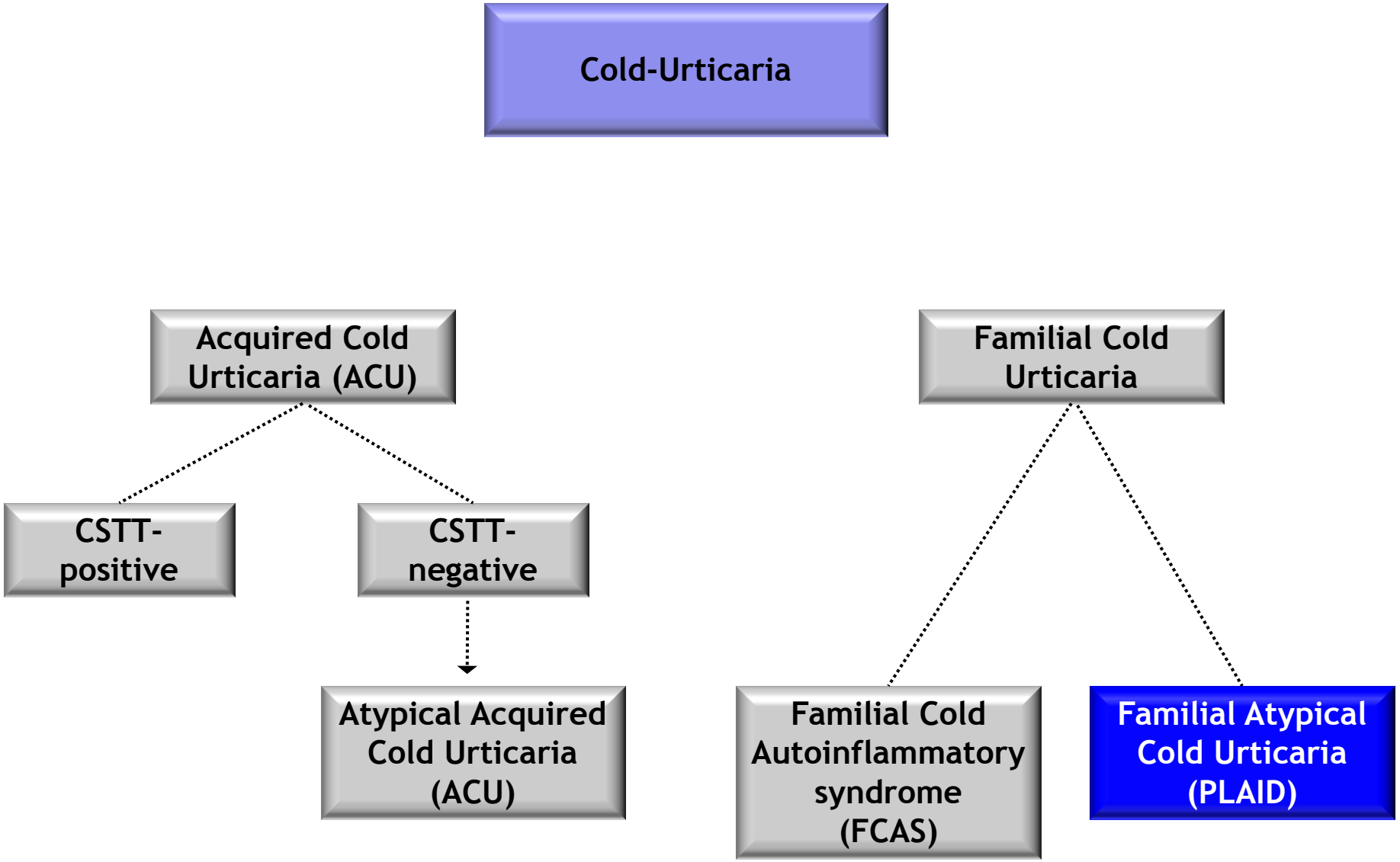


Varón: 11
Mujer: 7

Varón: 5
Mujer: 4

Varón: 3
Mujer: 3

Herencia Autosomica Dominante


Cold-Urticaria
Acquired Cold Urticaria (ACU)
CSTT-positive
CSTT-negative
Atypical Acquired Cold Urticaria (ACU)
Familial Cold Urticaria
Familial Cold Autoinflammatory syndrome (FCAS)
Familial Atypical Cold Urticaria (PLAID)

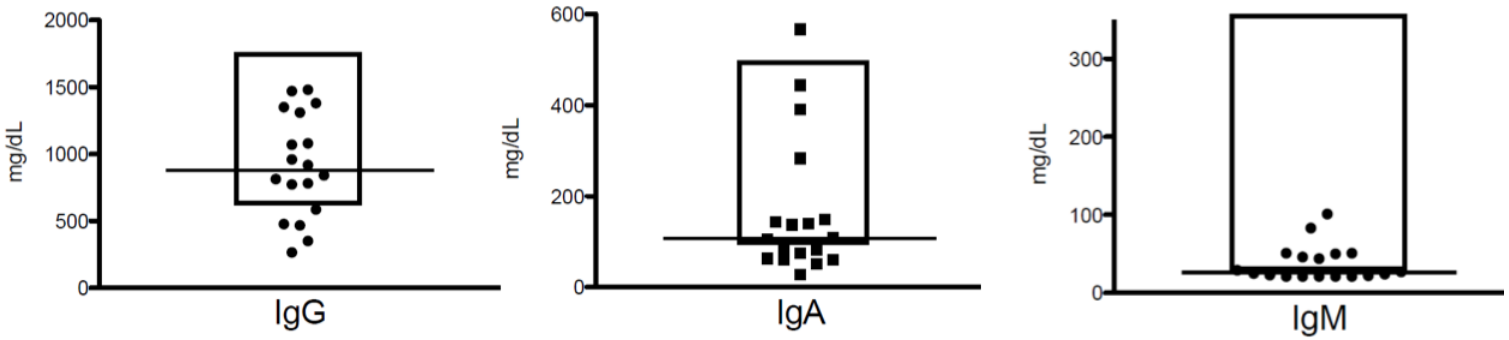
Cold Urticaria

	FACU	ACU	FCAS
Inheritance pattern	Autosomal dominant	Usually sporadic	Autosomal dominant
Known genetic mutation	Unknown	Unknown	*NLRP3*
Onset in early childhood	++	−	++
Lifelong duration	+++	−	+++
Atmospheric cold elicitation	++	+	++
Immediate onset after cold exposure	+++	+++	−
Onset with ingestion of cold foods	++	++	−
Pruritus	+++	+++	+
Respiratory symptoms (bronchospasm)	+	++	−
CV collapse/ syncope	+	++	−
Fever or chills	−	−	+++
Extremity pain	−	−	+++
CSTT	−	+++	−
Antihistamines effective	++	+++	+

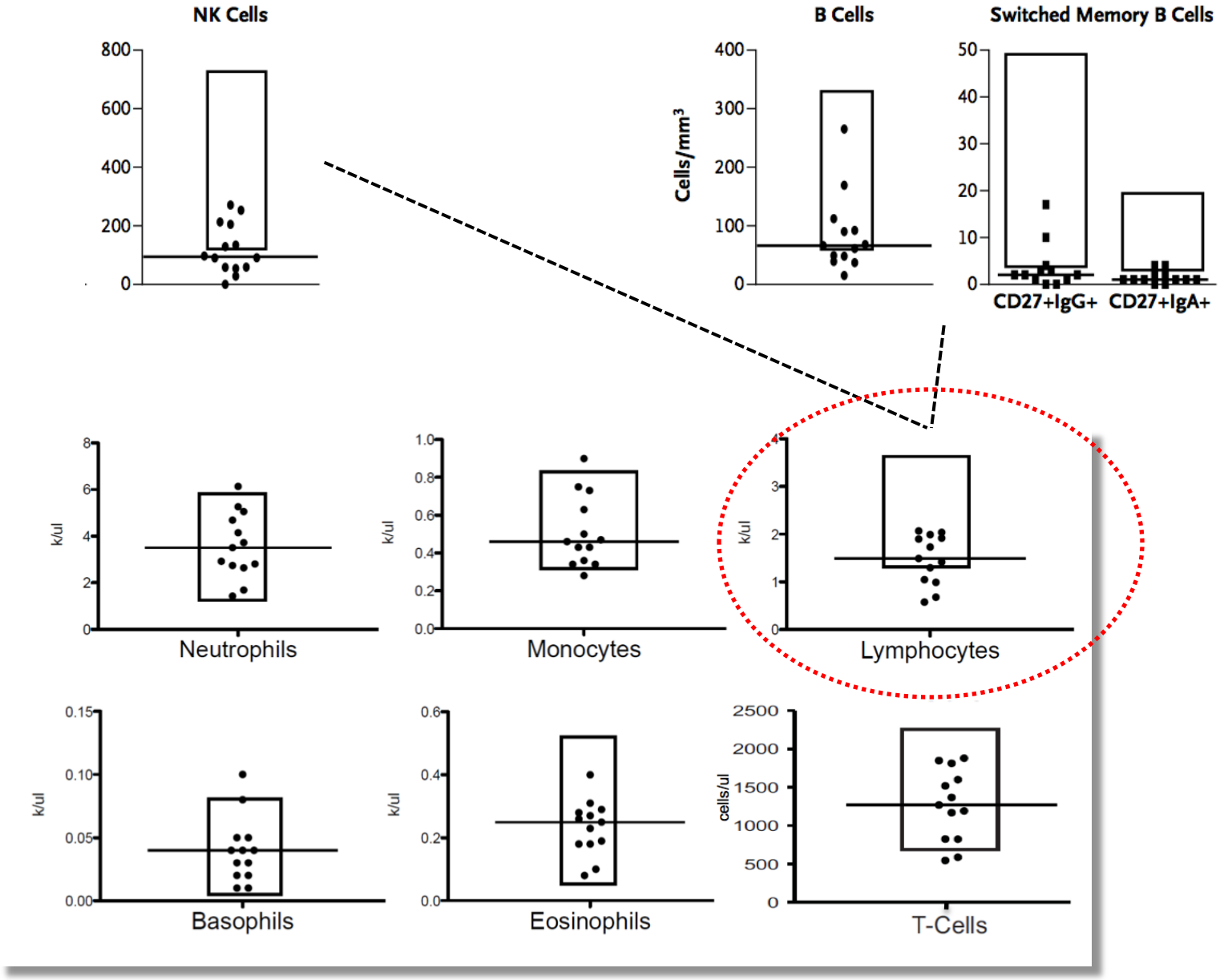
J Allergy Clin Immunol 2009; 124: 1245

Table 1. Summary of the Clinical Manifestations of Phospholipase Cγ_2–Associated Antibody Deficiency and Immune Dysregulation in the Subjects.

Clinical Manifestation	Frequency
	no./total no. (%)
Cold urticaria	27/27 (100)
Recurrent sinopulmonary infection	12/27 (44)
Antibody deficiency*	15/20 (75)
Common variable immunodeficiency	3/27 (11)
Symptomatic autoimmune disease†	7/27 (26)
Positive test for antinuclear antibodies‡	13/21 (62)
Symptomatic allergic disease	15/27 (56)



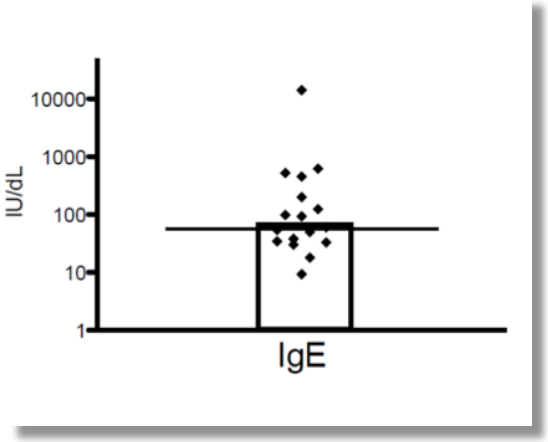
N Eng J Med 2012; 366: 330

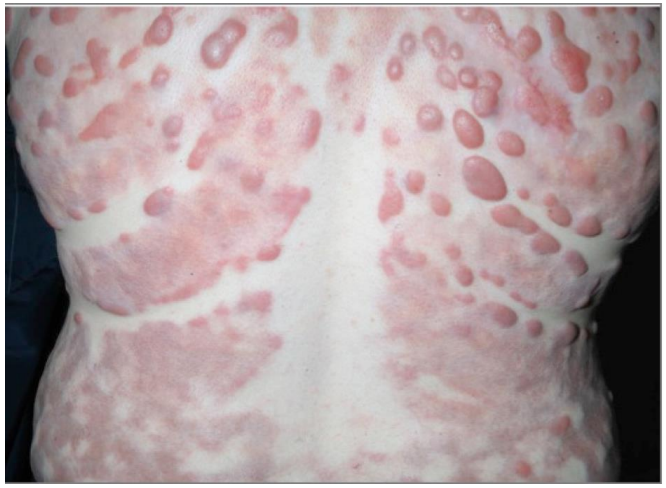


N Eng J Med 2012; 366: 330

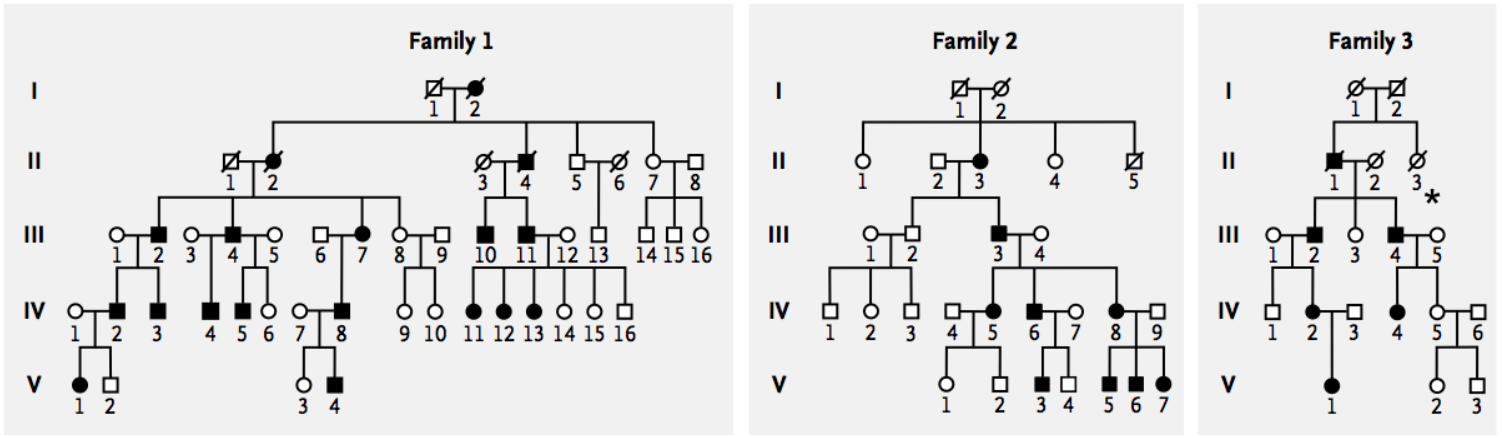
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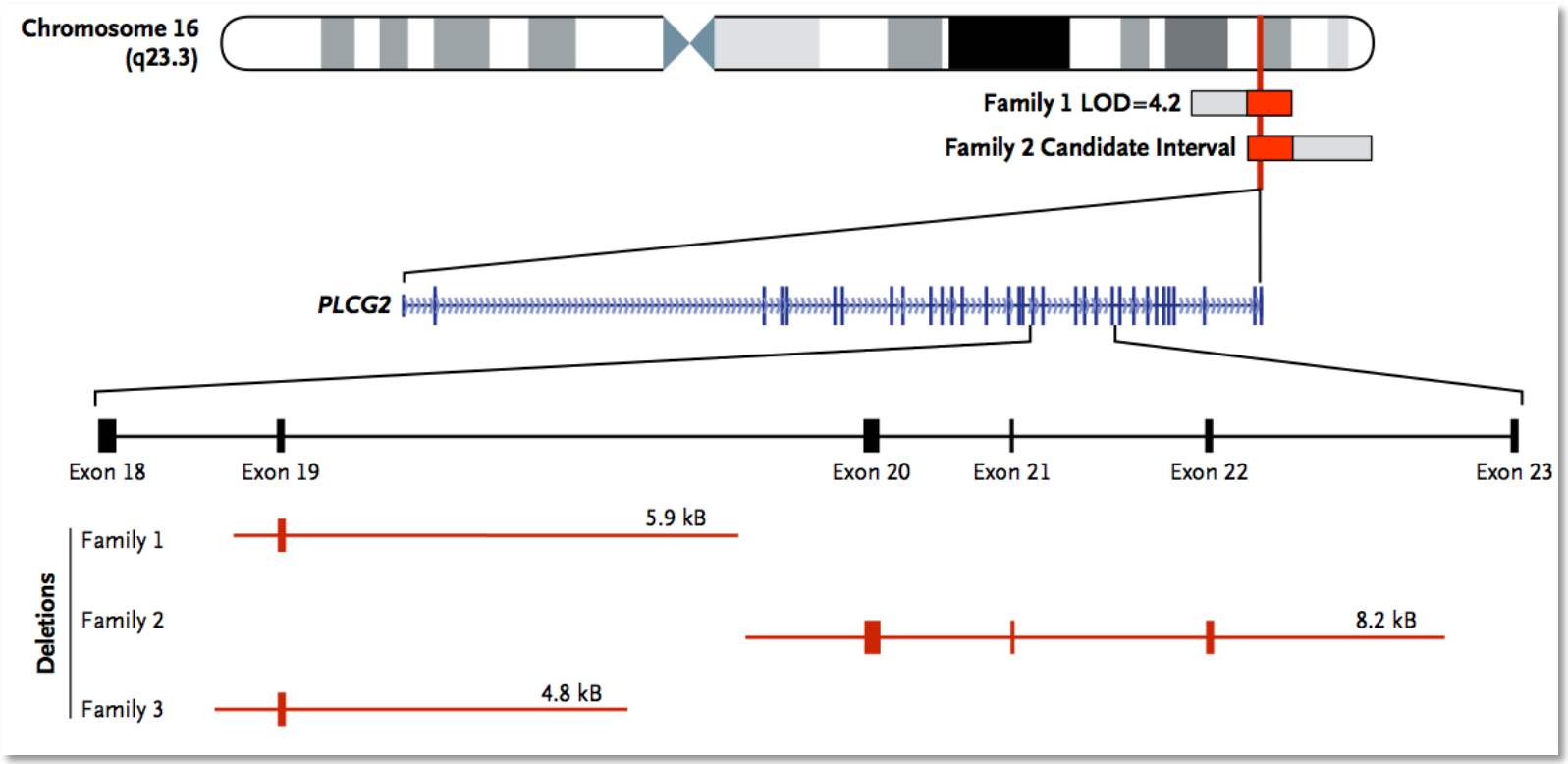
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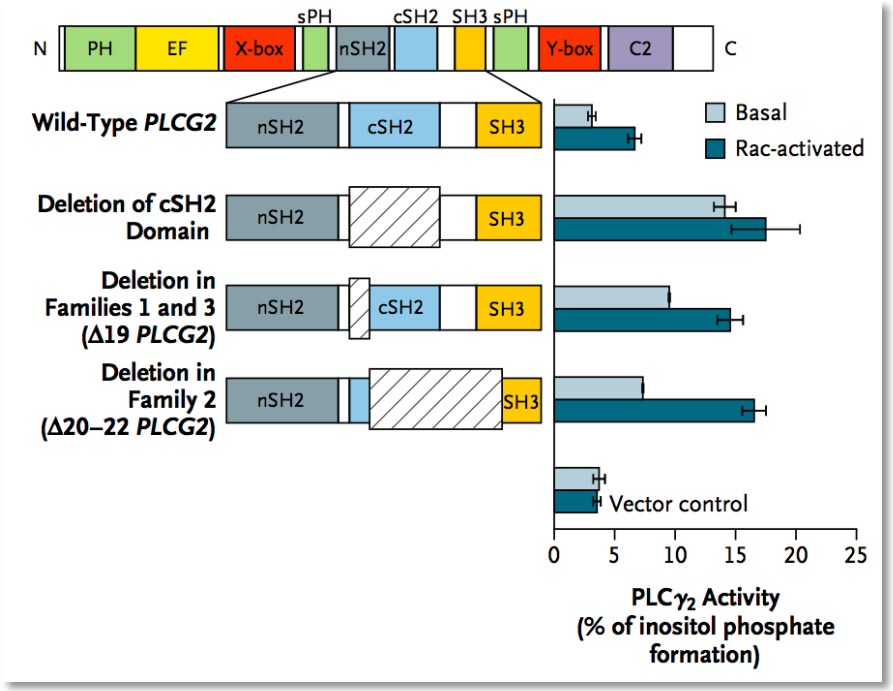


N Eng J Med 2012; 366: 330

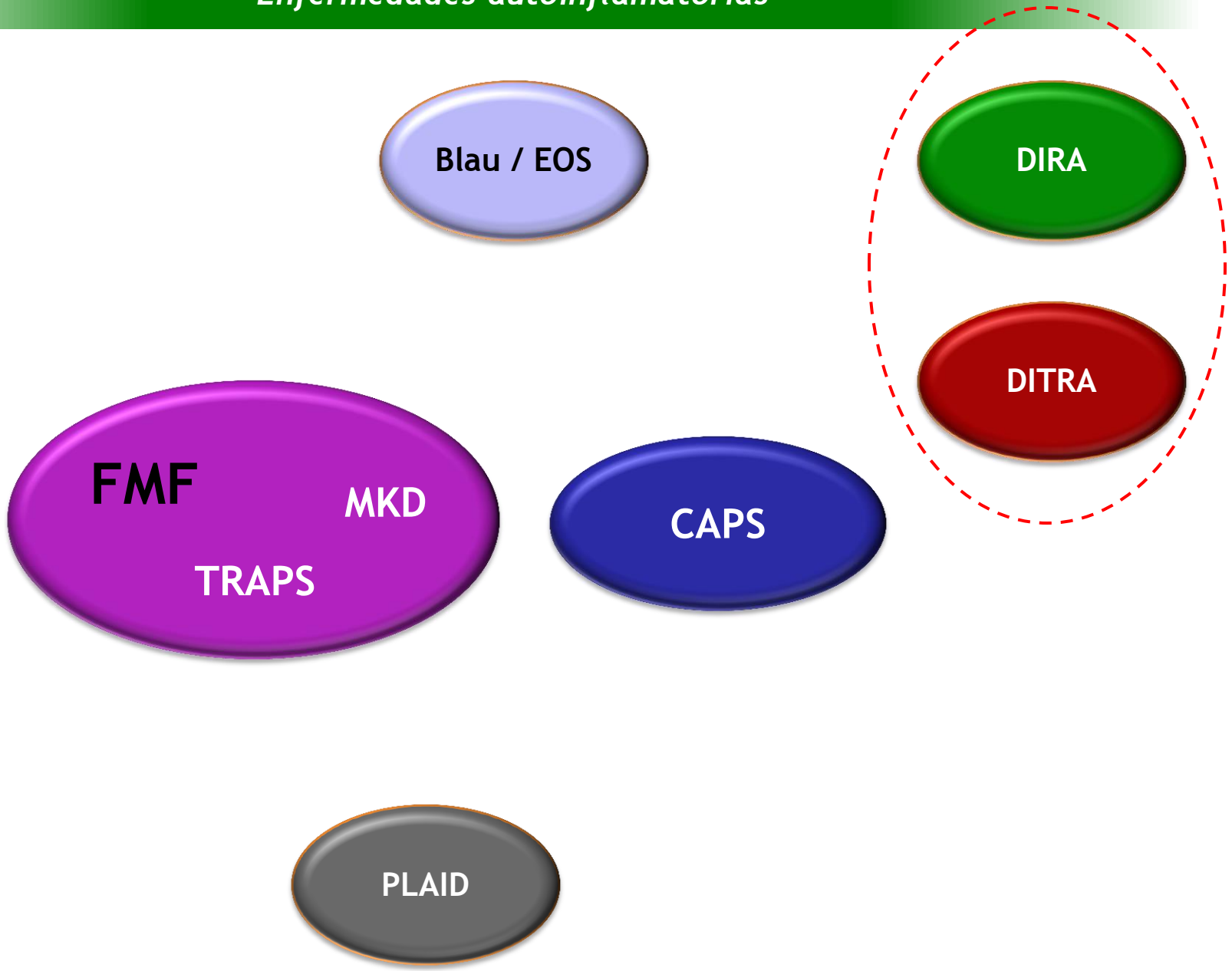




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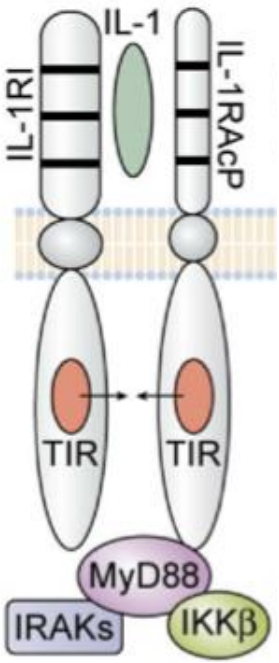


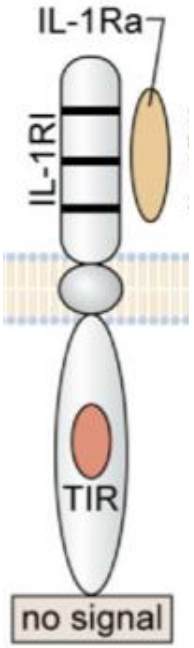
N Eng J Med 2012; 366: 330


Blau / EOS
DIRA
DITRA
FMF
MKD
TRAPS
CAPS
PLAID

Deficiencia del antagonista de IL-1 (DIRA)

Deficiencia del antagonista de IL-36 (DITRA)





Blood 2011; 117: 3720

An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist

Ivona Aksentijevich, M.D., Seth L. Masters, Ph.D., Polly J. Ferguson, M.D., Paul Dancey, M.D., Joost Frenkel, M.D., Annet van Royen-Kerkhoff, M.D., Ron Laxer, M.D., Ulf Tedgård, M.D., Ph.D., Edward W. Cowen, M.D., Tuyet-Hang Pham, M.T., Matthew Booty, B.S., Jacob D. Estes, Ph.D., Netanya G. Sandler, M.D., Nicole Plass, R.N., Deborah L. Stone, M.D., Maria L. Turner, M.D., Suvimol Hill, M.D., John A. Butman, M.D., Ph.D., Rayfel Schneider, M.D., Paul Babyn, M.D., Hatem I. El-Shanti, M.D., Elena Pope, M.D., Karyl Barron, M.D., Xinyu Bing, B.S., Arian Laurence, M.D., Chyi-Chia R. Lee, M.D., Ph.D., Dawn Chapelle, R.N., Gillian I. Clarke, M.D., Kamal Ohson, M.D., Marc Nicholson, M.D., Massimo Gadina, Ph.D., Barbara Yang, B.S., Benjamin D. Korman, B.S., Peter K. Gregersen, M.D., P. Martin van Hagen, M.D., A. Elisabeth Hak, M.D., Marjan Huizing, Ph.D., Proton Rahman, M.D., Daniel C. Douek, M.D., Ph.D., Elaine F. Remmers, Ph.D., Daniel L. Kastner, M.D., Ph.D., and Raphaela Goldbach-Mansky, M.D.

N Eng J Med 2009; 360: 2426

An Autoinflammatory Disease Due to Homozygous Deletion of the *IL1RN* Locus

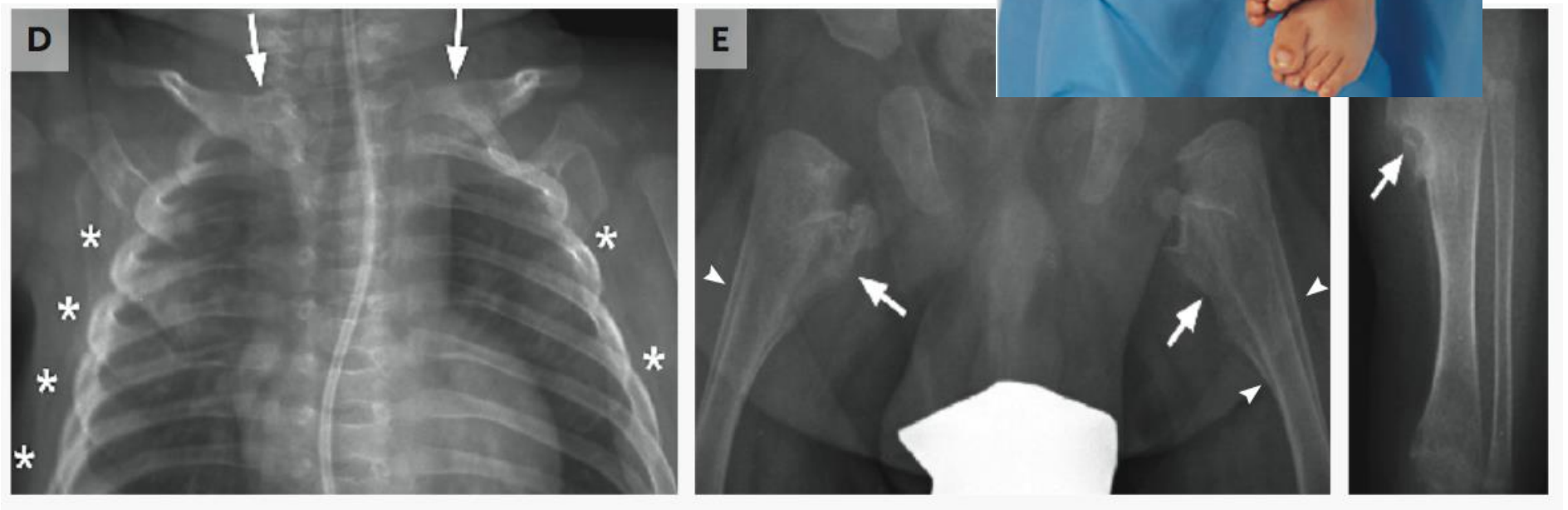
Sreelatha Reddy, Ph.D., Shuang Jia, M.S., Rhonda Geoffrey, B.S., Rachel Lorier, B.S., Mariko Suchi, M.D., Ph.D., Ulrich Broeckel, M.D., Martin J. Hessner, Ph.D., and James Verbsky, M.D., Ph.D.

N Eng J Med 2009; 360: 2438

Enfermedades autoinflamatorias



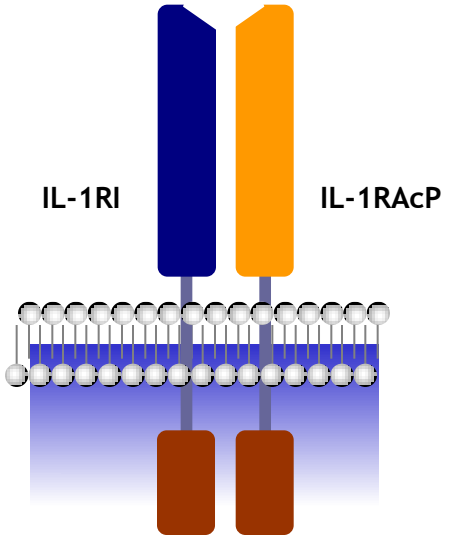


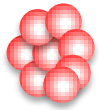
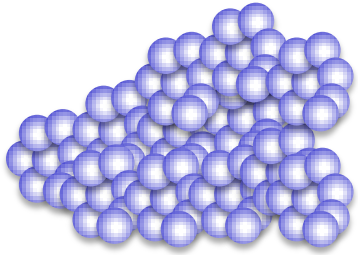
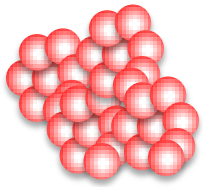
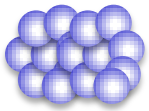
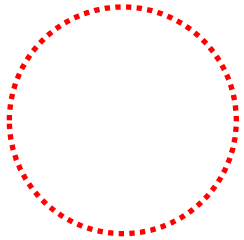


N Eng J Med 2009; 360: 2426

IL-1Ra **ANTAGONISTAS**

AGONISTAS IL-1β - IL-1α



	IL-1 beta (Agonista)	IL-1Ra (Antagonista)	
Individuo Sano			Equilibrio
CAPS			↑↑↑ IL-1beta
DIRA			anakinra



Before treatment



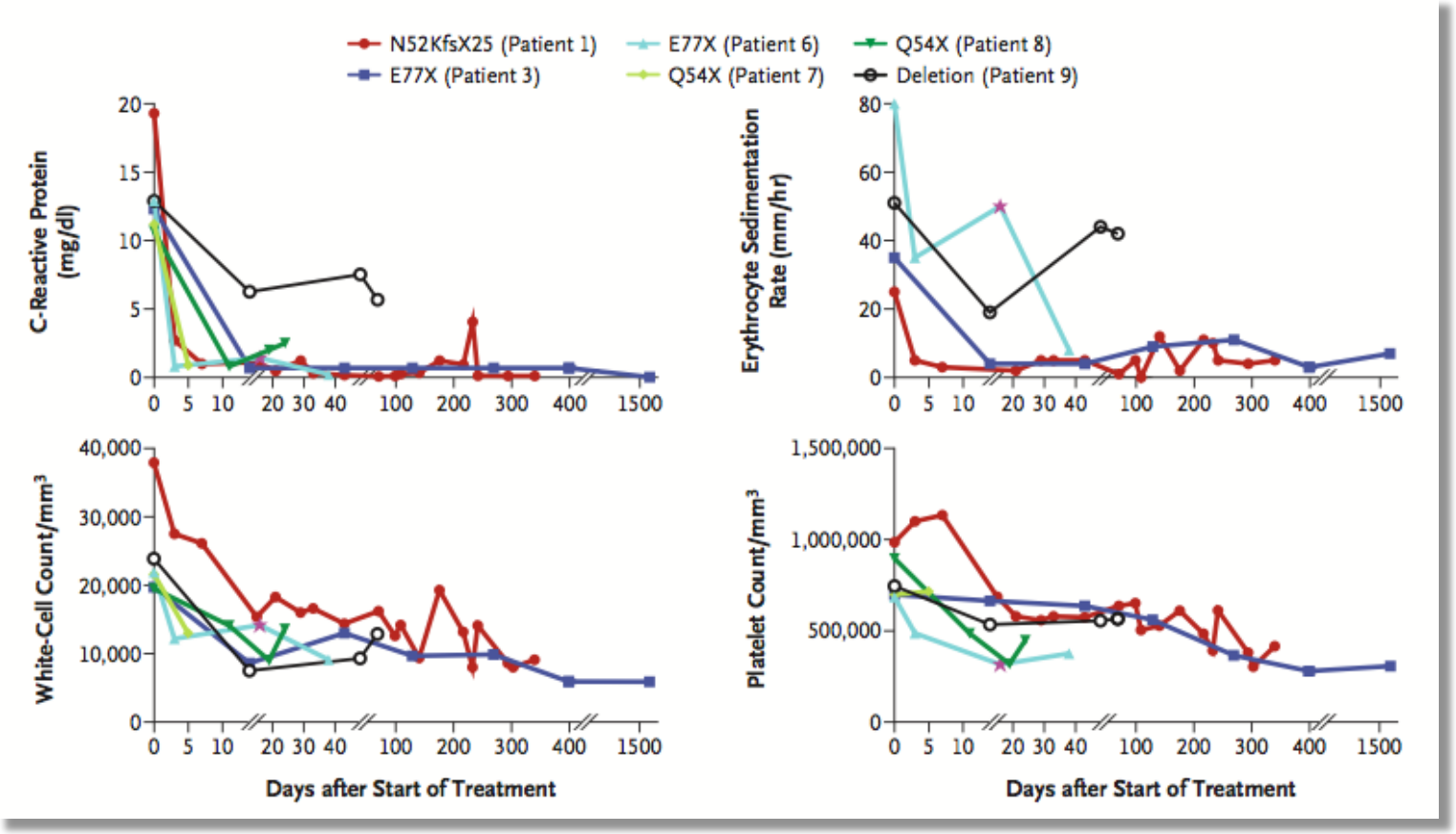
After treatment



7 días

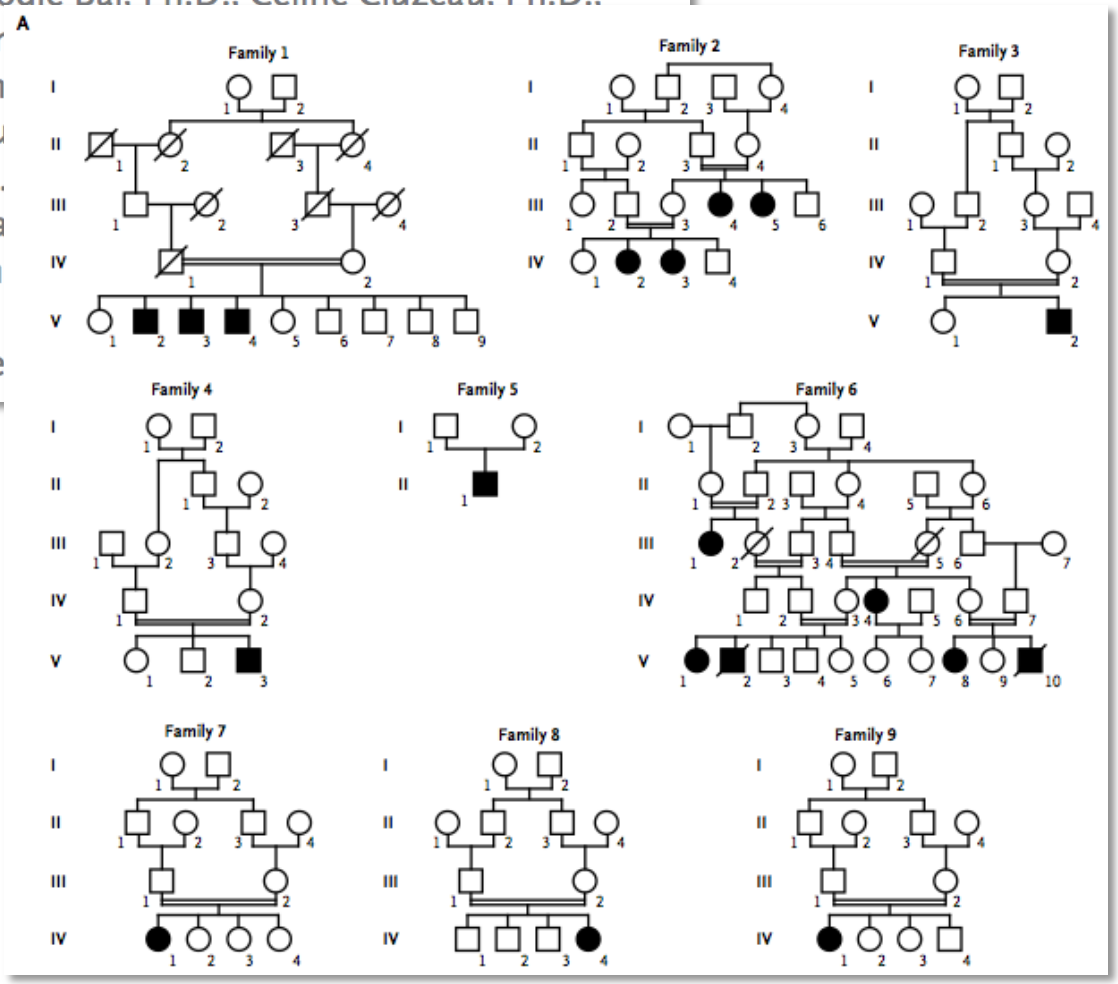


N Eng J Med 2009; 36(



Interleukin-36–Receptor Antagonist Deficiency and Generalized Pustular Psoriasis

Slaheddine Marrakchi, M.D., Ph.D., Philippe Guigue, Ph.D.,
Blair R. Renshaw, B.S., Anne Puel, Ph.D., Xue-Yuan Pei, Ph.D.,
Sylvie Fraitag, M.D., Jihen Zribi, M.D., Elodie Bal. Ph.D.. Céline Cluzeau. Ph.D..
Maya Chrabieh, M.Sc., Jennifer E. Towr
Christian Pons, M.Sc., Sourour Man
Hafedh Makni, M.D., Nadia Mahfou
Christine Bodemer, M.D., Ph.
Smail Hadj-Rabia, M.D., Ph.D., Michel Fa
Mourad Sahbatou, Ph.D., Arn
Jean-Laurent Casanova, M.D.,
Hamida Turki, M.D., Ph.D., Hervé Bachele



Debut





Cortesía de la Dra. Vicente - Hospital Sant Joan de Deu



N Eng J Med 2011; 365: 620

Mutations in *IL36RN/IL1F5* Are Associated with the Severe Episodic Inflammatory Skin Disease Known as Generalized Pustular Psoriasis

Alexandros Onoufriadis,[1,4] Michael A. Simpson,[1,4] Andrew E. Pink,[2] Paola Di Meglio,[2] Catherine H. Smith,[2] Venu Pullabhatla,[1] Jo Knight,[1] Sarah L. Spain,[1] Frank O. Nestle,[2] A. David Burden,[3] Francesca Capon,[1] Richard C. Trembath,[1,*] and Jonathan N. Barker[2,*]

Am J Hum Genet 2011; 89: 432

Whole exome sequencing

Table 2. Numbers of Candidate Genes Highlighted by Exome Sequencing

Any x of five individuals	1	2	3	4	5
Genes with homozygous or compound-heterozygous nonsynonymous, splice-site, or insertion/deletion variants	6721	5141	4030	3108	2162
With an estimated frequency < 0.01	80	5	1	0	0

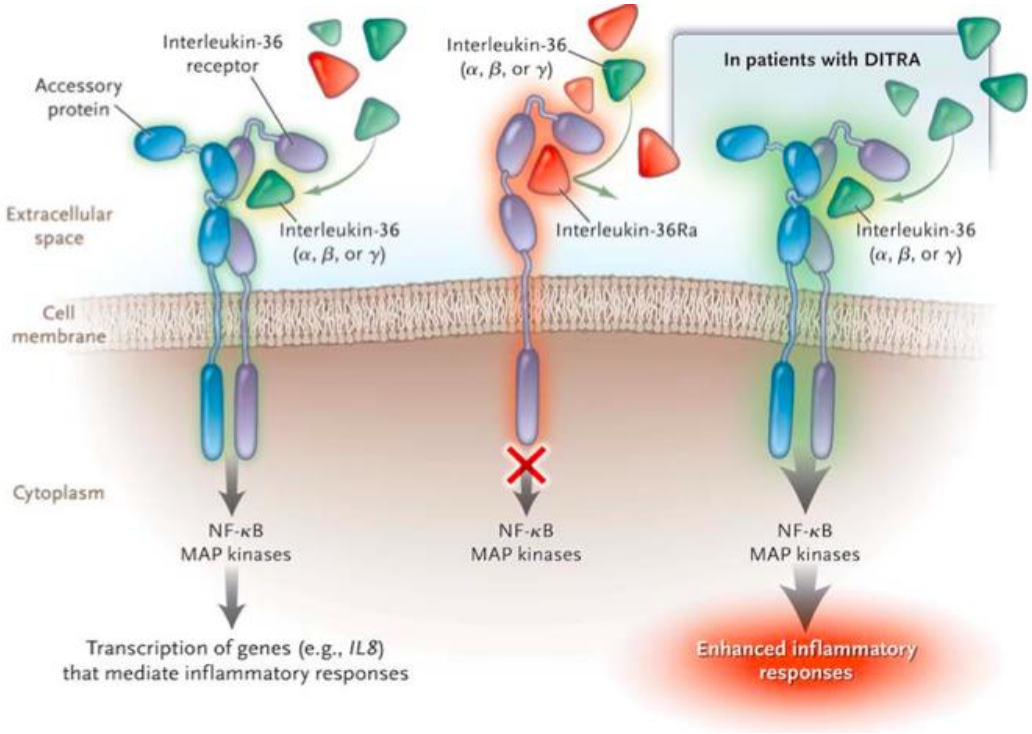


IL36RN

Table 1. Clinical and Genetic Data for the Five GPP Cases in Whom Exome Sequencing Was Performed

Individual	Gender	Ethnicity	Age at Onset (years)	GPP	PPP	CPP	Inflammatory Arthritis	Triggers of Exacerbations	Past Treatments / Response[a]	Systemic Features during Flares
GPP-01 II:5	female	European	51	yes	no	no	no	stress	acitretin / no methotrexate / no ciclosporin / yes fumaderm / no etanercept / initial infliximab / initial adalimumab / partial	fever > 38°C: yes malaise: yes CRP > 100 mg/l: yes ESR > 50 mm/hr: yes neutrophilia > 15 × 10^9/l: yes
GPP-02 II:1	male	European	5	yes	no	no	no	stress, medication (penicillin, codeine), viral infection	prednisolone / yes acitretin / no methotrexate / yes ciclosporin / yes	fever > 38°C: yes malaise: yes CRP > 100 mg/l: yes ESR > 50 mm/hr: yes neutrophilia > 15 × 10^9/l: yes
GPP-03 II:2	female	European	7	yes	no	no	no	stress, medication (paracetamol), viral infection, pregnancy	prednisolone / yes acitretin / no isotretinoin / no methotrexate / yes ciclosporin / yes infliximab / yes	fever > 38°C: yes malaise: yes CRP > 100 mg/l: yes ESR > 50 mm/hr: yes neutrophilia > 15 × 10^9/l: yes
GPP-04 I:1	female	European	10	yes	yes	no	no	stress, pregnancy	prednisolone / no methotrexate / yes ciclosporin / no infliximab / yes	fever > 38°C: yes malaise: yes CRP > 100 mg/l: no ESR > 50 mm/hr: yes neutrophilia > 15 × 10^9/l: yes
GPP-05 I:1	female	European	45	yes	yes	no	no	-	acitretin / yes ciclosporin / yes	fever > 38°C: no malaise: no CRP > 100 mg/l: no ESR > 50 mm/hr: no neutrophilia > 15 × 10^9/l: no

Am J Hum Genet 2011; 89: 432



N Eng J Med 2011; 365: 620

Recombi
human IL



First Clinical Description of an Infant With Interleukin-36-Receptor Antagonist Deficiency Successfully Treated With Anakinra

AUTHORS: Linda Rossi-Semerano, MD,[a] Maryam Piram, MD,[a] Christine Chiaverini, MD, PhD,[b] Dominique De Ricaud, MD,[c] Asma Smahi, PhD,[d] and Isabelle Koné-Paut, MD, PhD[a]

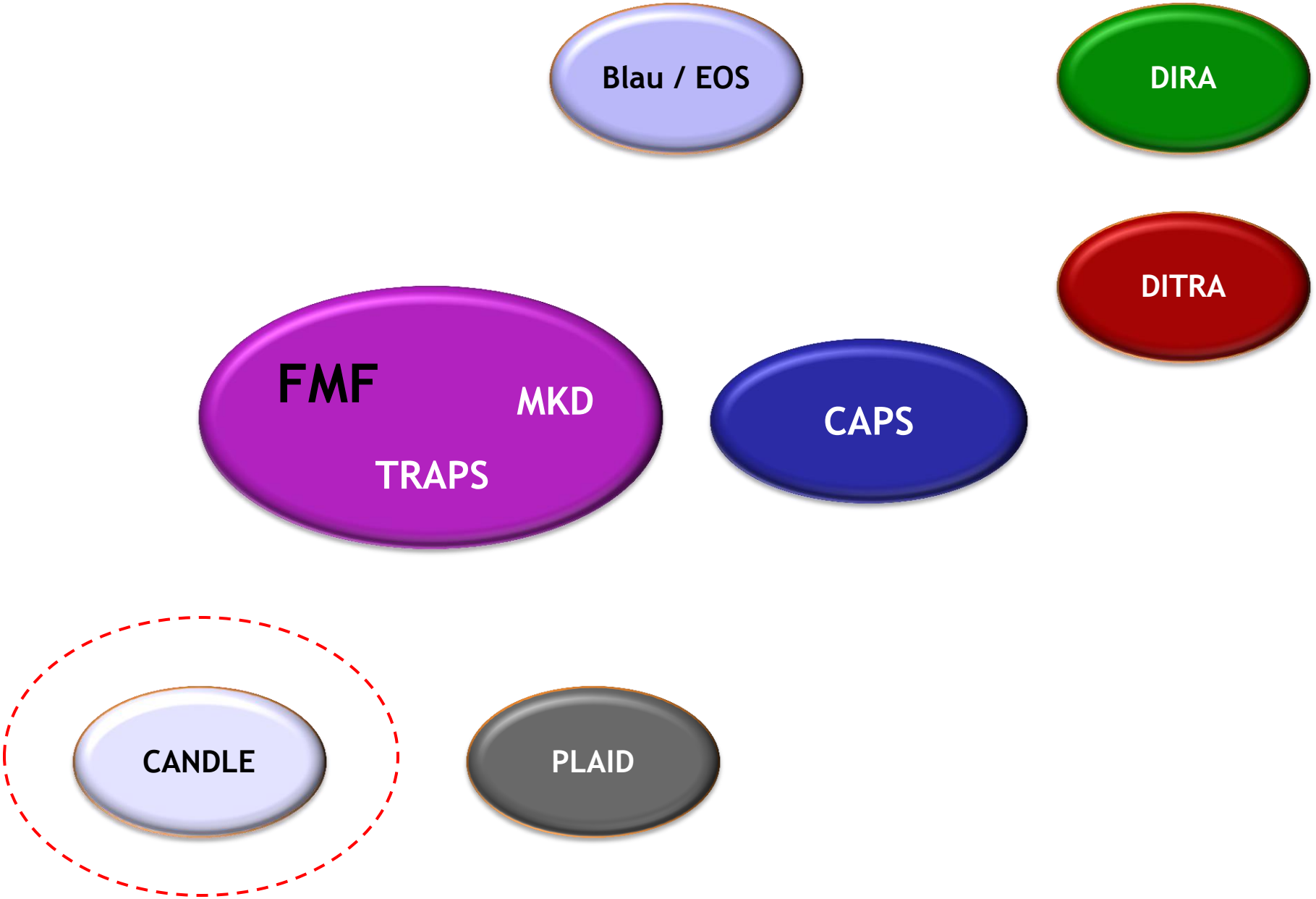
Pediatrics 2013; 132: e1043

Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying *IL36RN* mutations

Hüffmeier U, Wätzold M, Mohr J, Schön MP, Mössner R

British J Dermatol - In press

Enfermedades autoinflamatorias



Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome

Antonio Torrelo, MD,[a] Sapna Patel, MD,[b] Isabel Colmenero, MD,[c] Dolores Gurbindo, MD,[d] Francisco Lendínez, MD,[c] Angela Hernández, MD,[a] Juan Carlos López-Robledillo, MD,[f] Ali Dadban, MD,[g] Luis Requena, MD,[h] and Amy S. Paller, MD[b]

J Am Acad Dermatol 2010; 62: 489-95

An Autosomal Recessive Syndrome of Joint Contractures, Muscular Atrophy, Microcytic Anemia, and Panniculitis-Associated Lipodystrophy

Abhimanyu Garg, Maria Dolores Hernandez, Ana Berta Sousa, Lalitha Subramanyam, Laura Martínez de Villarreal, Heloísa G. dos Santos, and Oralia Barboza

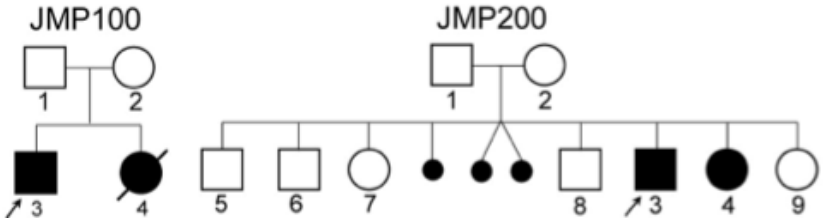
J Clin Endocrinol Metab 2010; 95: E58-E63

Síndrome Nakajo-Nishimura

1939-Nakajo
1950-Nishimura et al.

1975-Kitano et al. (English)

Fiebre Japonesa Familiar



Main Clinical Features

- Early-onset of the disease (<6mo)
- Recurrent fever
- Low weight and height
- Inflammatory markers
- Hypochromic anemia
- Hepatomegaly Splenomegaly
- Neutrophilic dermatosis
- Panniculitis-associated lipodystrophy
- Musculoeskeletal
  - Arthritis
  - Joint contractures
  - Muscular atrophy
- Persistent eyelid violaceous swelling

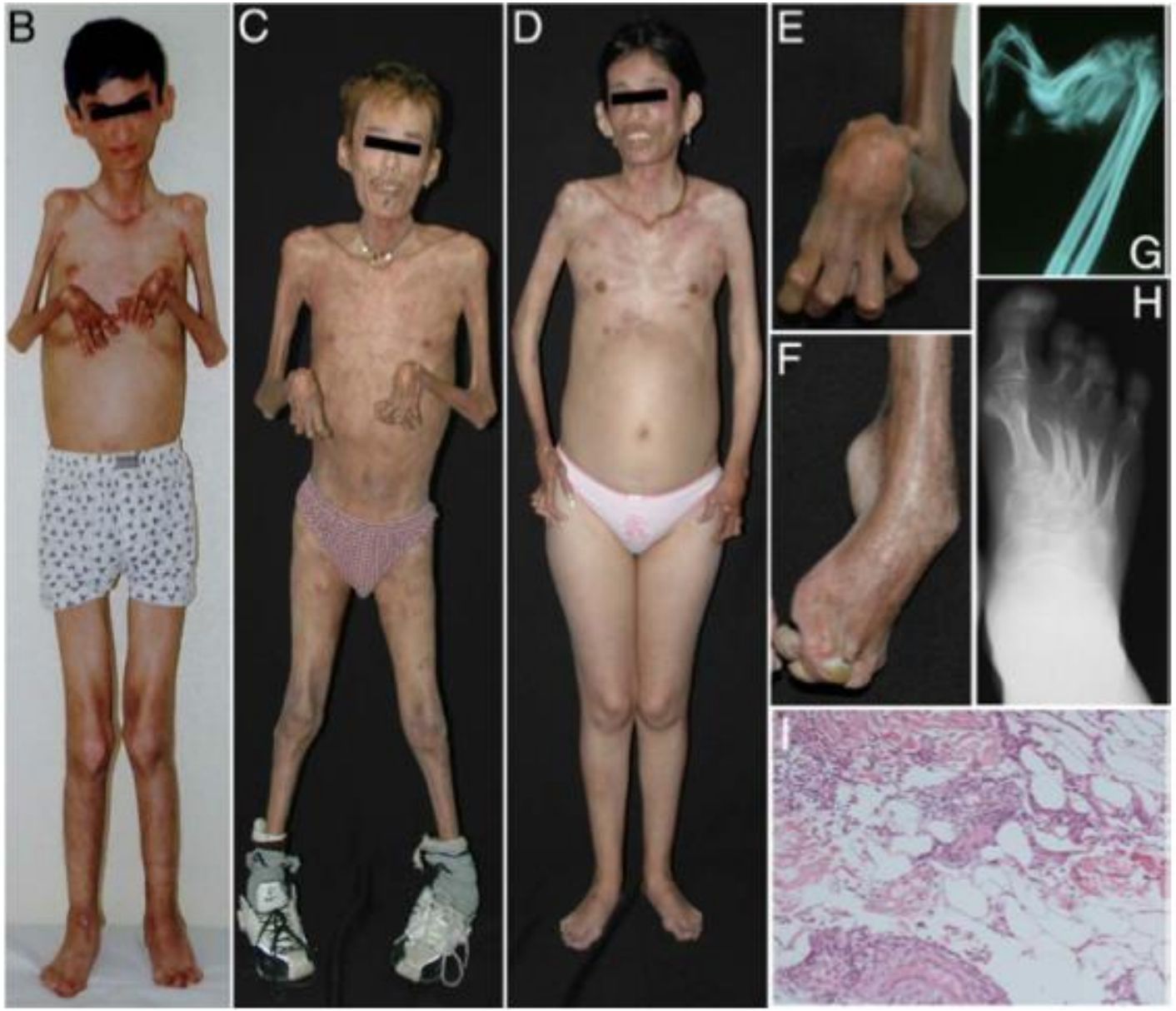




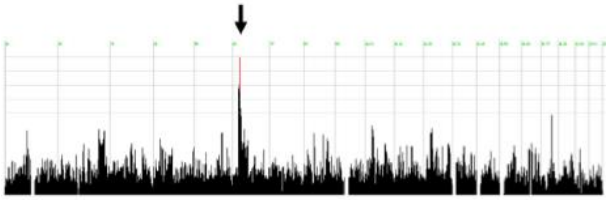




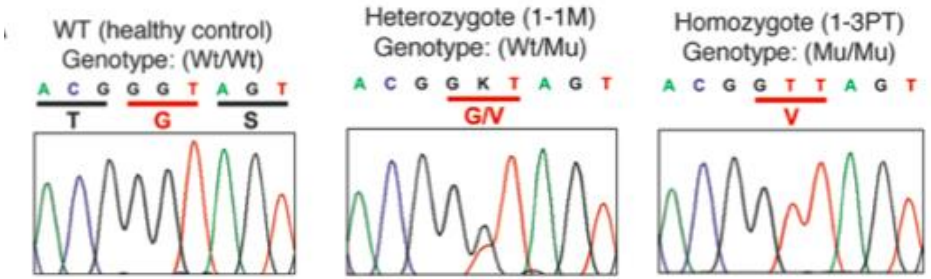
J Am Acad Dermatol 2010; 62: 489-95



J Clin Endocrinol Metab 2010; 95: E58-E63

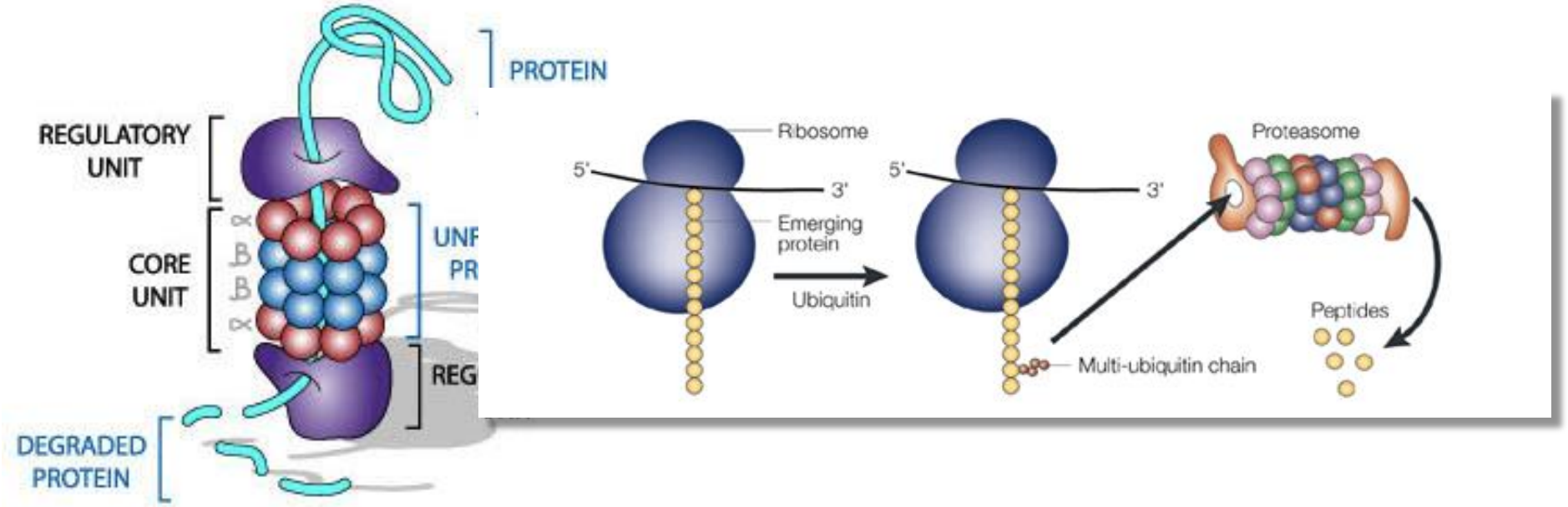


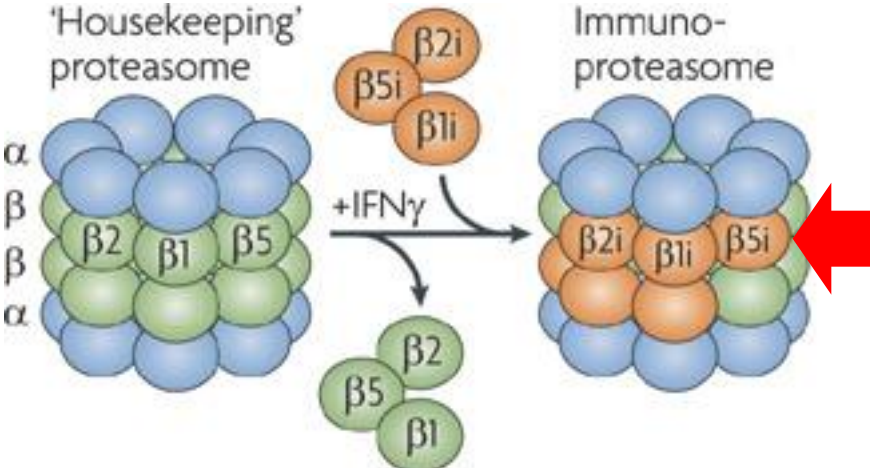


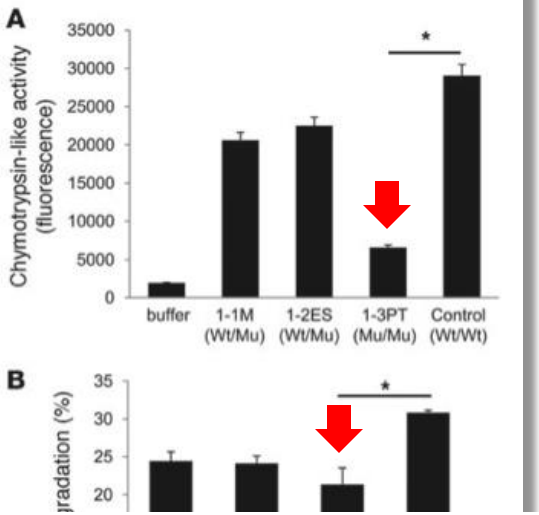


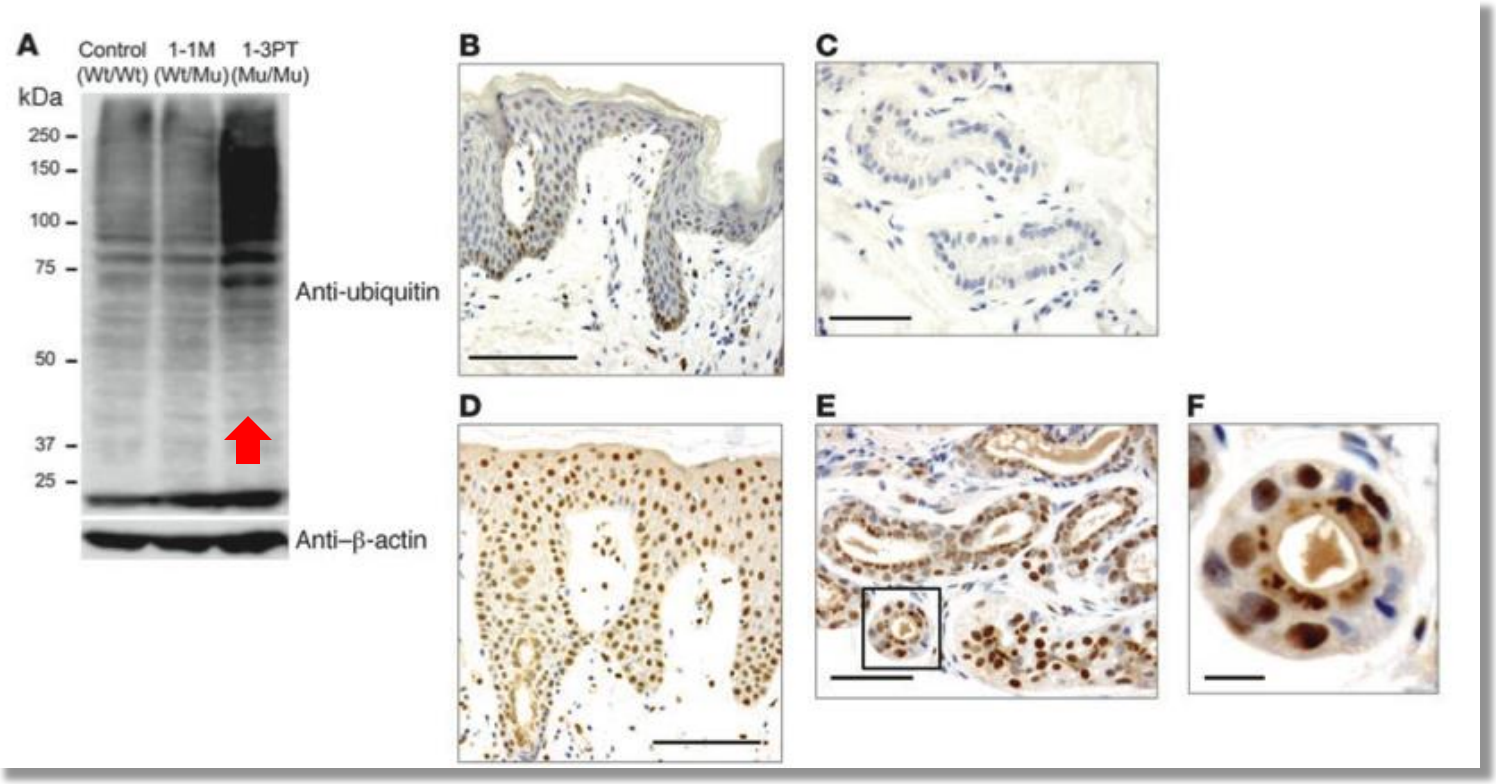
Gen PSMB8

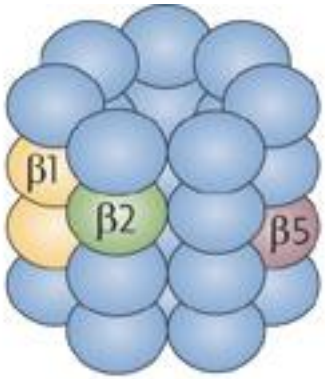
Subunidad ß5i
immunoproteosoma




'Housekeeping' proteasome
Immuno-proteasome
+IFNγ
α
β
β
α
β2
β1
β5
β2i
β5i
β1i


A
Chymotrypsin-like activity (fluorescence)
35000
30000
25000
20000
15000
10000
5000
0
buffer
1-1M (Wt/Mu)
1-2ES (Wt/Mu)
1-3PT (Mu/Mu)
Control (Wt/Wt)
*
B
35
30
25
20
*


A
Control (Wt/Wt)
1-1M (Wt/Mu)
1-3PT (Mu/Mu)
kDa
250
150
100
75
50
37
25
Anti-ubiquitin
Anti–β-actin
B
C
D
E
F

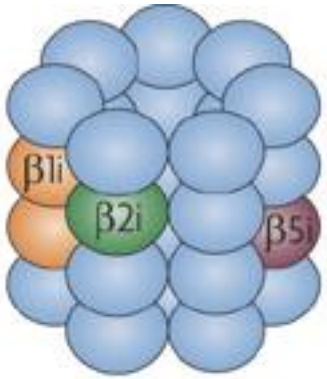


Constitutive proteasome

β1 (PSMB6, Y, δ)

β2 (PSMB7, Z, MC14)

β5 (PSMB5, X, MB1, ε)



Immunoproteasome

β1i (PSMB9, LMP2)

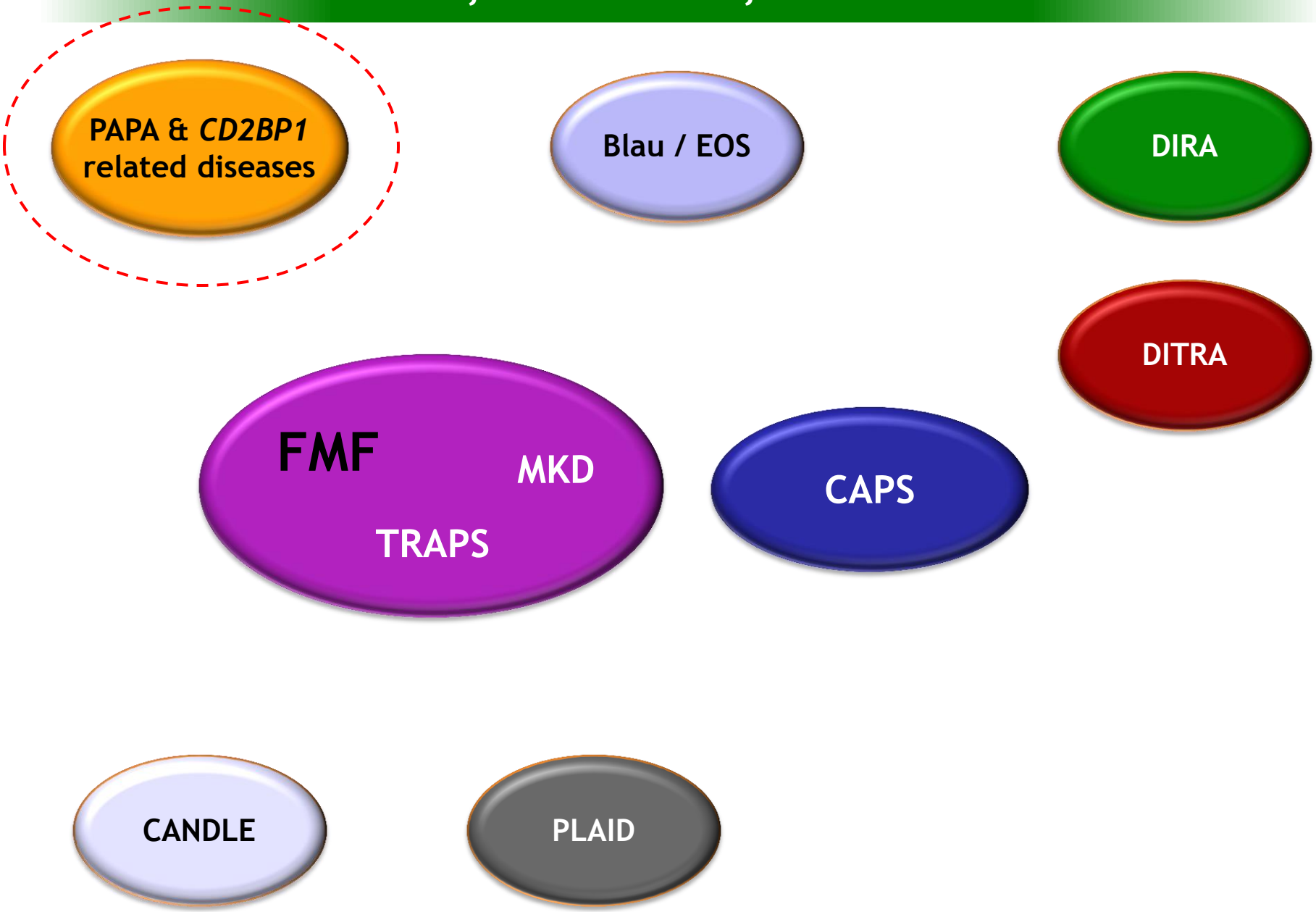
β2i (PSMB10, LMP10, MECL1)

β5i (PSMB8, LMP7)

Herencia digénica

Gen PSMB8
Gen PSMB9
Gen PSMA3
Gen PSMA4

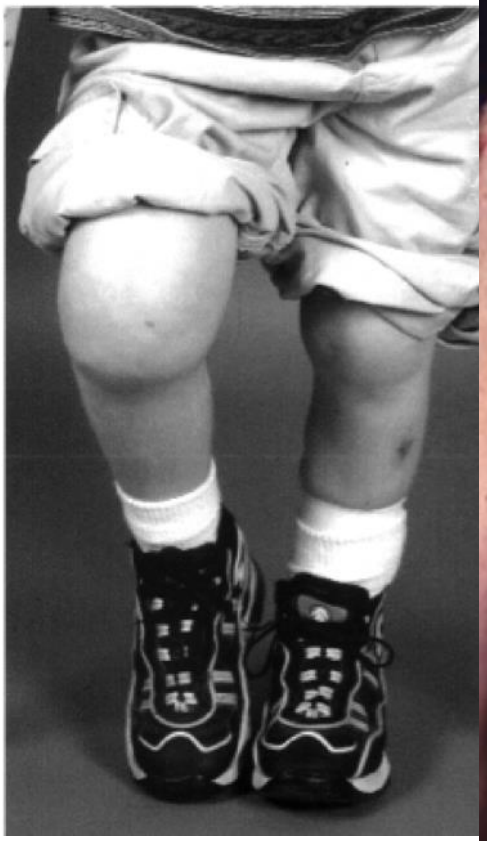
Enfermedades autoinflamatorias



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

NORALANE M. LINDOR, M.D., TODD M. ARSENAULT, M.D., HERMAN SOLOMON, M.D., CHRISTINE E. SEIDMAN, M.D., AND MARIAN T. MCEVOY, M.D.

Mayo Clin Proc 1997; 72: 611



Hum Mol Genet 2002; 11: 961



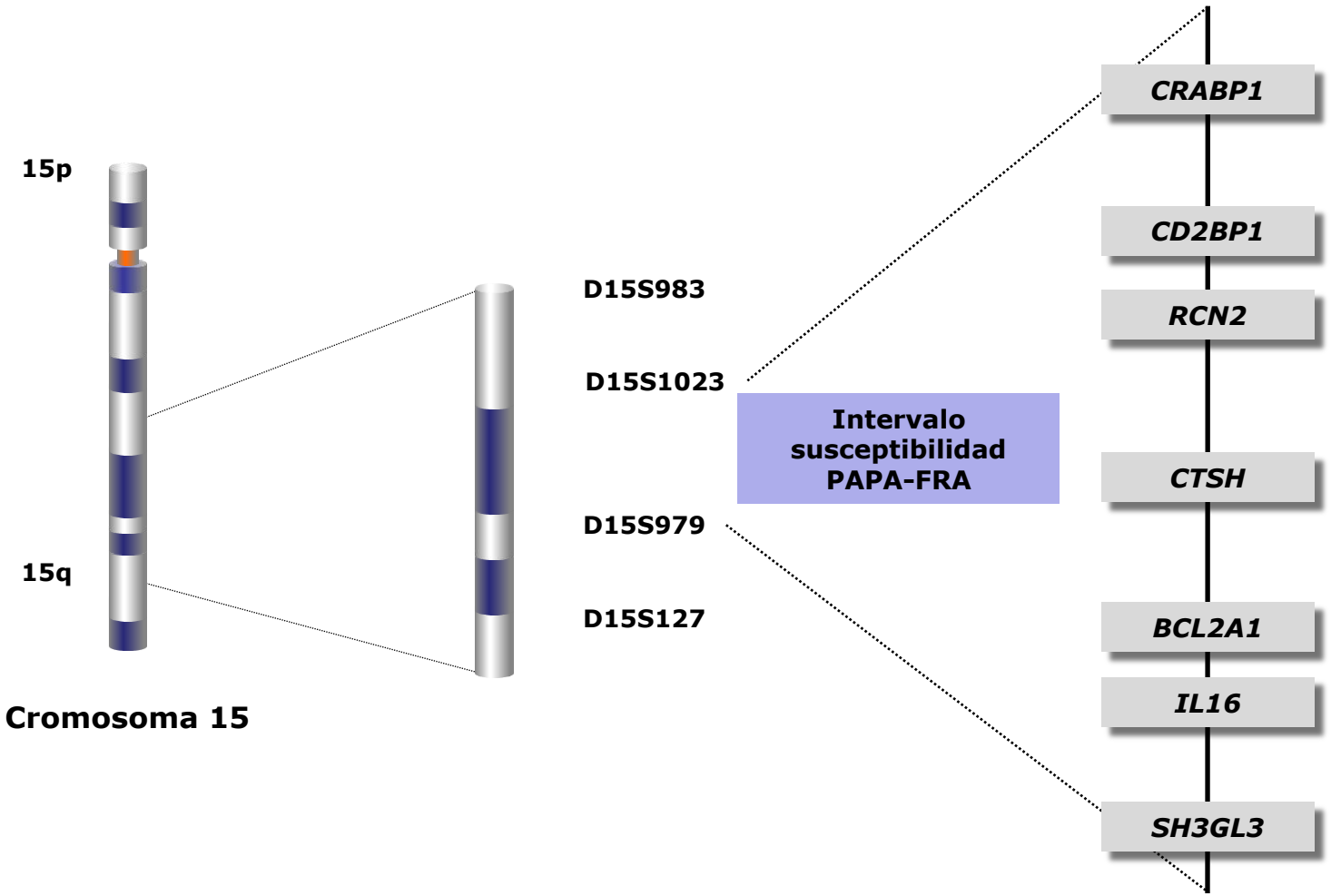


diatric Dermatology 2005; 22: 262

LOCALIZATION OF A GENE FOR FAMILIAL RECURRENT ARTHRITIS

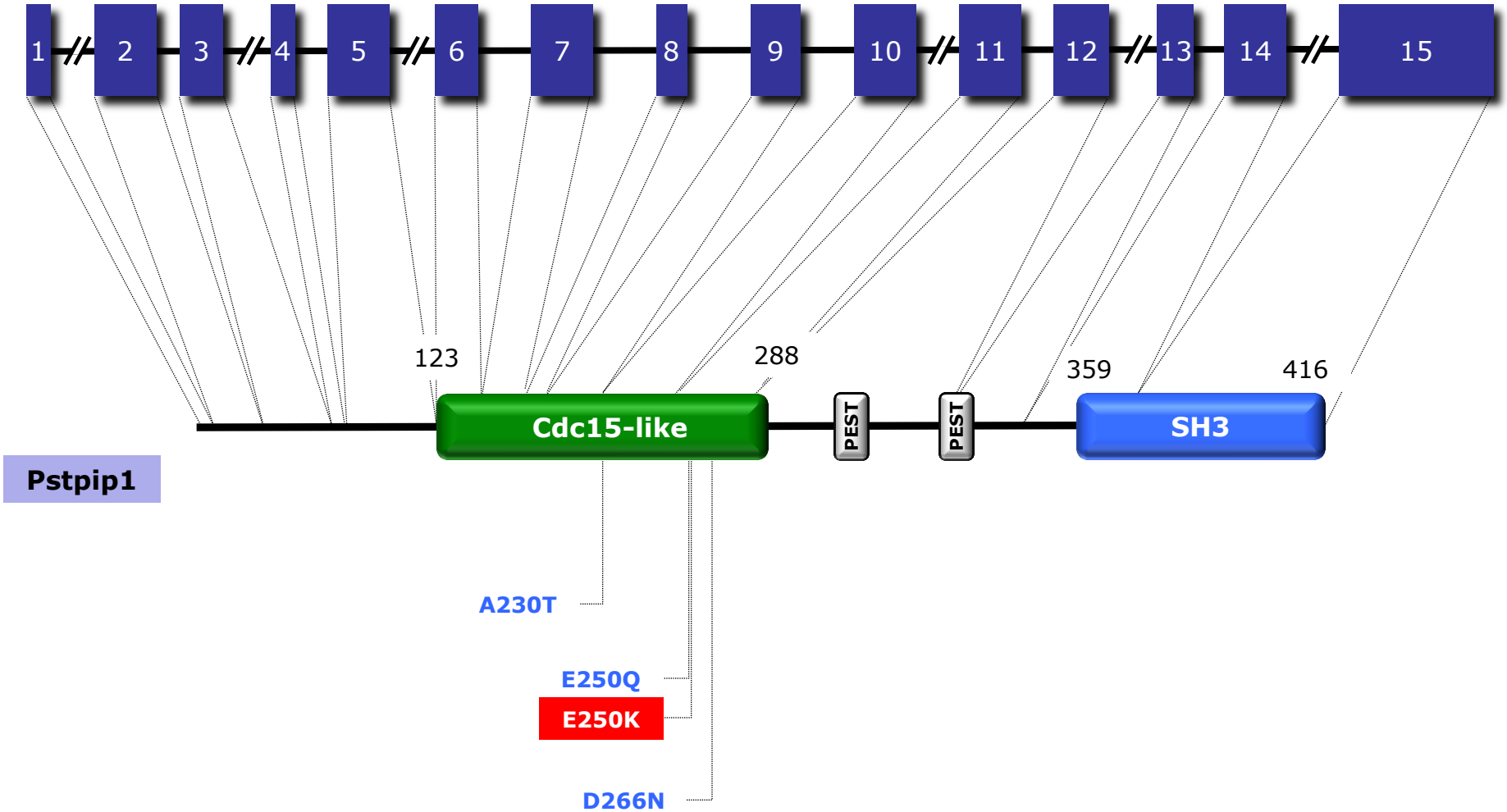
CAROL A. WISE, LYNDA B. BENNETT, VIRGINIA PASCUAL, JOSEPH D. GILLUM, and ANNE M. BOWCOCK

Arthritis Rheum 2000; 43: 2041



Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder

Wise CA, et al. Hum Mol Genet 2002; 11: 961



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

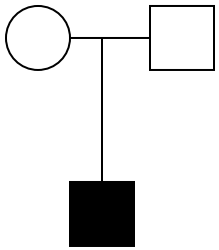
Barry Sampson, Magne K Fagerhol, Cord Sunderkötter, Barbara E Golden, Peter Richmond, Nigel Klein, Ilya Z Kovar, John H Beattie, Beata Wolska-Kusnierz, Yoshiaki Saito, Johannes Roth

Lancet 2002; 360: 1742-45

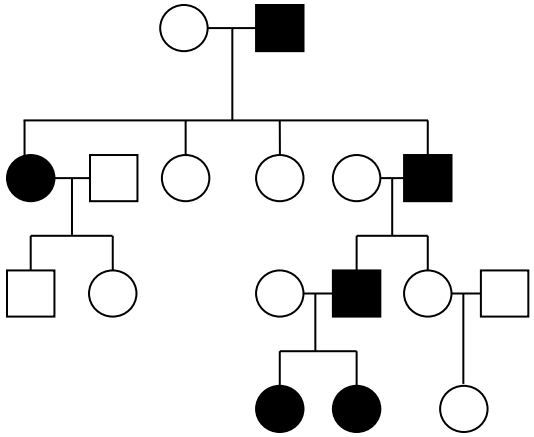
	Age (y)	Sex	Onset	Arthritis	Stunted growth	Hepato-splenomegaly
Patient	14	M	Neonate	+	+	+
Mother	35	F	9 y	+	–	+
Hambidge et al[3]	18	M	Infancy	+	—	—
Sampson et al,[4] Richmond et al[6]	11	M	Neonate	–	+	+

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

J Pediatr 2002; 140: 267-9



CASOS ESPORÁDICOS



CASOS FAMILIARES

	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.

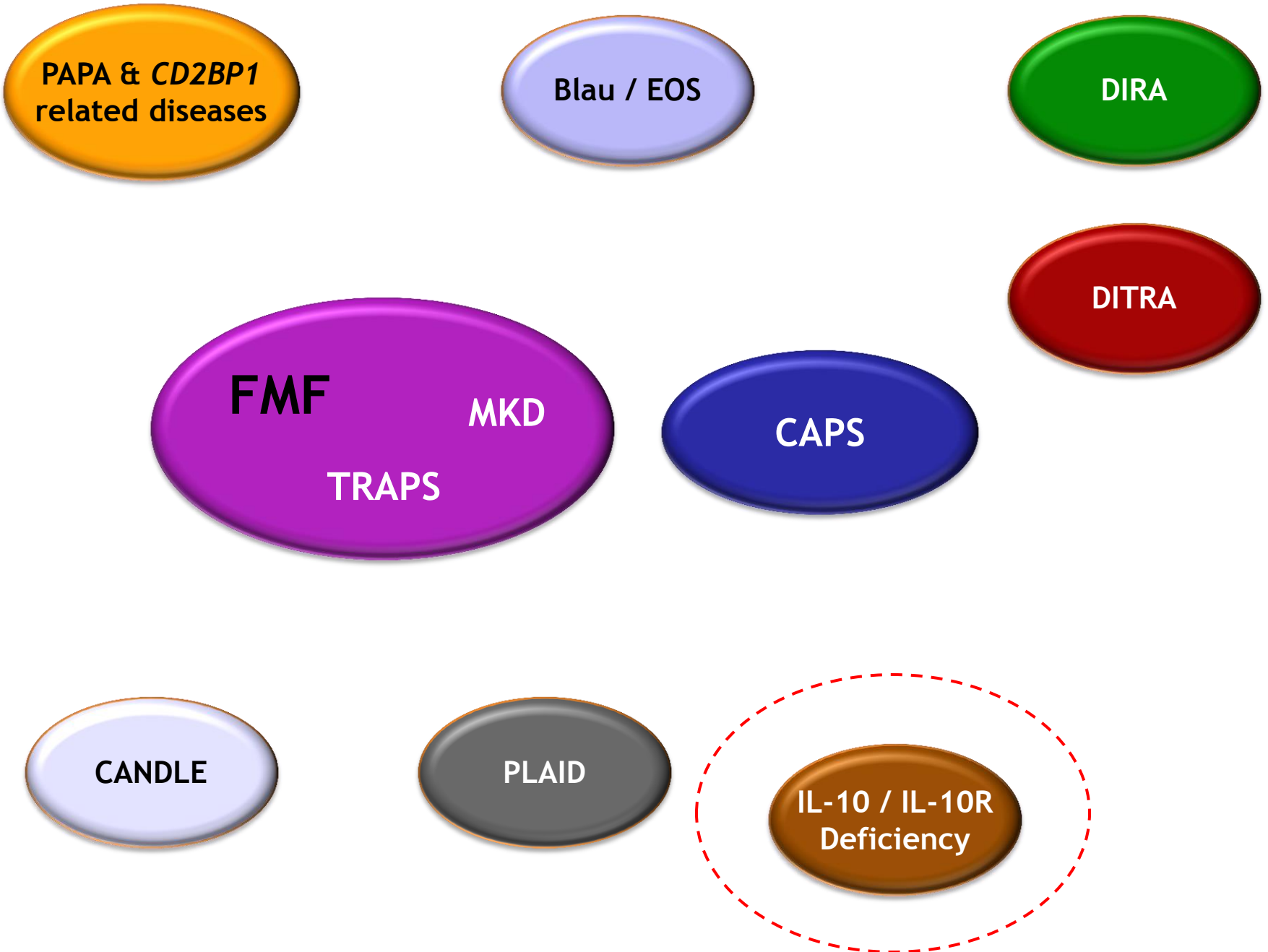
Lancet 2002; 360: 1742-45





Zn **Calprotectin**

Enfermedades autoinflamatorias

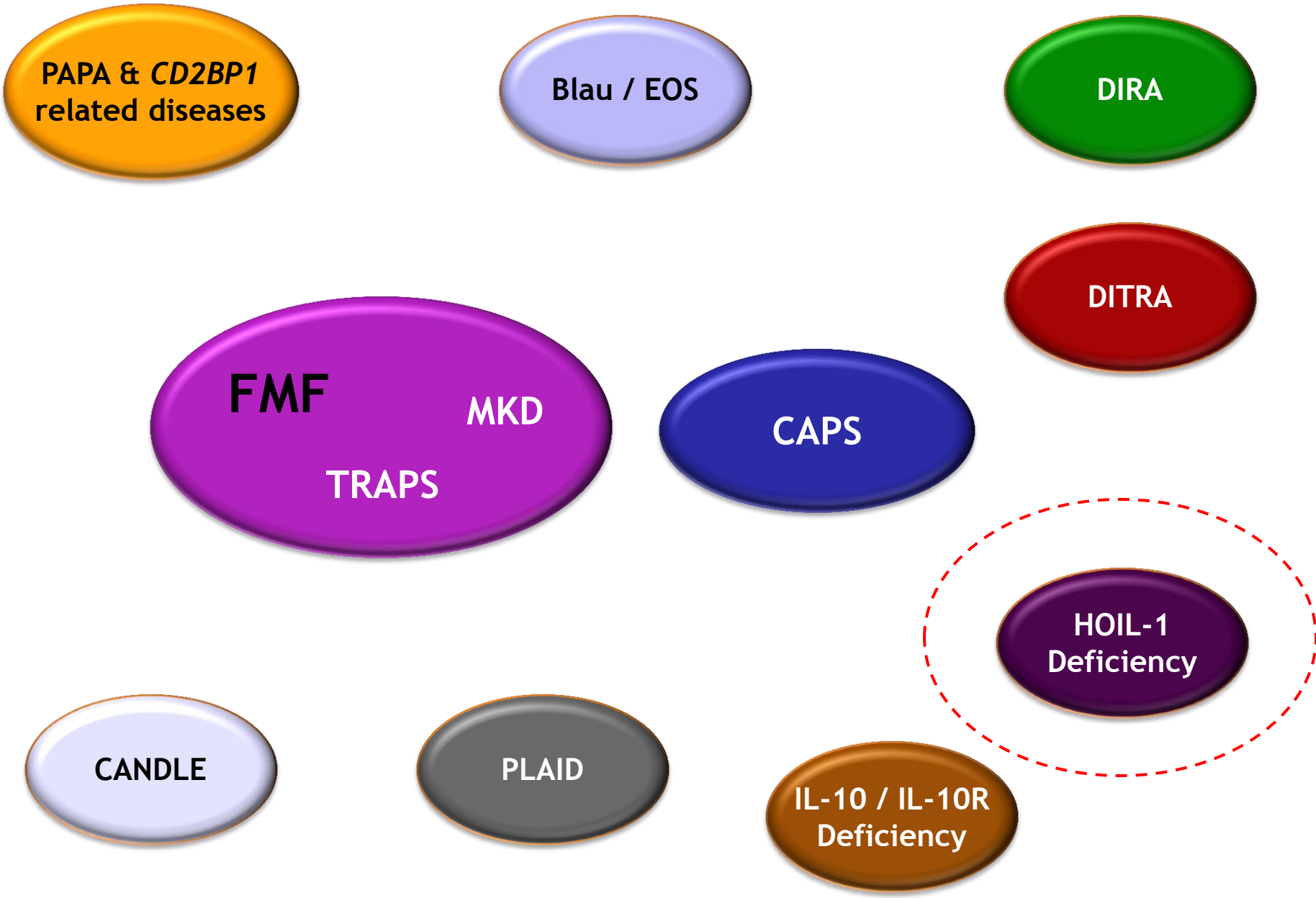


Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

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., and Christoph Klein, M.D., Ph.D.

N Eng J Med 2009; 361:2033-45

Enfermedades autoinflamatorias



Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency

Bertrand Boisson[1,18], Emmanuel Laplantine[2,18], Carolina Prando[1,18], Silvia Giliani[3], Elisabeth Israelsson[4], Zhaohui Xu[5], Avinash Abhyankar[1], Laura Israël[6,7], Giraldina Trevejo-Nunez[1], Dusan Bogunovic[1], Alma-Martina Cepika[5], Donna MacDuff[8], Maya Chrabieh[6,7], Marjorie Hubeau[6,7], Fanny Bajolle[9], Marianne Debré[10], Evelina Mazzolari[3], Donatella Vairo[3], Fabrice Agou[11], Herbert W Virgin[8], Xavier Bossuyt[12], Caroline Rambaud[13], Fabio Facchetti[14], Damien Bonnet[7,9], Pierre Quartier[7,10], Jean-Christophe Fournet[7,15], Virginia Pascual[5], Damien Chaussabel[4,5], Luigi D Notarangelo[16], Anne Puel[6,7], Alain Israël[2,18], Jean-Laurent Casanova[1,6,7,10,18] & Capucine Picard[6,7,10,17,18]

Nat Immunol 2012; 13: 1178-86


« Sólo sé
que quieren
que no sepa
nada »

Facultativos

.....

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Pacientes y familias

Unidad de Enfermedades Autoinflamatorias

Fina Rius

María Carmen Antón

Anna Mensa

Eva González Roca

Estíbaliz Ruiz Ortiz de Arrizabaleta

Jordi Yagüe


Muchas gracias por su atención