# Autoinflammatory Syndromes

João Bosco Oliveira, MD, PhD
IMIP-PE, Brazil
bosco.oliveira@imip.org.br

# Most common genetically defined

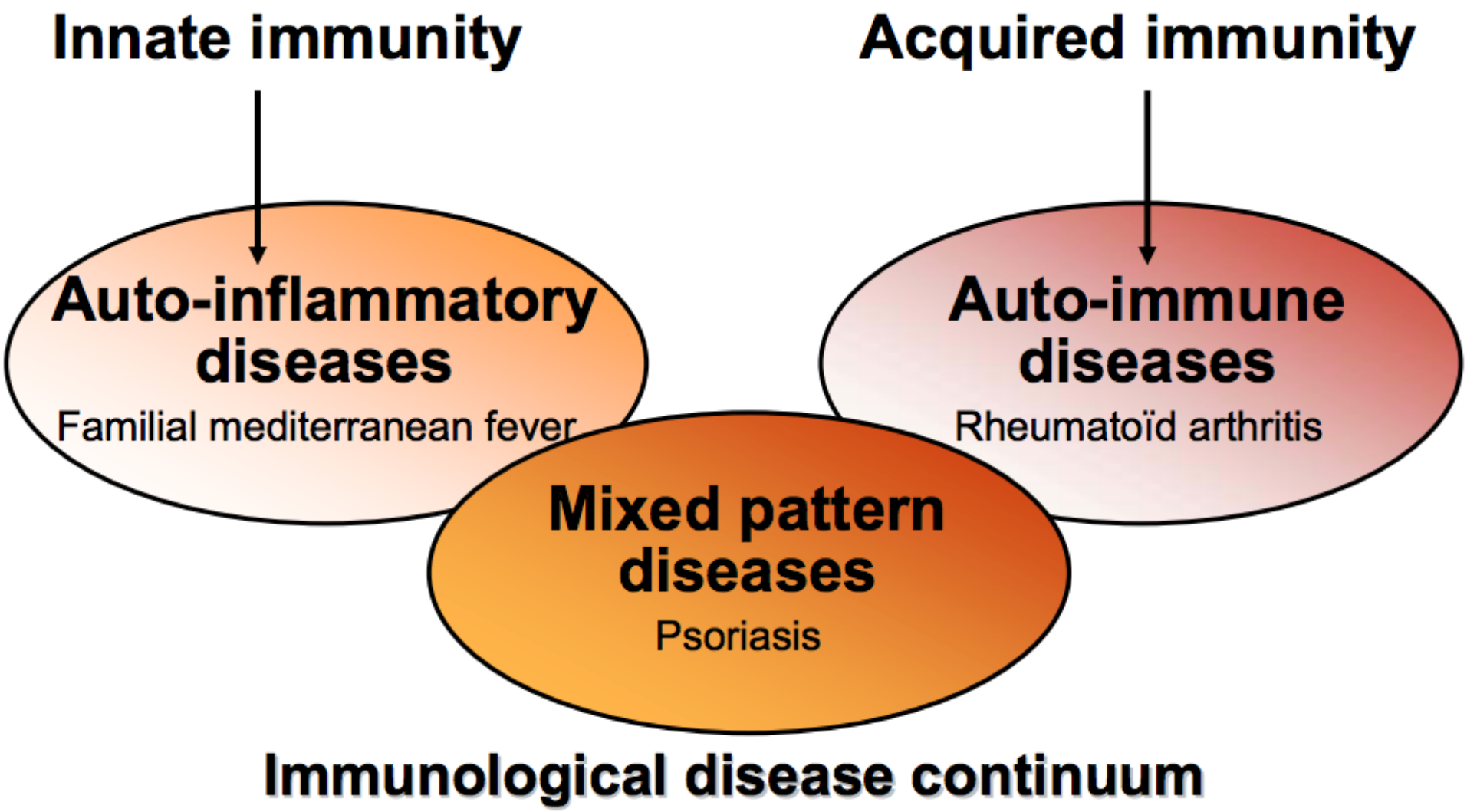
- Familial Mediterranean fever
- TNF-receptor associated period fever syndrome
- Cryopirinopathies
- Hiper IgD
- DIRA
- Many others: Blau, PAPA, PFAPA, HID, Majeed, Behcets, etc.

# Periodic Fever Syndromes

- Heberden, 1806: "pains which are regularly intermittent, the fits of which return periodically as those of an ague… ... such parts suffer in days and recur for years at remarkably regular short intervals. At that time periodic such a manner"
- Osler, 1895: Recurrent pain affecting the abdmones, thorax and extremities;
- Janeway e Rosenthal, 1908: 16 yo Jewish girl with recurrent abdominal pain + fever
- Reinman, 1948 coined the term
- Kastner, 1999, coined autoinflammatory

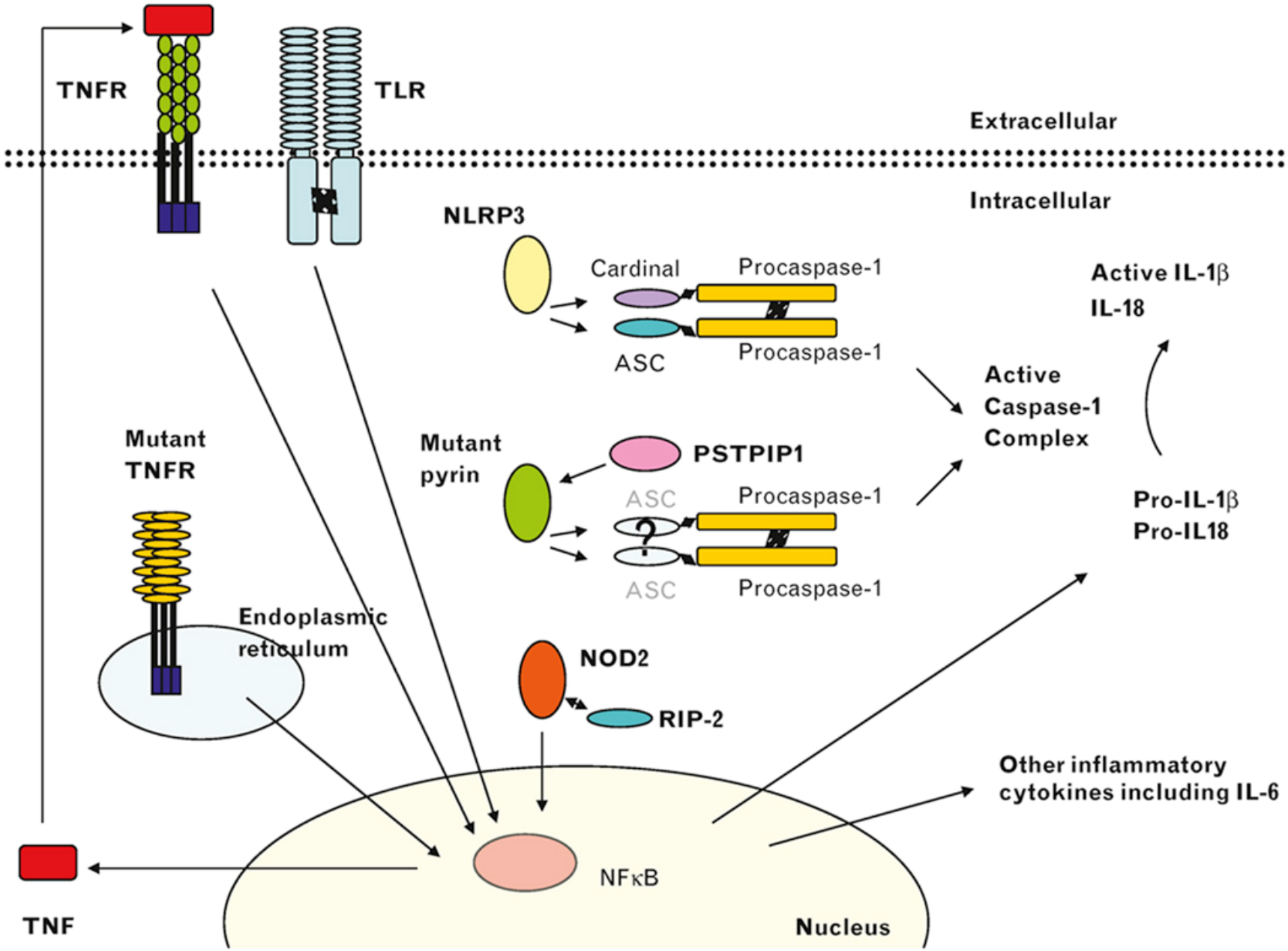
Heberden W. Commentaries on history and care of disease. London 1806; Chapter 29: p 151.
Osler W. On the visceral manifestations of erythema multiforme. Am J Med Sci 1895; 110: 629.
Janeway TC, Mosenthal HO. Trans Ass Am Phys 1908; 23: 504-18.
Reimann HA. Periodic disease. JAMA 1948; 141: 239-44.

# Autoreactive Phenomena



# Timeline of AIS Genetic Discoveries

| | |
|---|---|
| FFM | 1997 |
| TRAPS + HIDS | 1999 |
| FCAS/MWS/NOMID+BLAU | 2001 |
| PAPA | 2002 |
| Majeed | 2005 |
| DIRA | 2009 |
| DITRA | 2011 |
| Psoriasis + CANDLE/JMP | 2012 |


TNFR
TLR
Extracellular
Intracellular
NLRP3
Cardinal
Procaspase-1
ASC
Procaspase-1
Active IL-1β
IL-18
Active
Caspase-1
Complex
Mutant
TNFR
Mutant
pyrin
PSTPIP1
ASC
Procaspase-1
?
ASC
Procaspase-1
Pro-IL-1β
Pro-IL18
Endoplasmic
reticulum
NOD2
RIP-2
Other inflammatory
cytokines including IL-6
NFκB
TNF
Nucleus

# Cryopyrin Associated Diseases

- Mutations in *NLRP3* (CIAS1), coding for Cryopyrin*;*
- *Neonatal-Onset Multisystem Inflammatory Disease* (NOMID)/ *Chronic Infantile Neurologic Cutaneous Articular Syndrome* (CINCA)
- Muckle-Wells Syndrome
- *Familial Cold Autoinflammatory Syndrome (FCAS)*

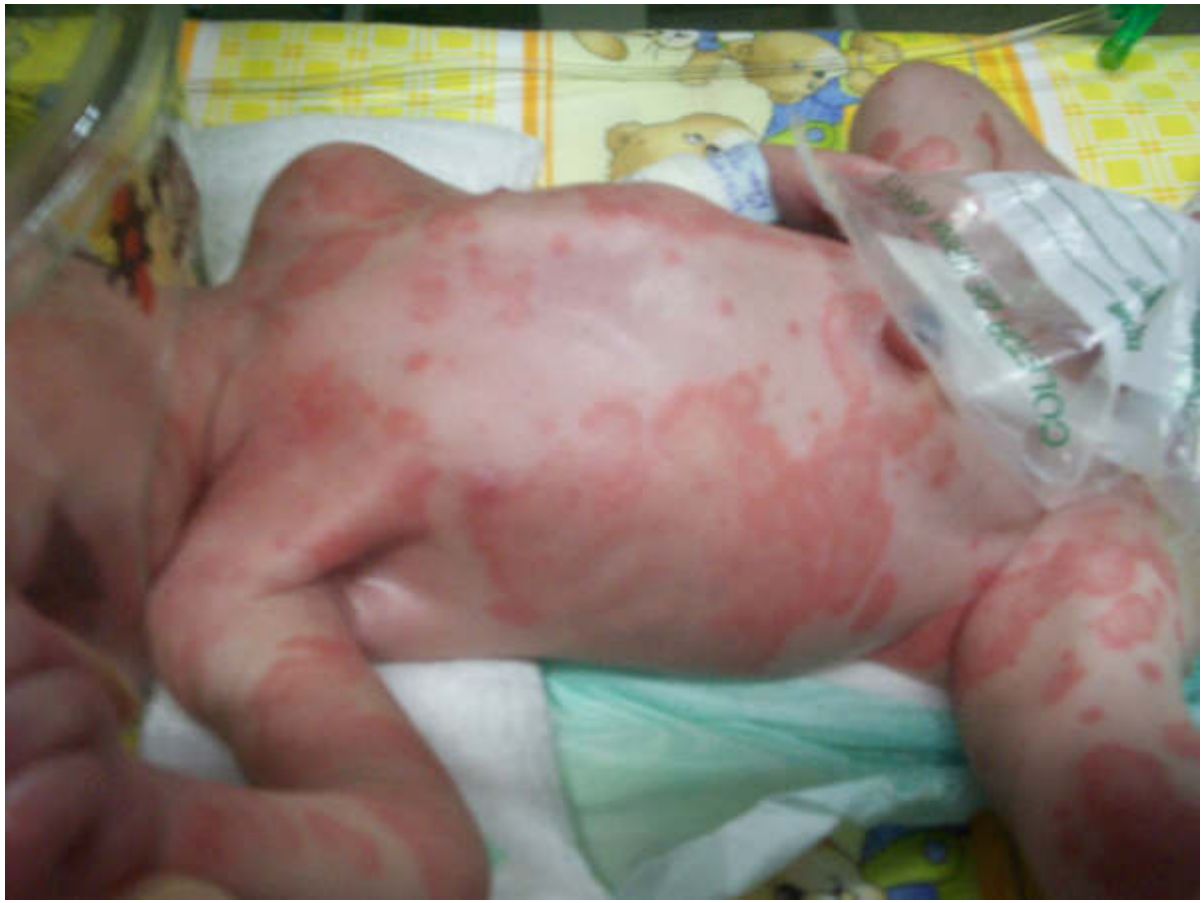
Hofman H et al, Nat Genet 2001; 29:301–5; Feldmann J, et al Am J Hum Genet 2002; 71:198–203

# NOMID- Clinical Findings

- Severe, early neonatal period;
- Triad: (almost continuous fever +) arthropathy, rash and CNS inflammation;
- Diffuse urticarial rash, non pruriginous (~100%);
- Arthropathy with frontal bossing, patella enlargement, deformities(50%);
- CNS: chronic meningites with headaches, seizures, mental retardation, speasticity and cranial nerves palsy.

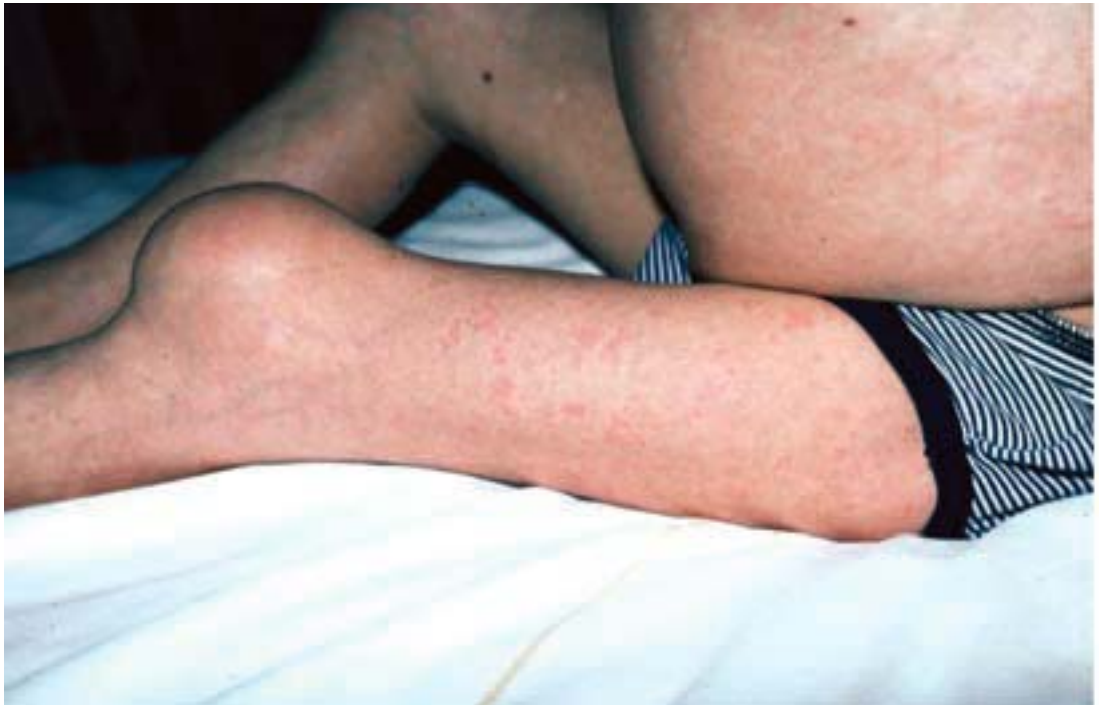
Prieur AM, Griscelli C. Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. J Pediatr. 1981

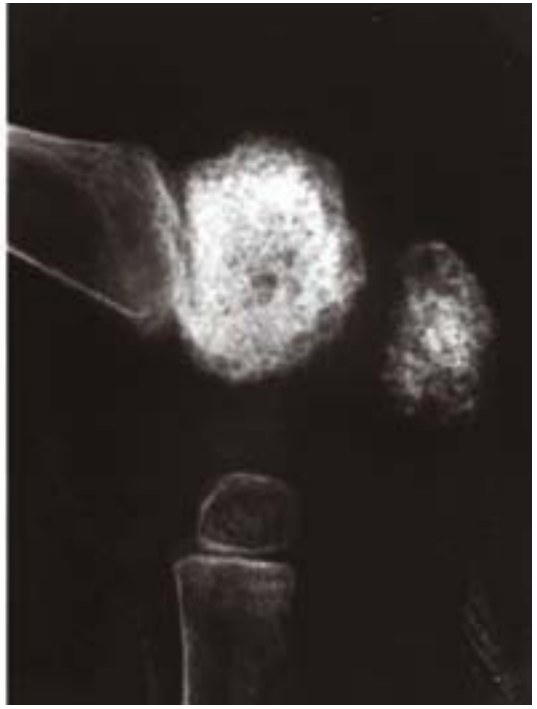
# NOMID- Skin lesions



Gesmar Segundo, Uberlandia, MG

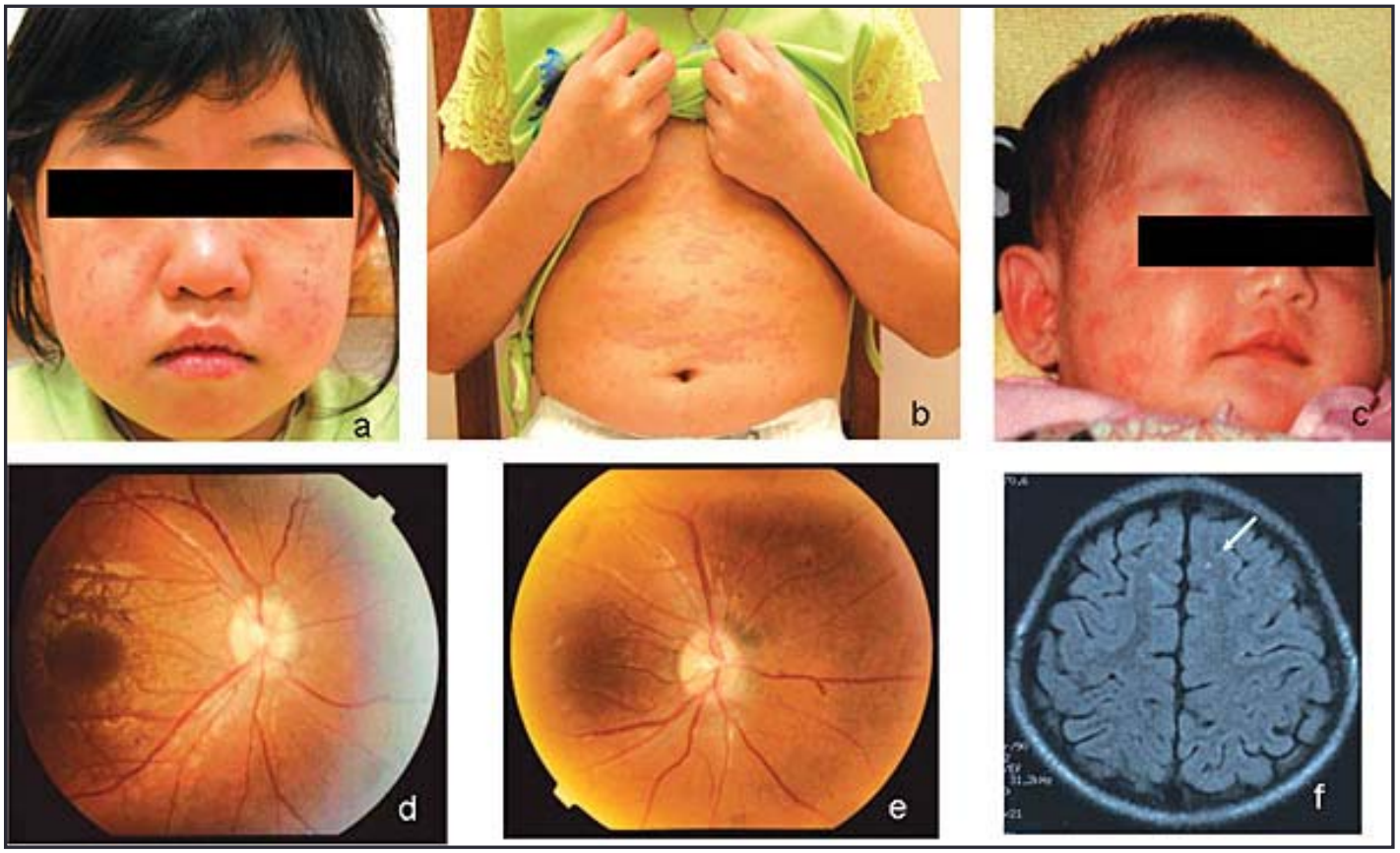
# NOMID-Arthropathy





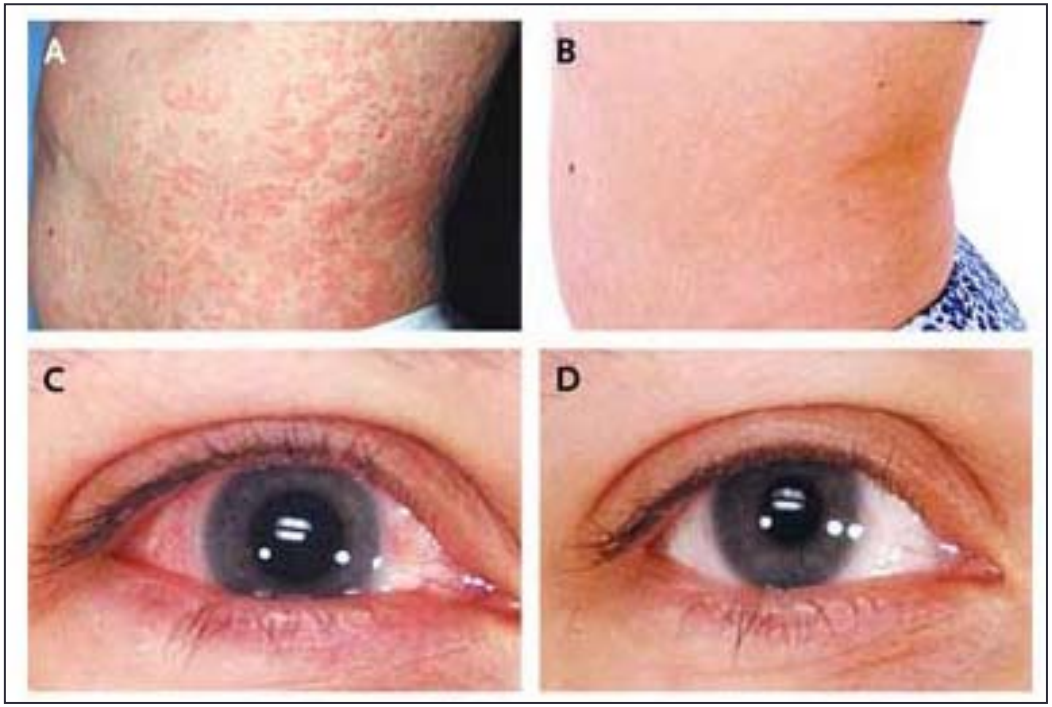
Neven B, Prieur A-M, Maire PQ. Nat Clin Pract Rheumatol. 2008 July

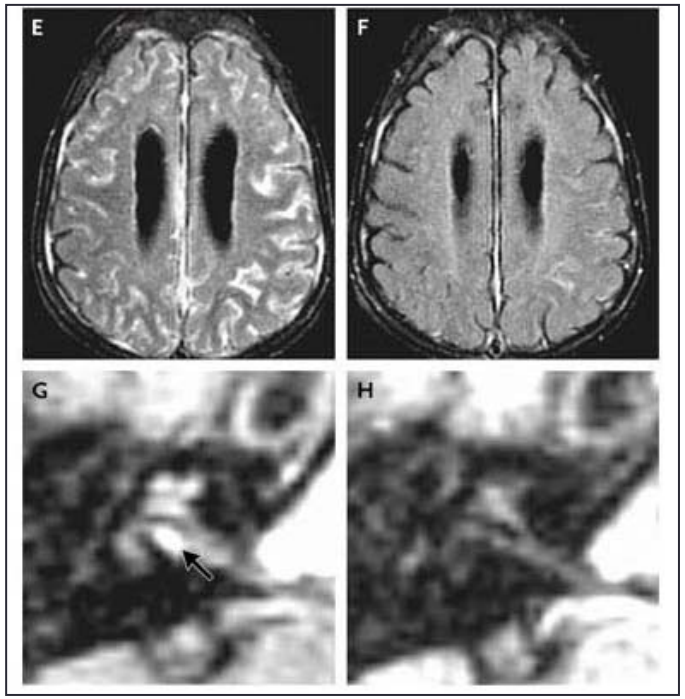
# NOMID-SNC




TL Lee, KW Chan, YL Lau. HK J Paediatr (New Series) 2006

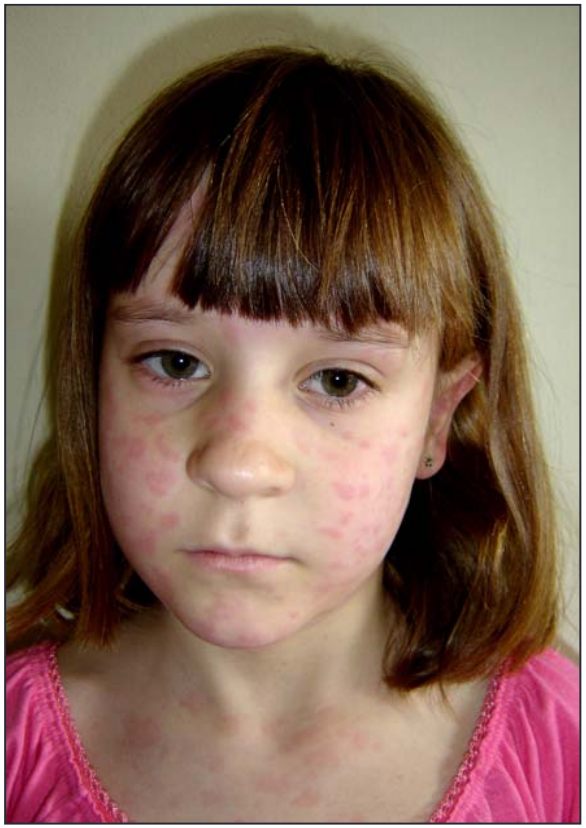
# Tratamento com Anakinra

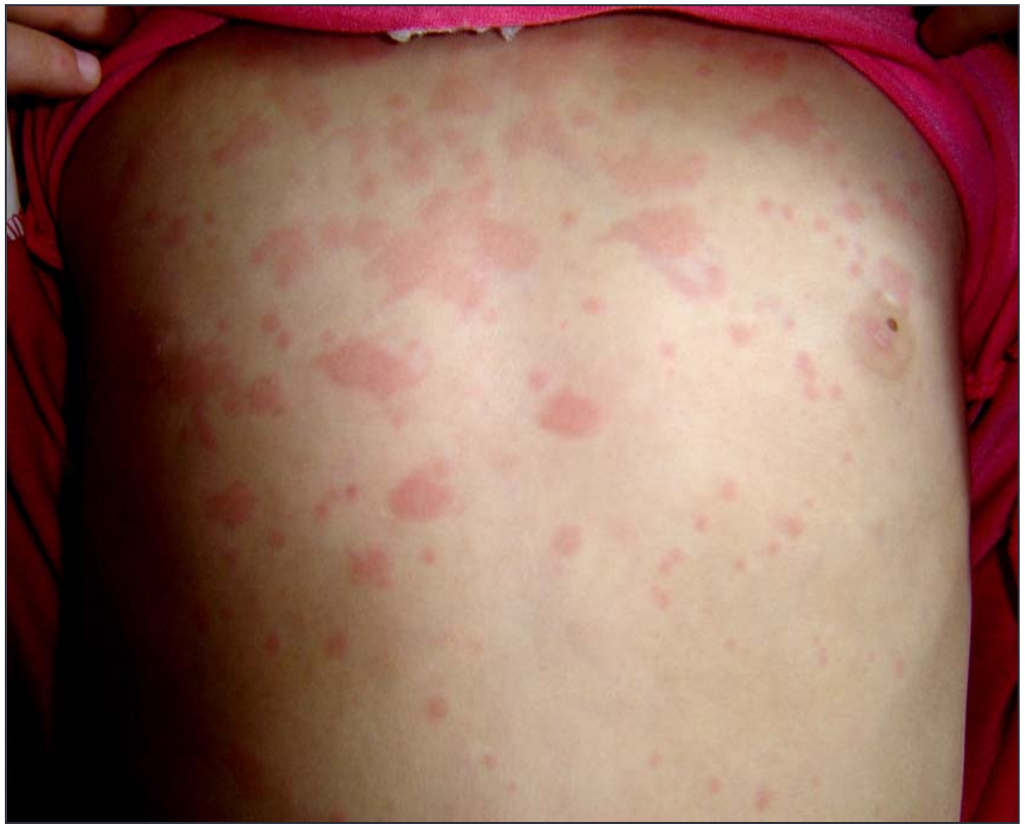



*Goldbach-Mansky R et al. NEJM, 2006.*

# FCAS- Skin lesions

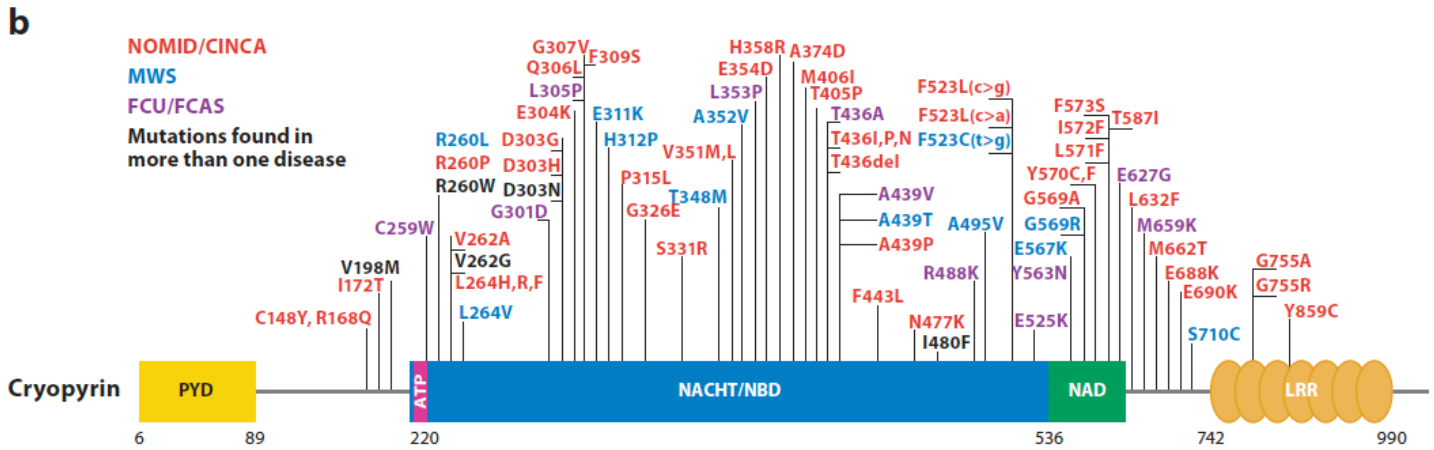




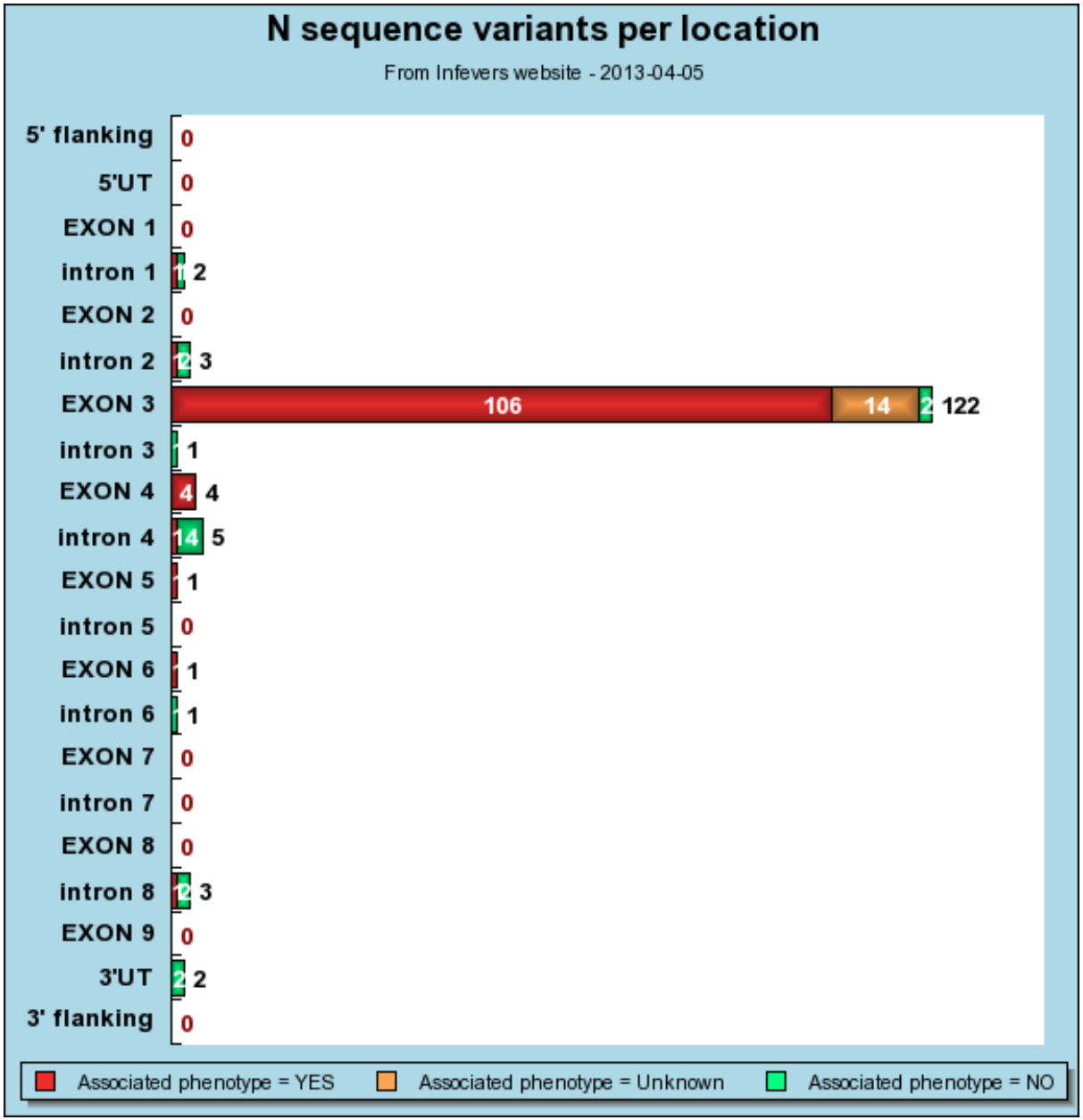
Jesus, AA, et al. J Clin Immunol, 2008

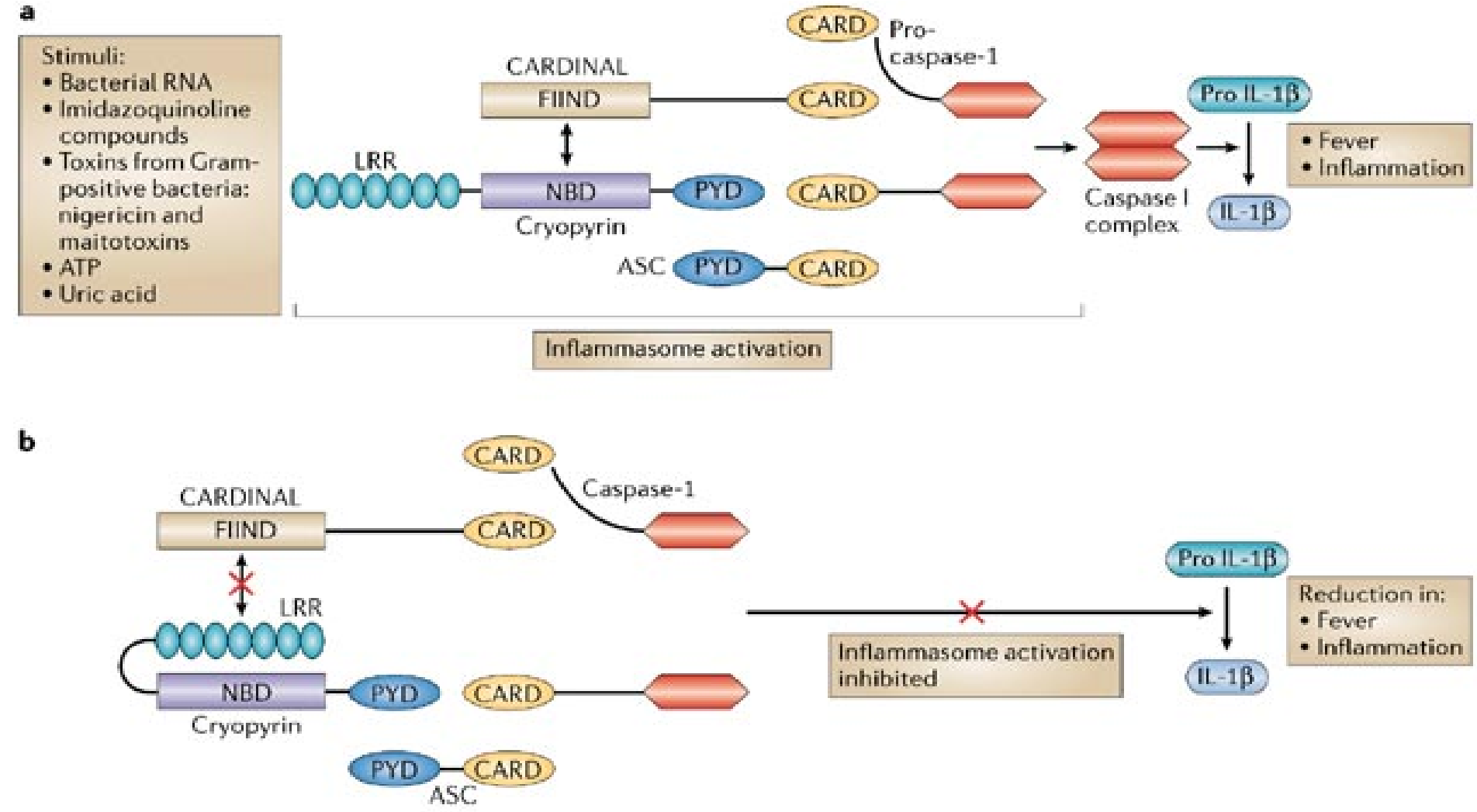
# Cryopyrinopathies- Genetics

- Autosomal dominant;
- 60% positive;
- >90% in exon 3;
- Second most common cause- SOMATIC mutations (70% of the mut negatives)




Hoffman GF, et al. Nat Genetics, 2001.
Feldmann J, et al. Am J Hum Genet, 2002.
Masters, SL. Annu. Rev. Immunol. 2009. 27:621-68


N sequence variants per location
From Infevers website - 2013-04-05
5' flanking
5'UT
EXON 1
intron 1
EXON 2
intron 2
EXON 3
intron 3
EXON 4
intron 4
EXON 5
intron 5
EXON 6
intron 6
EXON 7
intron 7
EXON 8
intron 8
EXON 9
3'UT
3' flanking
0
0
0
1 2
0
2 3
106 14 2 122
1
4 4
14 5
1
0
1
1
0
0
0
2 3
0
2 2
0
Associated phenotype = YES
Associated phenotype = Unknown
Associated phenotype = NO





**Nature Reviews** | Immunology

Ting *et al. Nature Reviews Immunology* **6**, 183–195 (March 2006) | doi:10.1038/nri1788

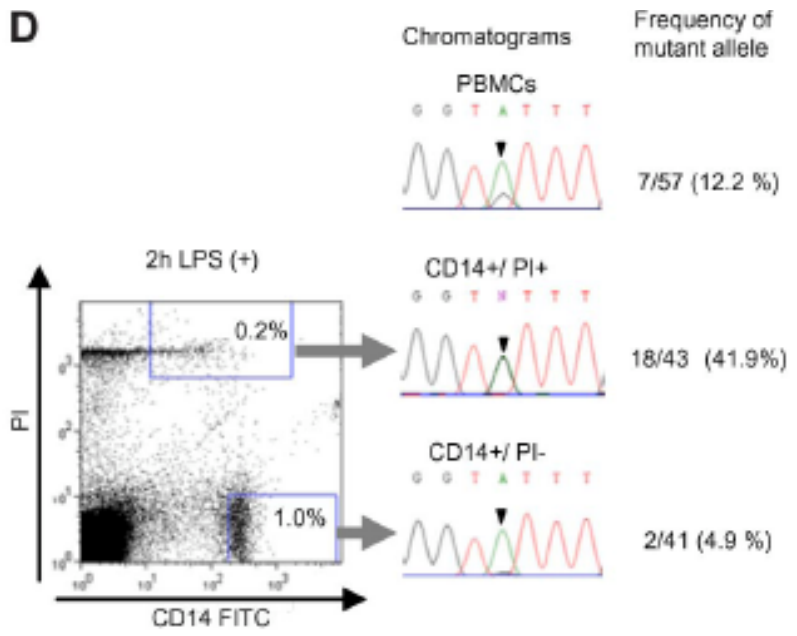
# Somatic Mutations in NLRP3

blood

2008 111: 2132-2141
Prepublished online December 6, 2007;
doi:10.1182/blood-2007-06-094201

**Disease-associated *CIAS1* mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients**

Megumu Saito, Ryuta Nishikomori, Naotomo Kambe, Akihiro Fujisawa, Hideaki Tanizaki, Kyoko Takeichi, Tomoyuki Imagawa, Tomoko Iehara, Hidetoshi Takada, Tadashi Matsubayashi, Hiroshi Tanaka, Hisashi Kawashima, Kiyoshi Kawakami, Shinji Kagami, Ikuo Okafuji, Takakazu Yoshioka, Souichi Adachi, Toshio Heike, Yoshiki Miyachi and Tatsutoshi Nakahata



ARTHRITIS & RHEUMATISM
Vol. 63, No. 11, November 2011, pp 3625–3632
DOI 10.1002/art.30512


# 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]

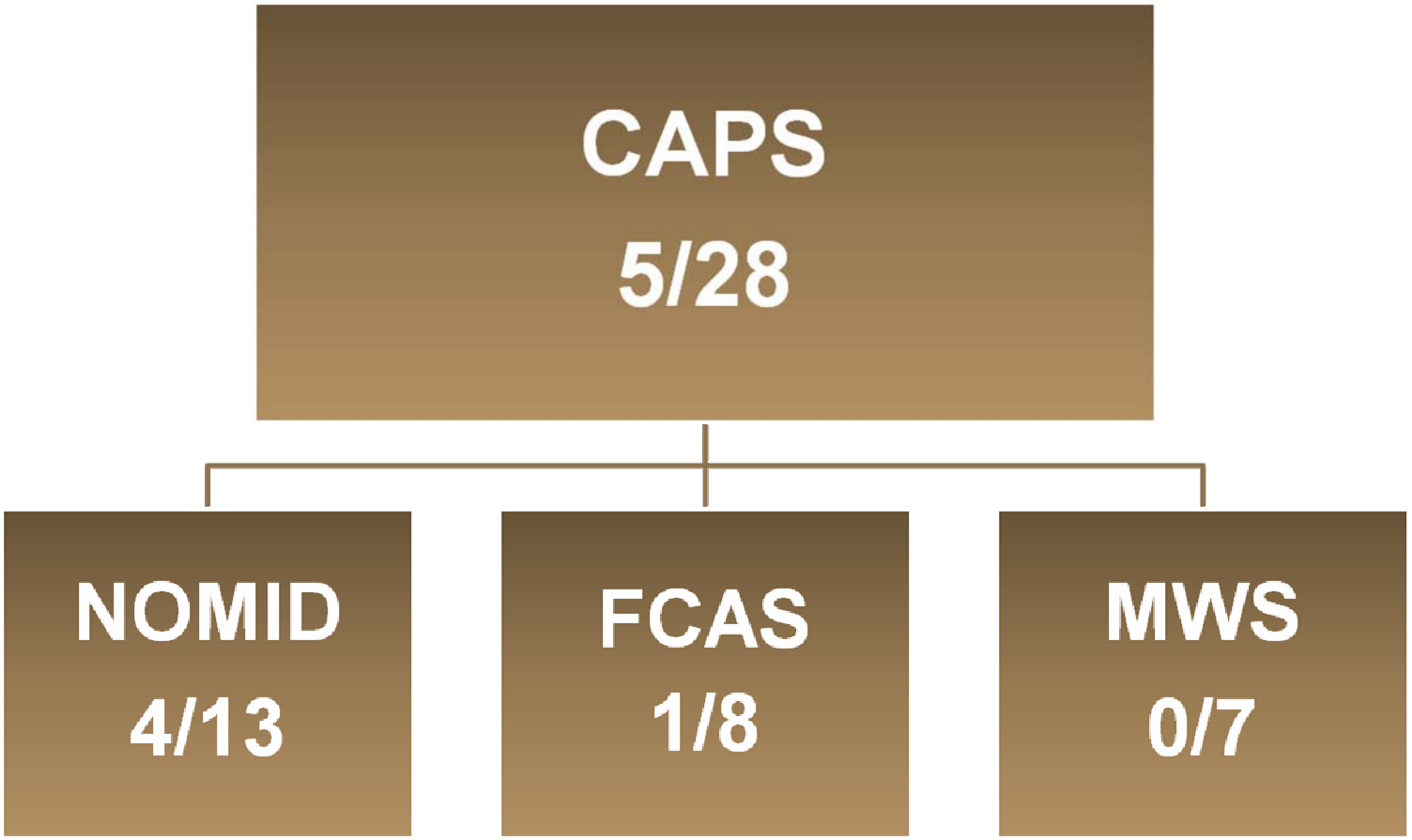
# Hereditary Autoinflammatory Syndromes:

# A Brazilian Multicenter Study

ADRIANA A. JESUS, ERIKA FUJIHIRA, MARIANA WATASE, MARIA T. TERRERI, MARIA O. HILÁRIO, MAGDA CARNEIRO-SAMPAIO, CLÁUDIO A. LEN, SHEILA K.OLIVEIRA, MARTA C. RODRIGUES, ROSA M. PEREIRA, BLANCA BICA, NILZIO A. SILVA, ANDRÉ CAVALCANTI, ROBERTO MARINI, FLÁVIO SZTAJNBOK, MARIA V. QUINTERO, VIRGÍNIA P. FERRIANI, DEWTON MORAES-VASCONCELOS, CLOVIS A. SILVA, JOÃO B. OLIVEIRA

Jornal of Clinical Immunology

## *NLRP3* mutations: 21% of germline mutation positive patients



# Familial Mediterranean Fever

- Described in 1945-58;
- Jews, Armenians, Turks, Arabs, Italians, Greeks;
- 1:250-500 in some Jewish populations;
- Carriers 1:5-7 in Armenians and Sephardic Jews;

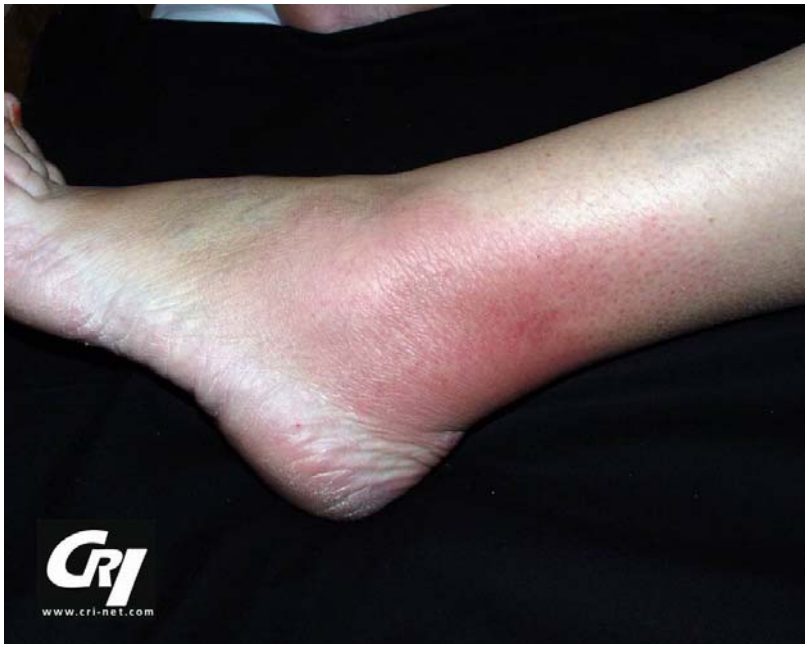
Siegal S. Benign paroxysmal peritonitis. Ann Intern Med 1945
Heller H, Sohar E, Sherf L. Familial Mediterranean fever. Arch Intern Med 1958

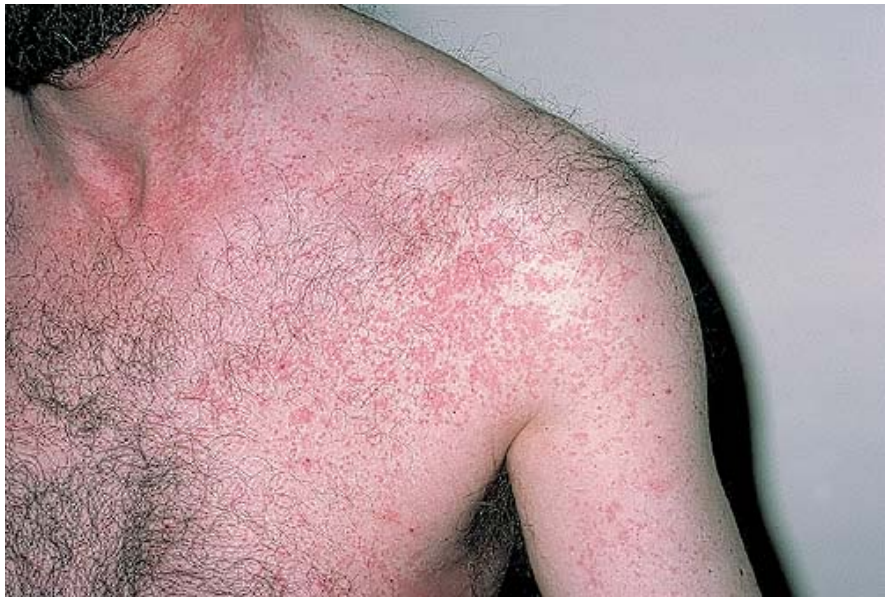
# FFM- Clinical Findings

- 90% before 20y;
- Sudden fever attacks during 24 to 48h;
- Serositis: severe peritonitis (95%) and pleuritis (30%);
- Monoarthritis: knees, ankles, wrist in 75%;
- Skin: erysipeloid erythema(7-40%), urticarial rash;
- Myalgia on LL + fever;
- Complication: secondary amyloidosis.

Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967; 43: 227-53

# FFM- Skin manifestations

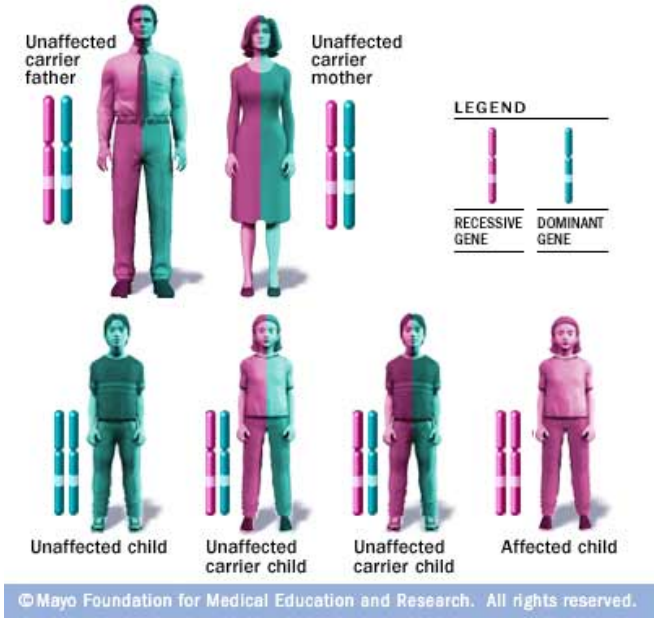


www.cri.net;
www.merckmedicus.com

# FFM- Genetics

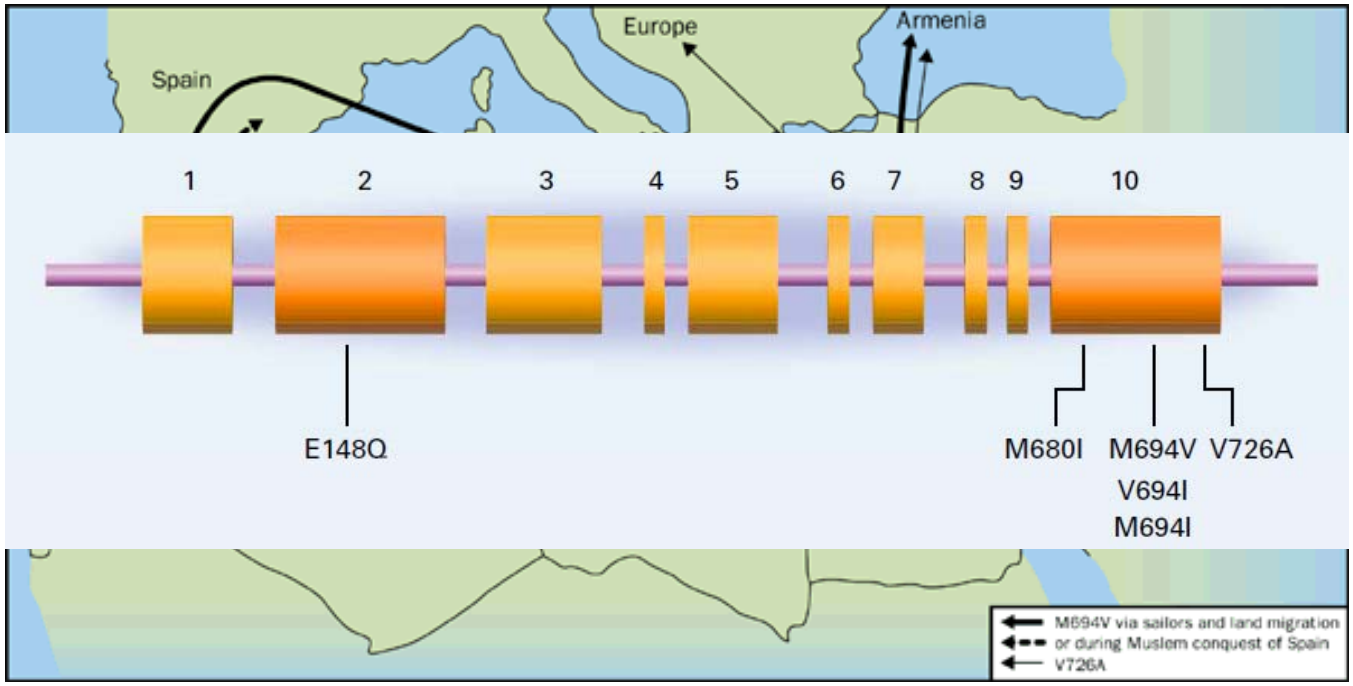
- Autosomal recessive
- *MEFV*- Cr 16q: pyrin/marenostrin
- Maturation and release of IL-1β



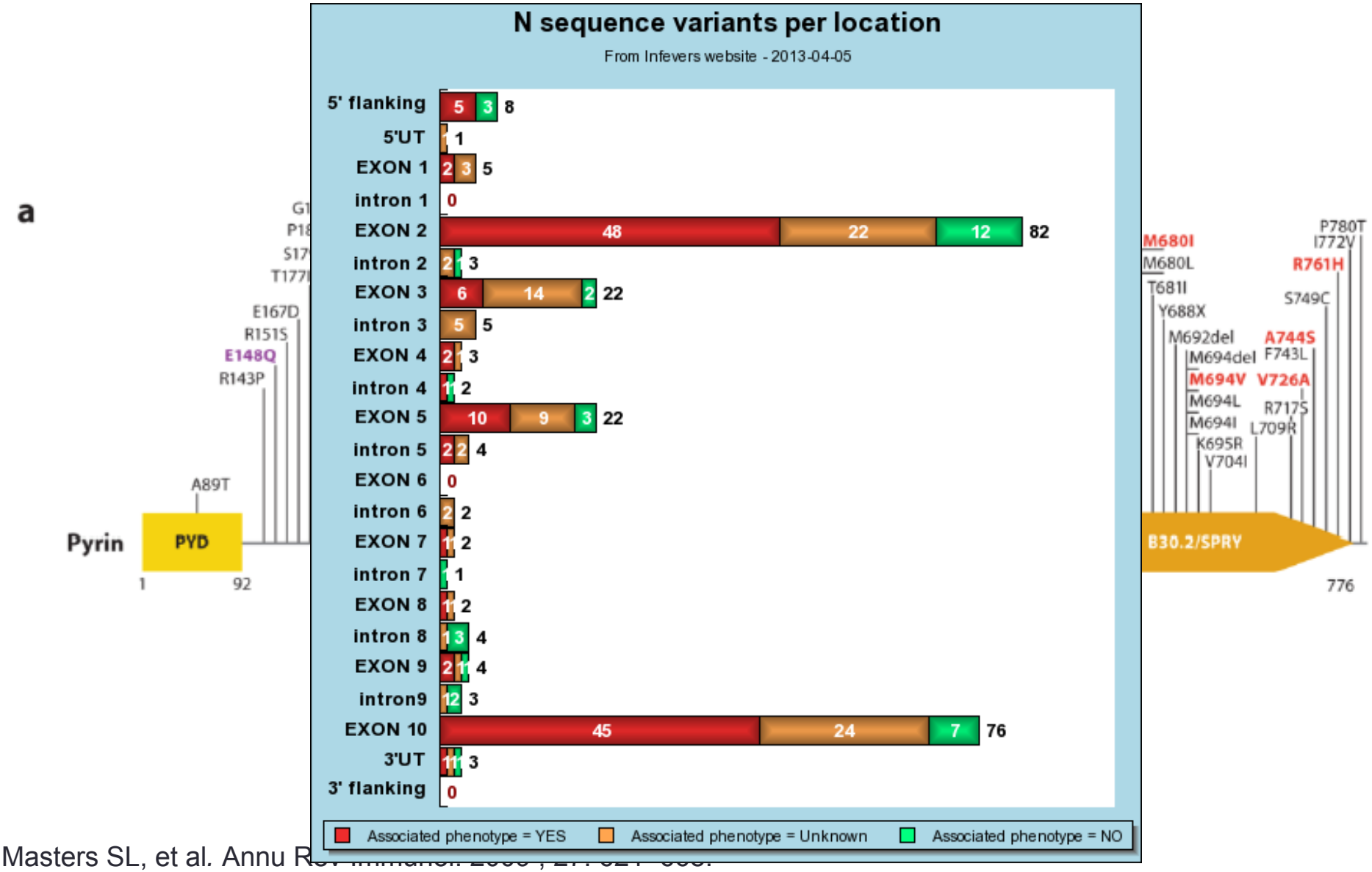

Pras E, Aksentijevich I, Gruberg L, et al. N Engl J Med 1992; The French FMF Consortium. Nat Genet 1997; The International FMF Consortium. Cell 1997.;

# FFM- Fisiopatologia e Genética

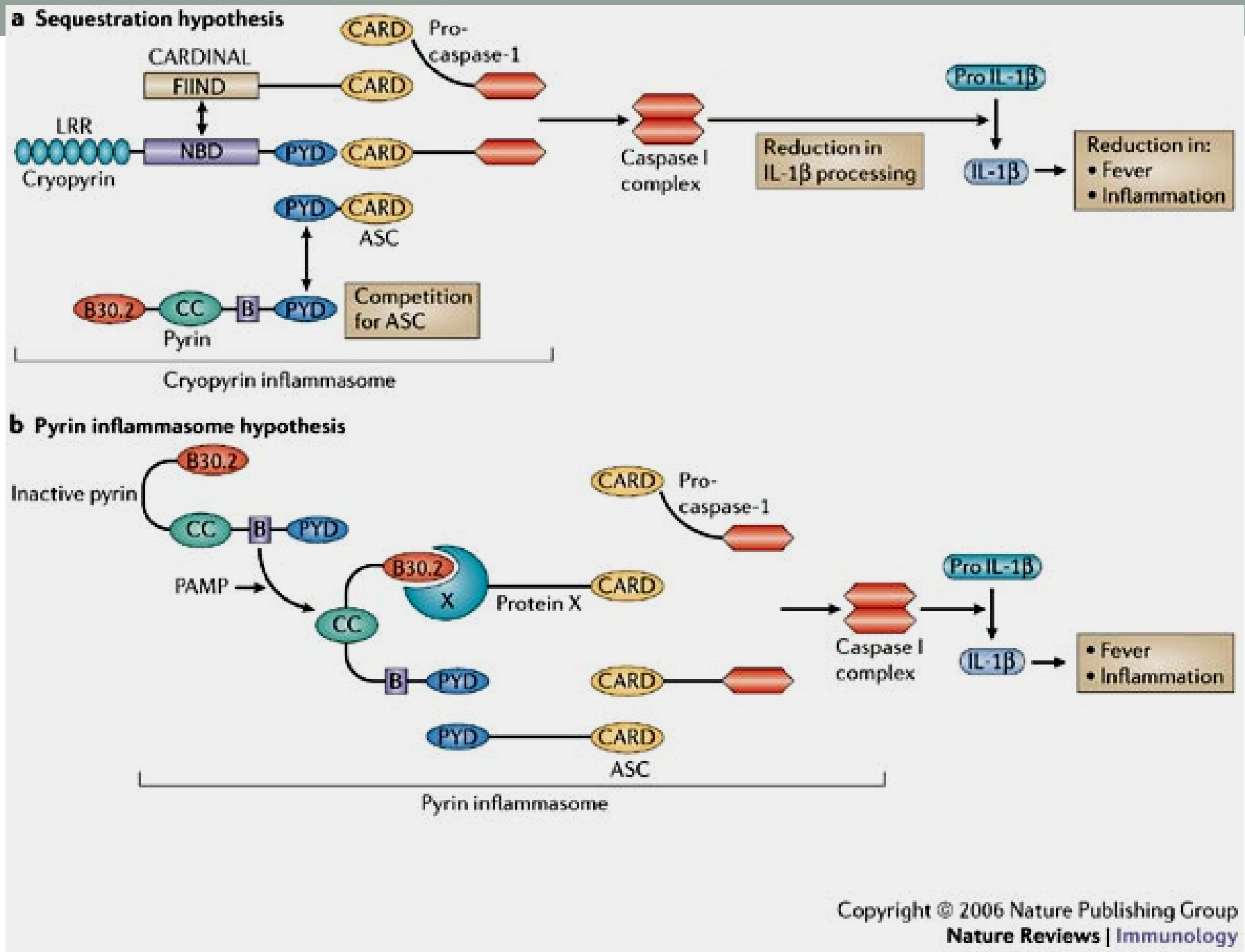
- M694V (20-67%): mais grave e maior risco de amiloidose; V726A (7 to 35 percent);
- "Founder effect"- 2500 anos atrás;



# SPECIFIC MUTATIONS or 2,3,5 and 10 NOT ENOUGH!




Masters SL, et al. Annu R




Ting *et al. Nature Reviews Immunology*, 2006

# TRAPS

- Second most prevalent;
- 1982- Familial hybernian fever: Irish/Scotish Family;
- All ethnic groups;

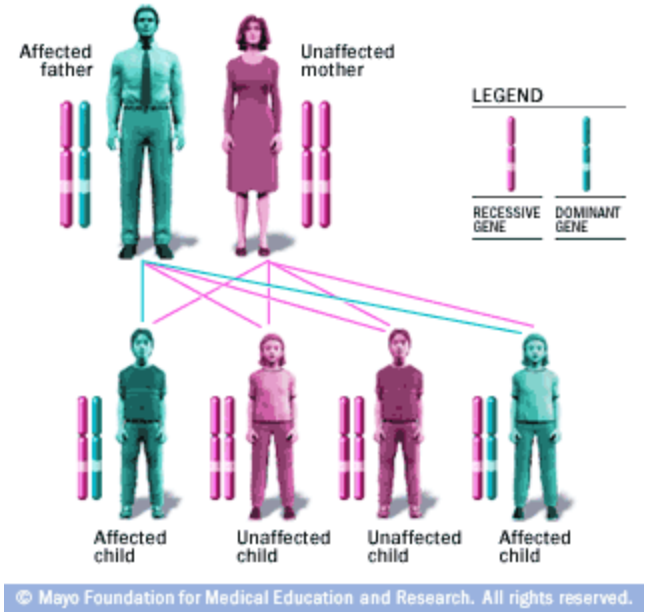
Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghill PJ. Familial Hibernian fever. Q J Med 1982;51:469-480

# TRAPS- Clinical Findings

- Long bouts of fever: average of 14 days;
- Abdominal pain - 77% (surgery - 33%);
- Localized and migratory myalgia (63-80%);
- Rash over myalgic areas or diffuse (60%);
- Arthralgia without arthritis;
- Conjunctivitis and periorbital edema (48%);
- Pleuritis, orchitis and headaches;
- Amyloidosis in 14-64%;

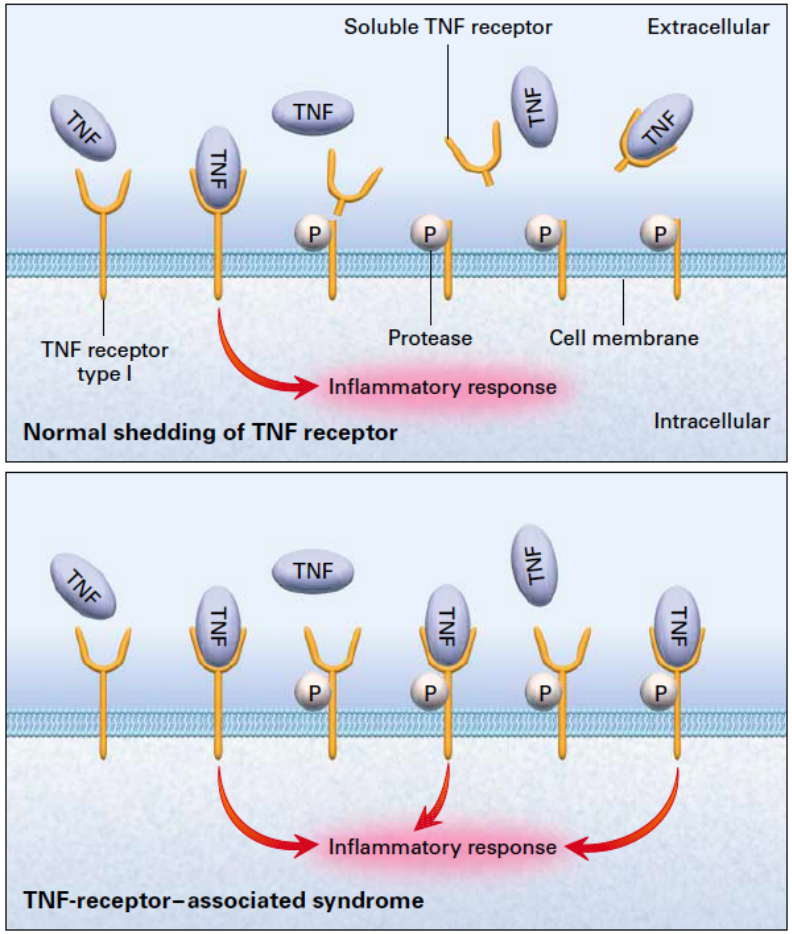
# TRAPS- Genetics

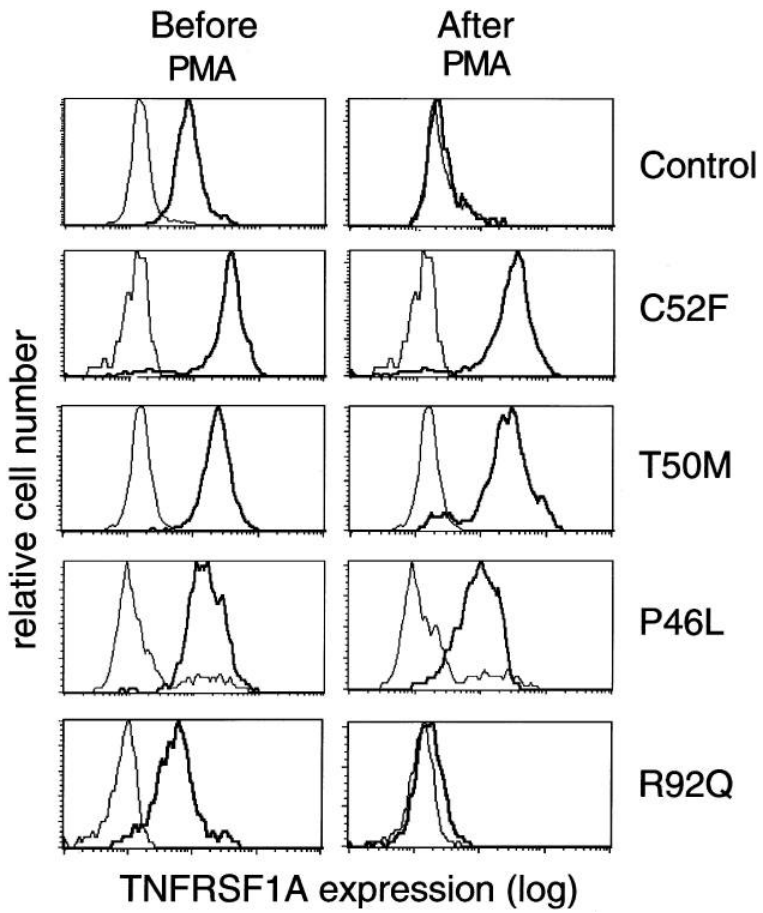
- Autosomal dominant;
  - *TNFRSF1A*- Cr 12p13.2: TNFR1 (p55);
  - P55 stuck on cell surface or with abnormal trafficking;




McDermott MF, Ogunkolade BW, McDermott EM, et al.. Am J Hum Genet 1998
McDermott MF, Aksentijevich I, Galon J, et al. Cell 1999

# TRAPS- Etiopatogenia e Genética




Dreth JPH, van der Meer JWM. NEJM 2001

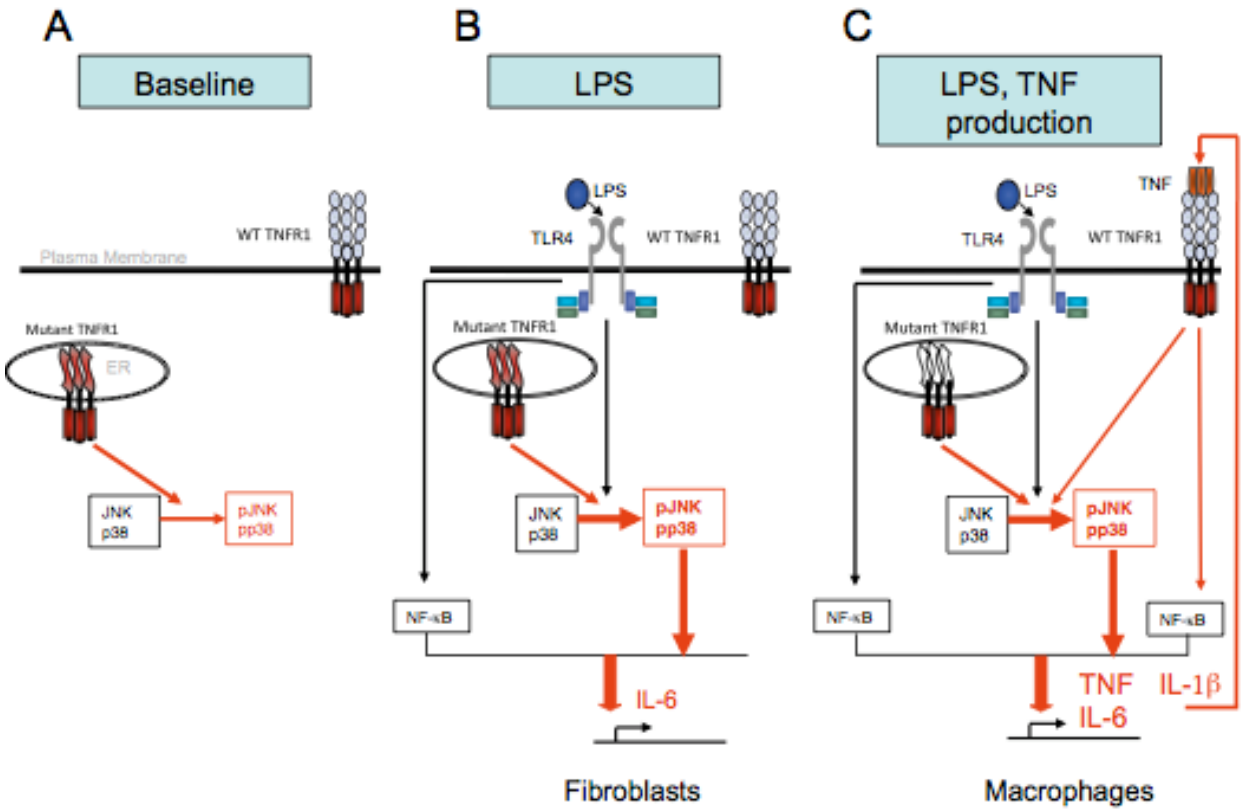
Aksentijevich I et al. Am J Hum Genet. 2001

PNAS

# Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome

Anna Simon[a,1,2], Heiyoung Park[b,2], Ravikanth Maddipati[b], Adrian A. Lobito[b,3], Ariel C. Bulua[b], Adrianna J. Jackson[a], Jae Jin Chae[a], Rachel Ettinger[b,4], Heleen D. de Koning[a,1], Anthony C. Cruz[b], Daniel L. Kastner[a], Hirsh Komarow[a,2], and Richard M. Siegel[b,2,5]

[a]Inflammatory Biology Section, Laboratory of Clinical Investigation and [b]Immunoregulation Section, Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892



# More refined models…

J Exp Med. 2011 March 14; 208(3): 519–533.
doi: 10.1084/jem.20102049
PMCID: PMC3058571

**Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS)**

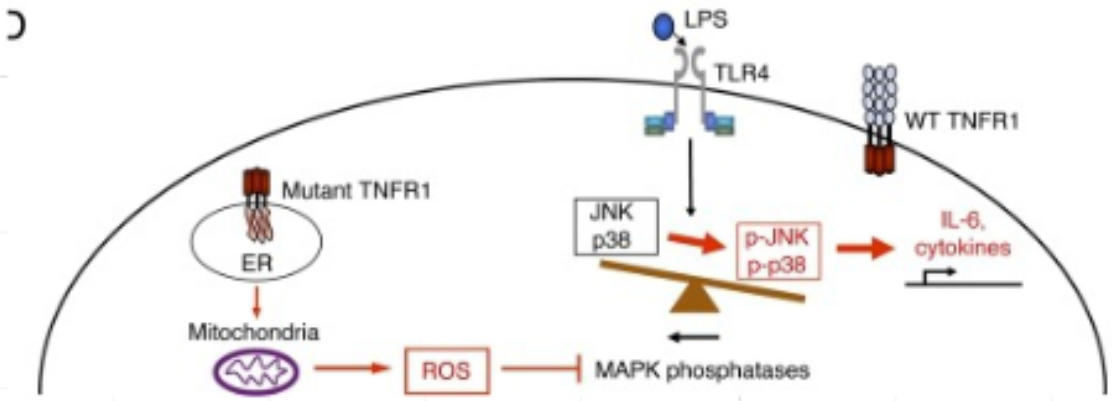
Ariel C. Bulua,[1,4] Anna Simon,[2] Ravikanth Maddipati,[1] Martin Pelletier,[1] Heiyoung Park,[1] Kye-Young Kim,[3] Michael N. Sack,[3] Daniel L. Kastner,[2] and Richard M. Siegel[1]

Ann Rheum Dis. 2012 Dec;71(12):2035-43. doi: 10.1136/annrheumdis-2011-201197. Epub 2012 Jun 7.

**Involvement of X-box binding protein 1 and reactive oxygen species pathways in the pathogenesis of tumour necrosis factor receptor-associated periodic syndrome.**

Dickie LJ, Aziz AM, Savic S, Lucherini OM, Cantarini L, Geiler J, Wong CH, Coughlan R, Lane T, Lachmann HJ, Hawkins PN, Robinson PA, Emery P, McGonagle D, McDermott MF.

27

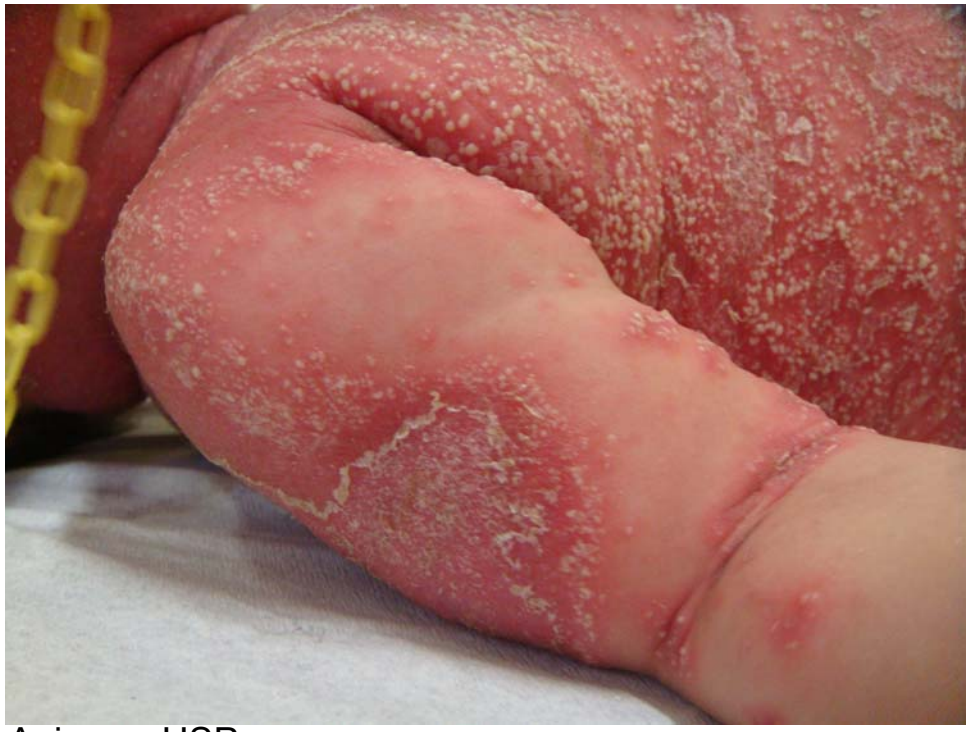


# TRAPS x FFM

- Longer attacks;
- Ocular manifestations;
- Localized myalgias;
- Frank monoarthritis is ucommon;
- No response to colchicine.

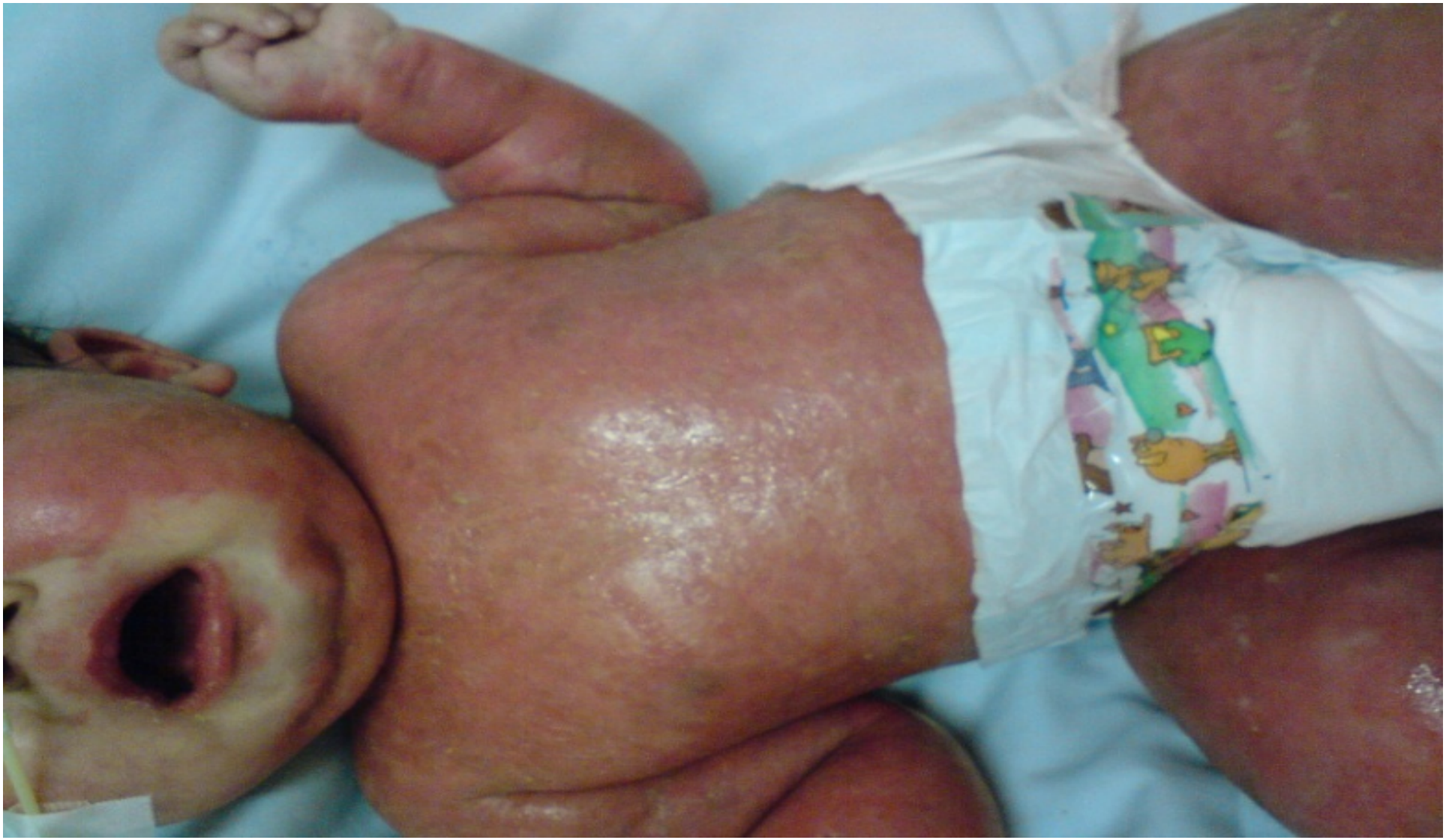
# Deficiency of the IL-1 Receptor Antagonist- DIRA

- Most recently described
- Neonatal onset multifocal osteomyelitis
- Periostitis
- Pustulosis

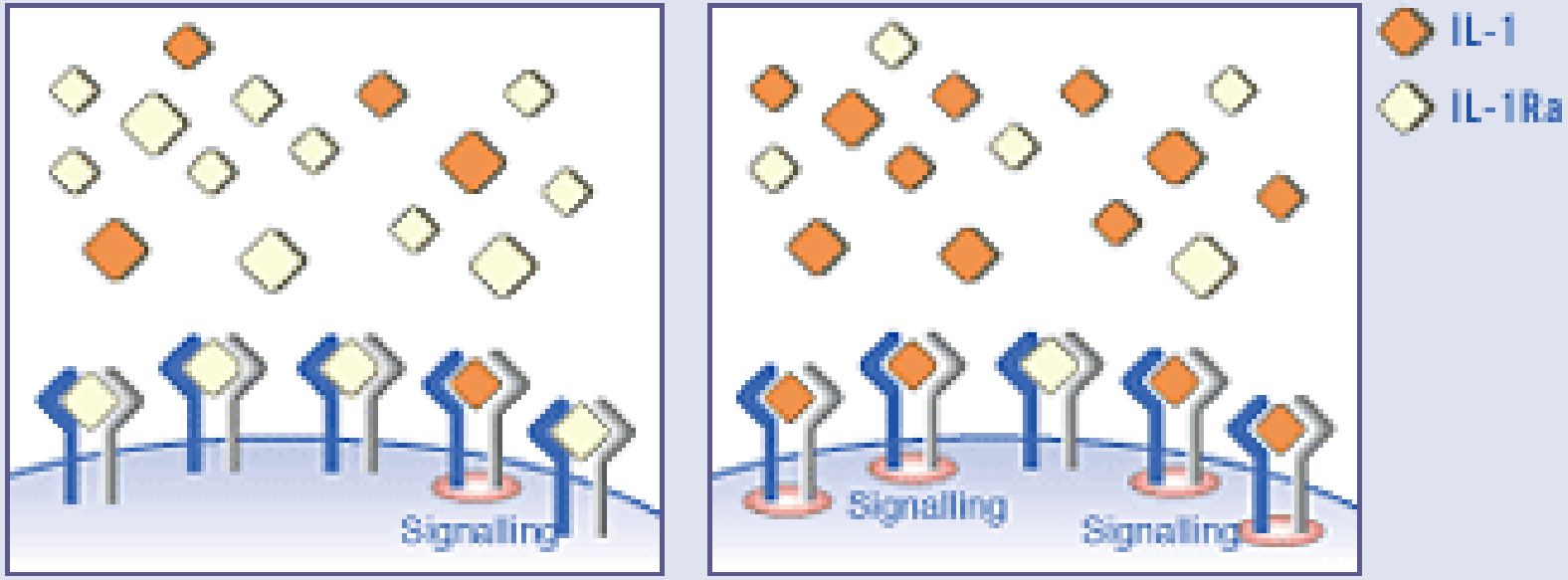


A. jesus, USP

Aksentijevich et al. NEJM, 2009



# “Deficiency of IL-1 Receptor Antagonist” (DIRA)




IL-1Ra competitively inhibits the binding of IL-1 to the IL-1 receptor

In RA, IL-1 levels cannot be countered sufficiently by endogenous IL-1Ra

# IL-1 Responsive AI Syndromes

**Table 2.** Autoinflammatory diseases responsive to interleukin (IL)-1 blockade.

| Syndrome | Studies |
|---|---|
| Monogenic disorders other than CAPS and DIRA | |
| Other diseases with IL-1 response | |
| Familial Mediterranean fever (FMF) | [78,119–125] |
| TNF receptor-associated periodic syndrome (TRAPS) | [126–129] |
| Hyper immunoglobulin (Ig)D syndrome (HIDS) | [130,131] |
| PAPA syndrome[†] | [132,133] |
| Polygenic disorders[‡] | |
| SOJIA[§] | [71,72,134] |
| AOSD[¶] | [135–141] |
| PFAPA | [73] |
| Behçet's disease | [77] |
| Schnitzler syndrome | [74–76] |
| 'Metabolic' autoinflammatory diseases | |
| Gout | [81–83] |
| Diabetes type 2 | [84] |

# Summary

- Innate immunity disorders
- FMF: short attacks (2-3 days) + monoarthritis;
- TRAPS: long attacks + myalgia w/ localized rash + conjunctivitis;
- Cryopyrinopathies:
  - NOMID: severe, arthropathy, meningitis
  - Muckle-Wells: deafness
  - FCAS: urticaria to cold exposure
- DIRA: Osteomyelitis, periostitis, pustulosis (DDx with Majeed)