Autoinflammatory syndromes 23 years!

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Auto-inflammatory diseases: Action plan

- Definitions and taxonomy
- Essential aspects of the phenotypes
- Mutation and hypotheses on downstream effect
- Strategy for initial management steps
- Where to find more? Google

AUTOINFLAMMATORY DISEASES: CLASSIFICATION

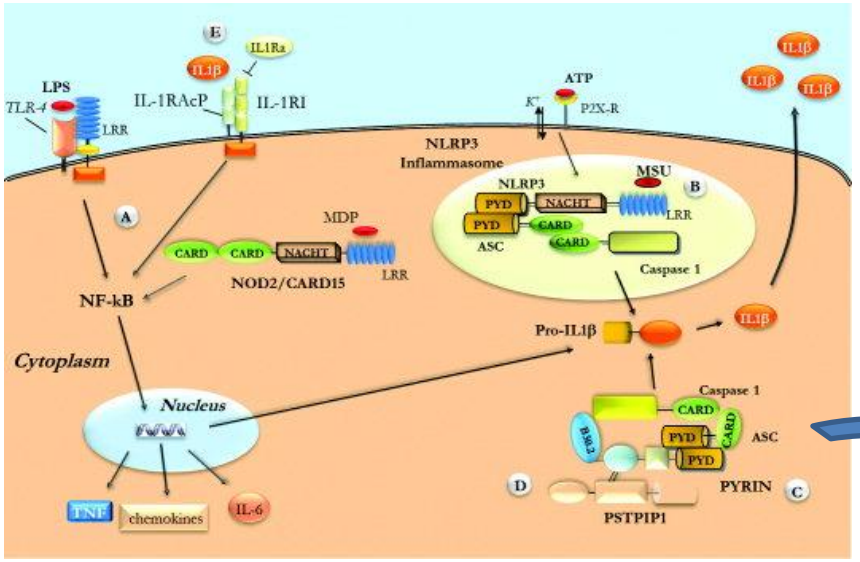
- MONOGENIC (Mendelian)
- COMPLEX GENETICS: so-JIA, **PFAPA**, CRMO, BS, PG and many others
- **INTERFERONOPATHIES**: AGS (*), SAVI (*), CANDLE (*), JDM, SLE

(*) monogenic

Autoinflammatory diseases by mechanism

- **NALP3 Inflamosome**:
  - Intrinsec: CAPS (CINCA, MWS, FCAS1)
  - Extrinsec or Pyrosome: PAPAS, FMF, HIDS, Majeed
- **NFkB activation**: Blau syndrome, CAMPS(CARD14)(*)FCAS2 (NLRP12)
- **Protein pocessing**: TRAPS, HIDS, Nakajo-Nashimura/CANDLE (**Proteasome)**
- **Cytokine Signaling**: DIRA, DITRA (IL-36Ra), STING related (SAVI)
- **Other intracellular effects**: APLAID (**)

- **Structural effect on tissue**: ADA2 deficiency associated vasculopathy



(*) CARD1 mediated pustular psoriasis
(**) Autoinflammation and PLCG2-associated antibody deficiency

SPEC FORMATION

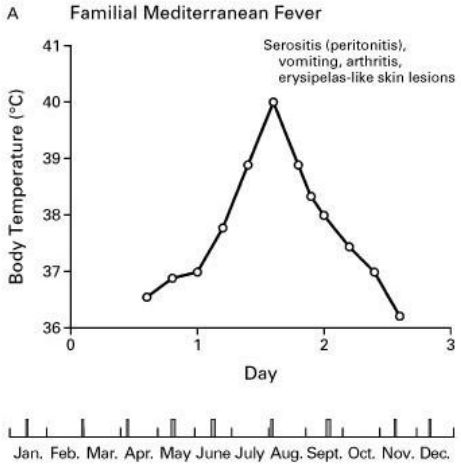
NAME	MUTATION	INHERITANCE	PROTEIN	Phenotype	REFERENCE
FMF	*MEFV*	AR (?)	Pyrin	Periodic fever	Int. FMF con .1997
TRAPS	*TNFRS1A*	*AD-de novo*	TNFR1	Periodic fever	Mac Dermott 1990
HIDS	*MVK*	*AR*	Meval. Kynase	Periodic fever	Drenth 1999
FCAS1	*NLRP3*	*AD*	Cryopirin	Cold induced AI	Hoffman 2001
FCAS2 (Guad.)	*NLRP12*	*AD*	NLRP12	Cold induced AI	Jeru , 2008
MWS	*NLRP3*	*AD*	Cryopirin	Urtic., sens. hl	Hoffman 2001
CINCA-NOMID	*NLRP3*	*AD-de novo*	Cryopirin	Severe AI	Aksentjevich 2002
PAPA	*PTSPPIP1*	*AD*	PTSPPIP1	Py.A, PG, Acne	Wise 2002
Blau	*NOD2*	*AD*	NOD2	Arthitis, uveitis	Miceli-Richard ,2001
PRP & CAMPS	*CARD14*	*AD*	CARD14	PPs	Fucks /Jordan,2012
Majeed	*LPN2*	*AR*	Lipin2	CRMO, myelodispl	Ferguson, 2005
DIRA	*IL-1RN*	*AR*	IL-1Ra	CRMO, PPs	Aksentjevich 2009
CANDLE	*PSMB-8*	*AR*		Pannic/lypodistr	Agarwal ,2010
DITRA	*IL-36RA*	*AR*	IL-36Ra	PPs	Marrakchi, 2011
H syndrome	*SLC29A3*	*AR*	hENT3	7 H's	Vered Molho, 2008
APLAID	*PLCG2*	AD	PLCG2	Bullae, ID	Zhou, 2012
ADA2	*CECR1*	*AR*	ADA2	Stroke/PAN	Zhou/Elkan 2014
SAVI	*TMEM173*	*AD?*	TMEM173	Skin vascul/ILD	Liu 2014
Rec. MAS	*NLRC4*	*AD?*	NLRC4 (IPAF)	Recurrent MAS	Canna 2014

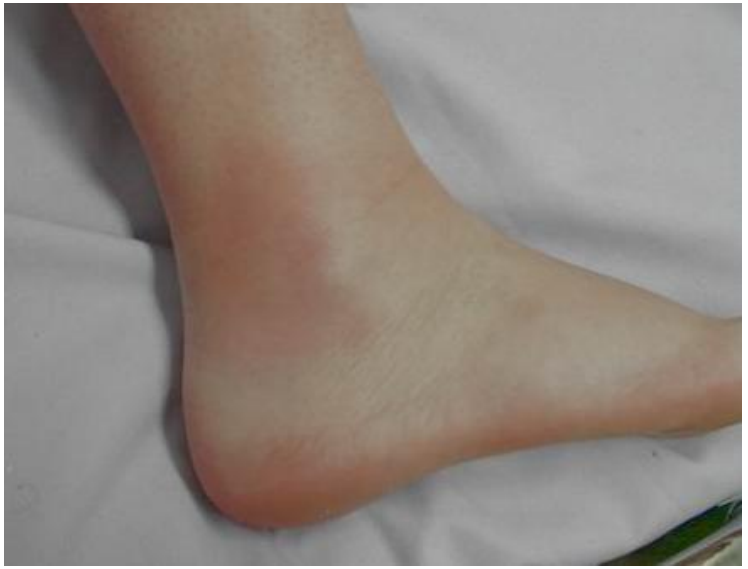
WHEN TO SUSPECT MONOGENIC AID?

- Periodic fever with variable inter-critical period and duration
- Intense but transient acute phase reaction and preserved growth (mostly)
- Age before 10 yr (mostly)
- Positive family history (recall: variable to absent phenotype)
- Ethnicity
- Urticarial rash, pustular psoriasis, pyoderma gangrenosum, Sweet's, panniculitis, lipoatrophy
- Seronegative chronic or recurrent arthritis
- Panuveitis
- Early onset sharp (livedoid) pernio, PAN and stroke
- Severe multiostotic osteitis

Pattern I: PERIODIC FEVERS

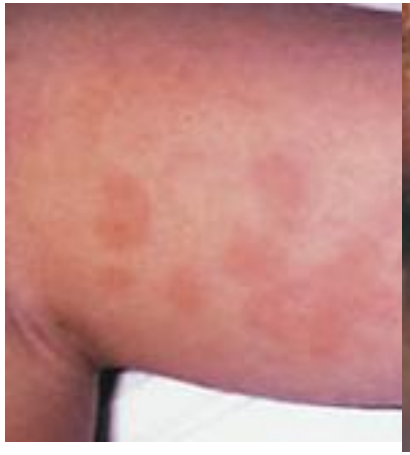
FMF clinical features

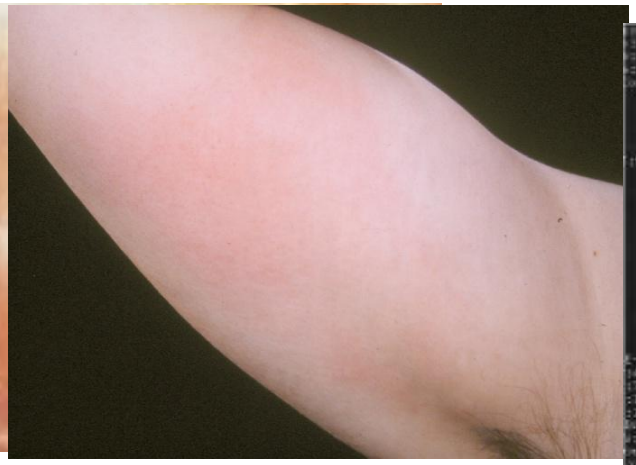


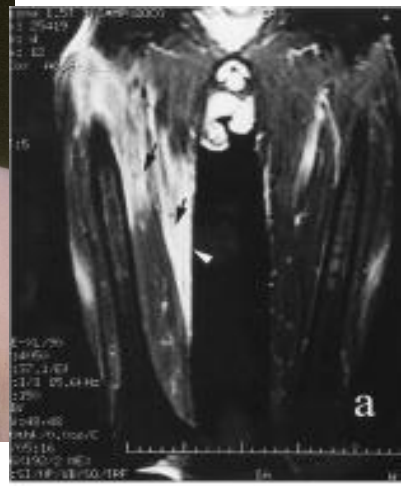


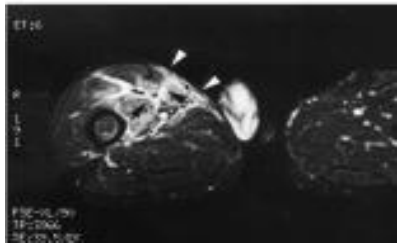
- Fever: sudden rise, short duration, irregular interval
- Sterile peritonitis (90%) and other serositis
- Erysipeloid erythema (40%)
- Intermittent monoarthritis (75%) (can be a distinct feature)
- Episodes of LCV (HSP-like)
- Recessive (big debate) MEFV1 coding for Pyrin. Secondary activation of NALP3 inflammasome vs direct activation of Caspase

TRAPS clinical features

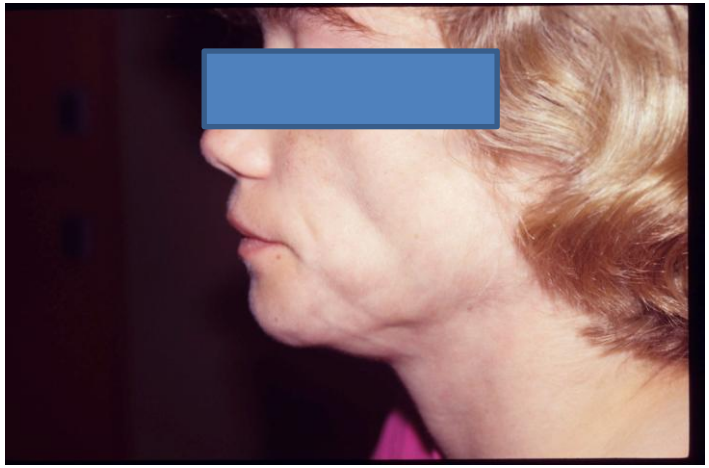




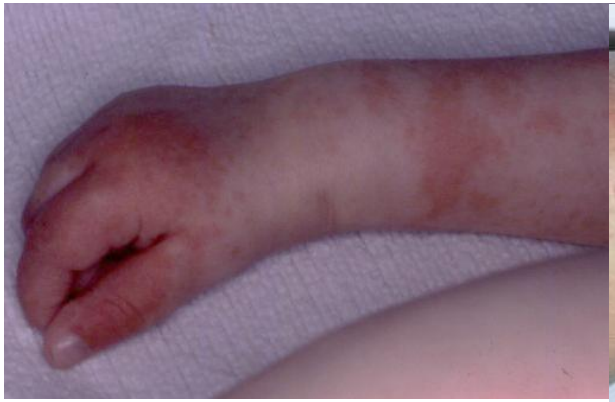


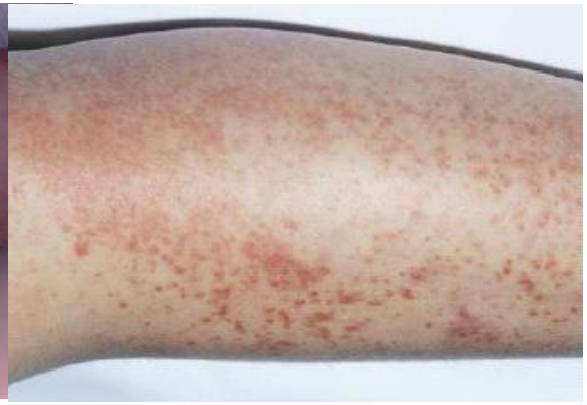


- Episodes can be very long and sporadic
- Migratory macular rash
- Conjunctivitis and/or periorbital edema
- Migratory myalgia, monoarthritis
- Serositis
- AD due to mutation in TNFR1. **Protein misfolding**



HIDS clinical features





•Onset before 1 year

•Constitutional Sxs followed by sharp rise in fever with chills for 3 to 7 days and gradual defervescence

•Maculo-papular rash (petechiae, purpura)

•Polyarthralgia, occasional arthritis/myalgia

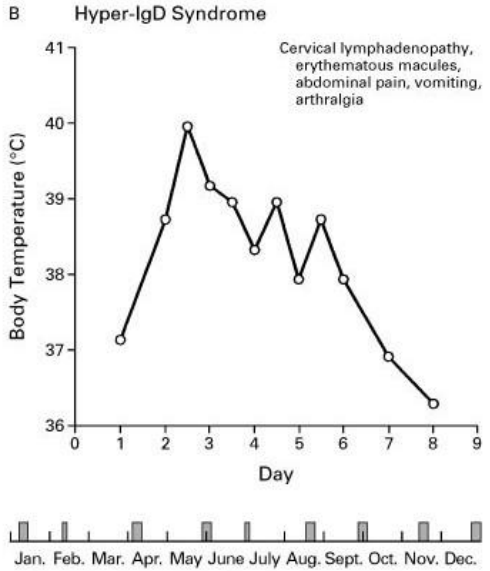
•Severe abdominal pain, vomiting, diarrhea, aphtous stomatitis (PFAPA-like)

•Prominent cervical Lymphadenopathy (PFAPA-like)

•H-Smegaly (not PFAPA like)

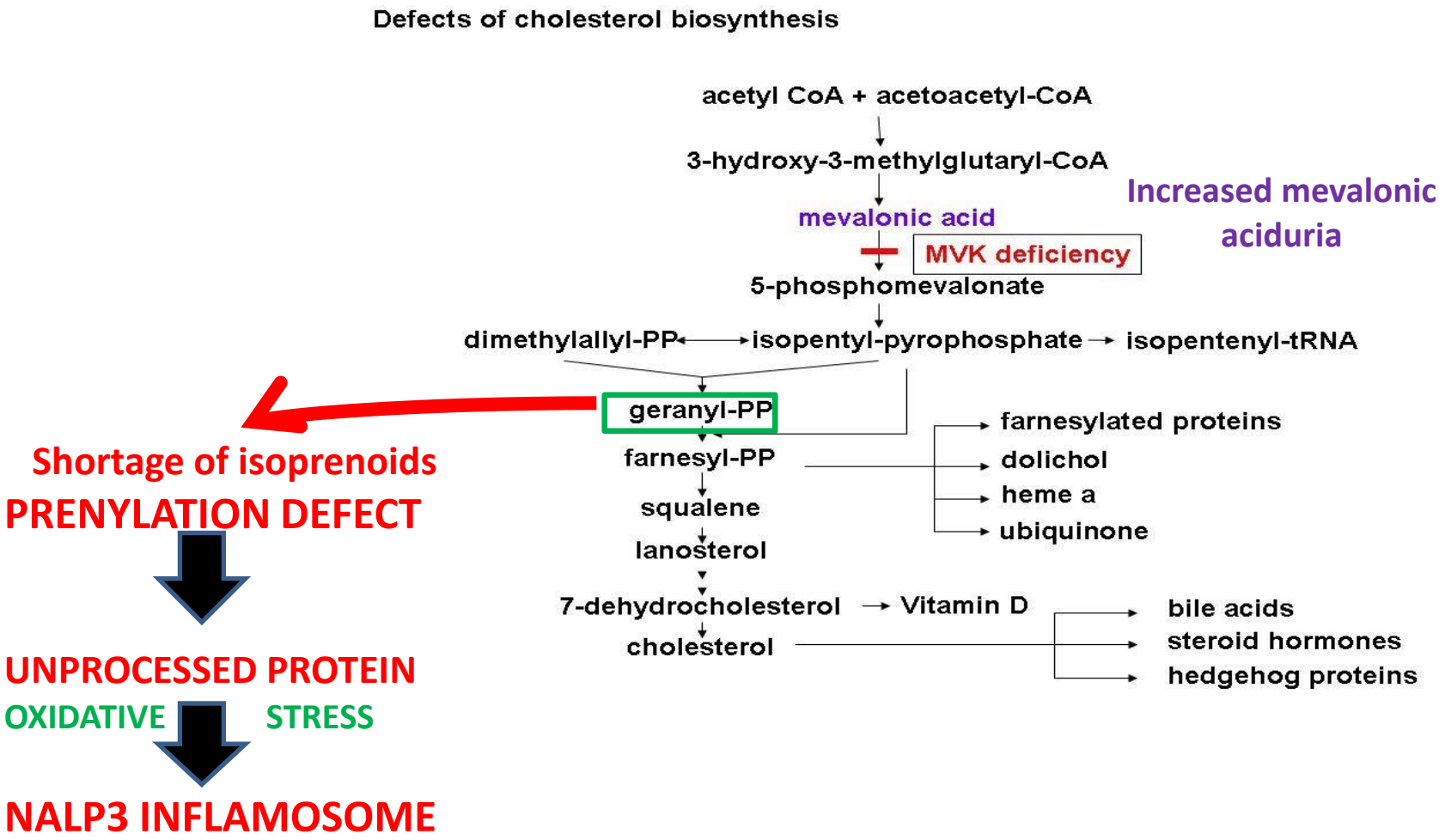
•High U/Mevalonic during attacks, IgD (>100 IU/ml)

•AR due to mutations in MVK**. Protein processing (prenilation defect)**



With appreciation to Carine Wouters MD, PhD UZ Leuven

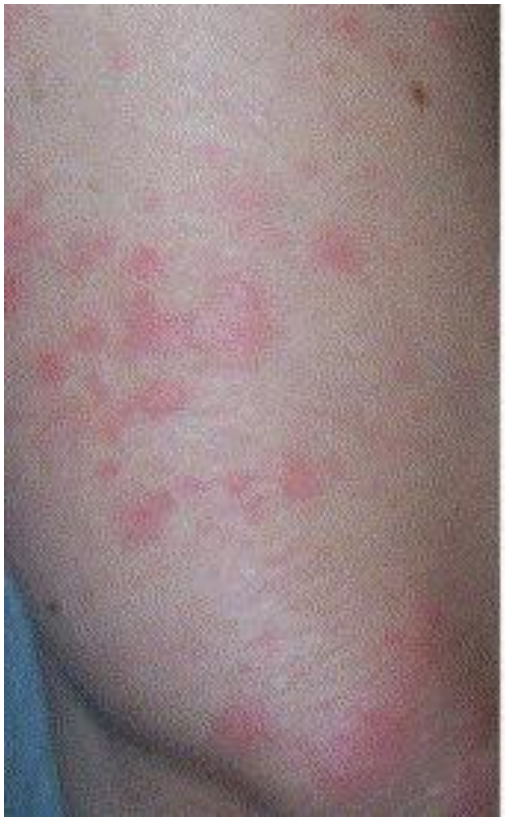
Mevalonate Kinase Deficiency



Pattern 2: PERSISTENT FEVER & CHRONIC INFLAMMATION

Boy 10 yrs with chronic recurrent urticaria since birth

- Conjunctivitis
- Headaches
- Arthralgia, myalgia
- Malaise
- Mother with hearing loss
- Sibling with urticaria since age 2
- Anemia, elevated ESR and CRP

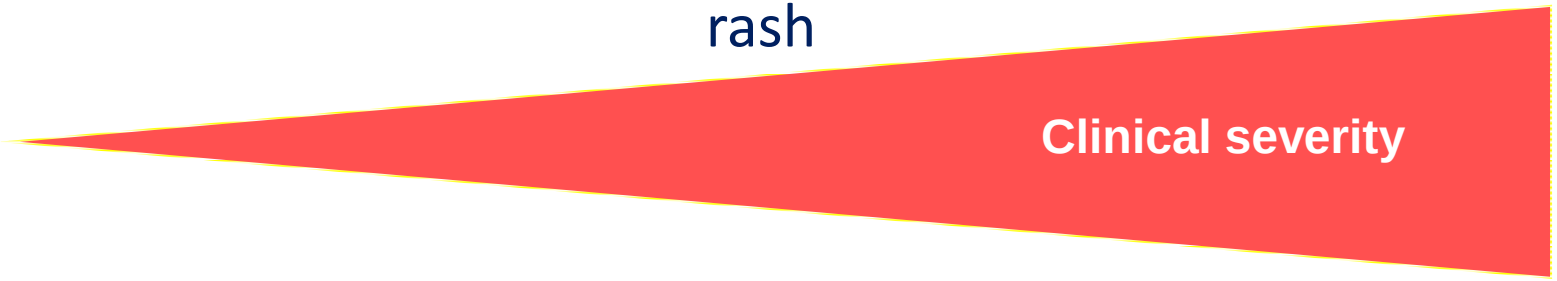


Heterogygous mutation p.Thr348Met in CIAS-1/NLRP-3 gene

With appreciation to Carine Wouters MD, PHd UZ Leuven

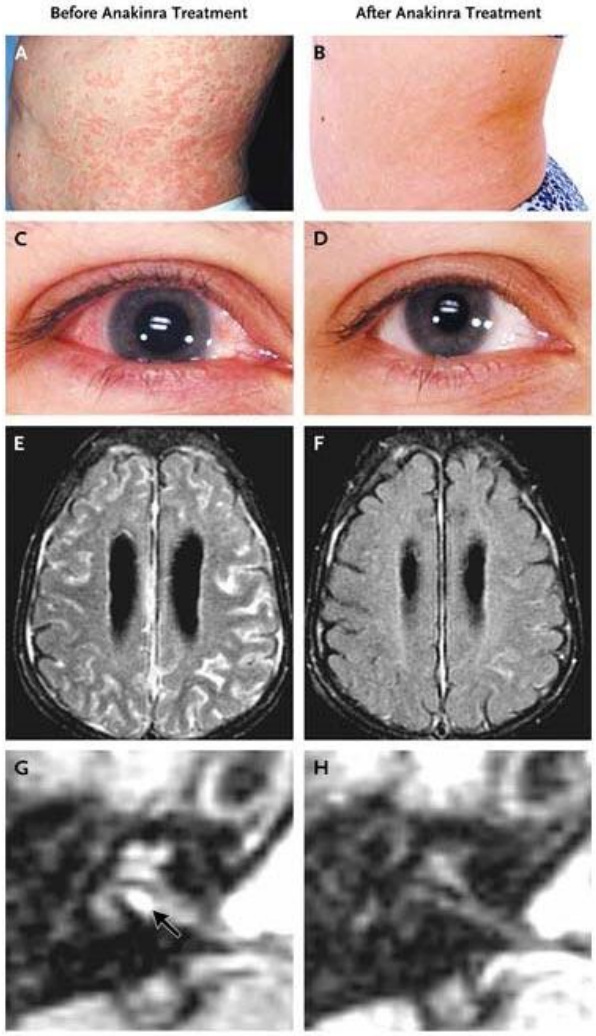
CAPS clinical features
Intrinsic inflammasome dysregulation

Non-periodic fever and urticarial rash



FCAS1	MWS	CINCA
Attacks after cold-exposure < 24 hr	Conjunctivitis Sensorineural hearing loss Cold urticaria Risk amyloidosis	Infantile-onset Chronic meningitis Arthropathy Amyloidosis Continuous with exacerbations

Inflammatory Organ Manifestations in Neonatal-Onset Multisystem Inflammatory Disease before (Panels A, C, E, and G) and after (Panels B, D, F, and H) Treatment with Anakinra.



DESIGN

Open label

n+=18 NOMID patients

Anakinra: 1-2 mg/kg

D/C @ 3months in11

End points:

- Score changes in diary
- Labs @ baseline, 3 mos. &flare
  - •Amyloid A
  - •ESR
  - •CRP

RESULTS

- •All 18 rapid response
- •Scores improved ($p<0.001$)
- •CRP median: 5.2 to 0.34
- •All labs $p<0.001$
- •Relapse within days after withdrawal
- •No AEs

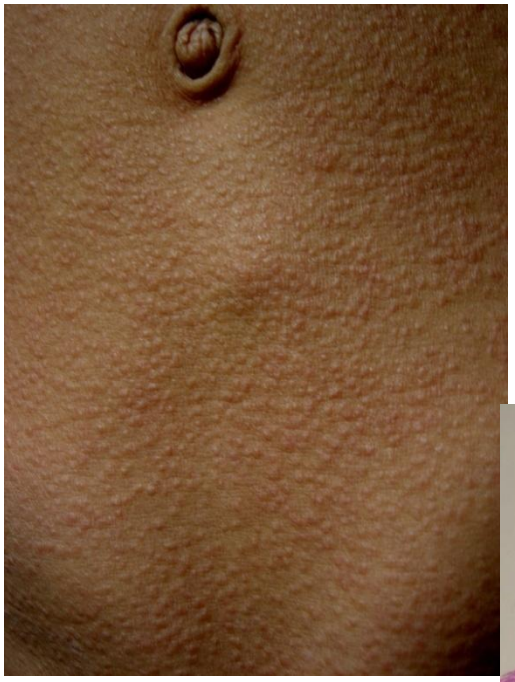
Long term still ongoing

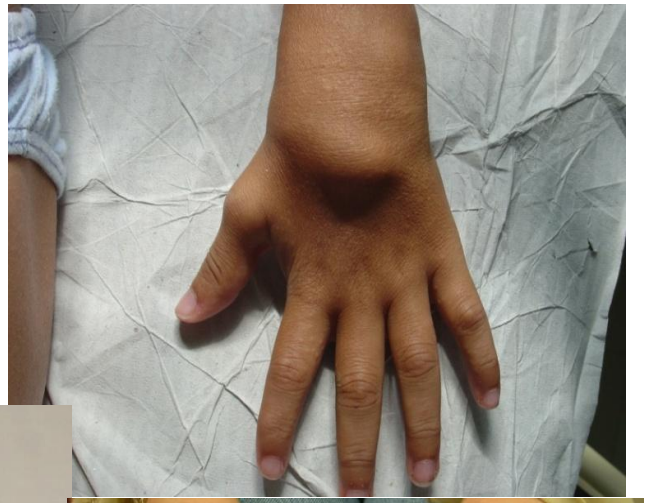
clinicaltrials.gov

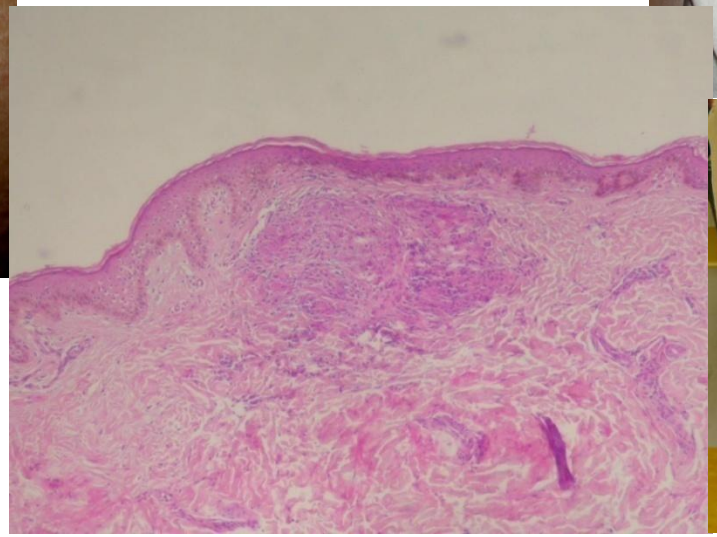
Goldbach-Mansky R et al. N Engl J Med 2006;355:581-592.

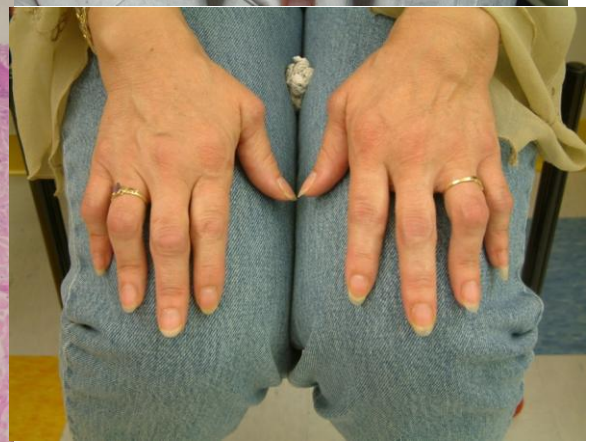
Pattern 3: CHRONIC & RECURRENT ARTHRITIS

BLAU SYNDROME









- Triad of polyarthritis, uveitis and granulomatous dermatitis
- Non-caseating epitheloid cell granulomas in biopsy tissue
- Familial (Blau syndrome) and sporadic (Early Onset Sarcoidosis) form
- Mutations in or near NACHT domain of *NOD2*

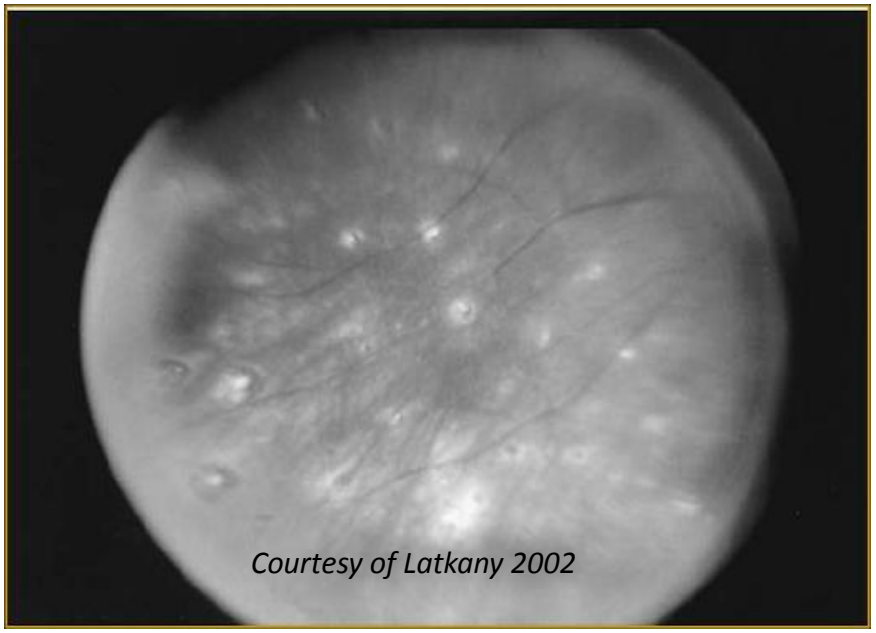
BLAU SYNDROME: OCULAR DISEASE

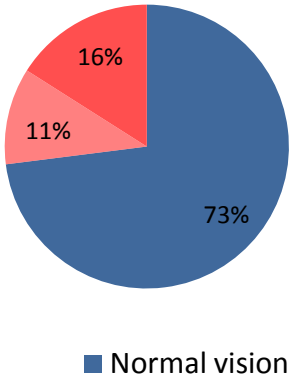
ANTERIOR

- KPs limbus
- Iris nodule
- BK
- Focal synechiae
- Cataract, Glaucoma

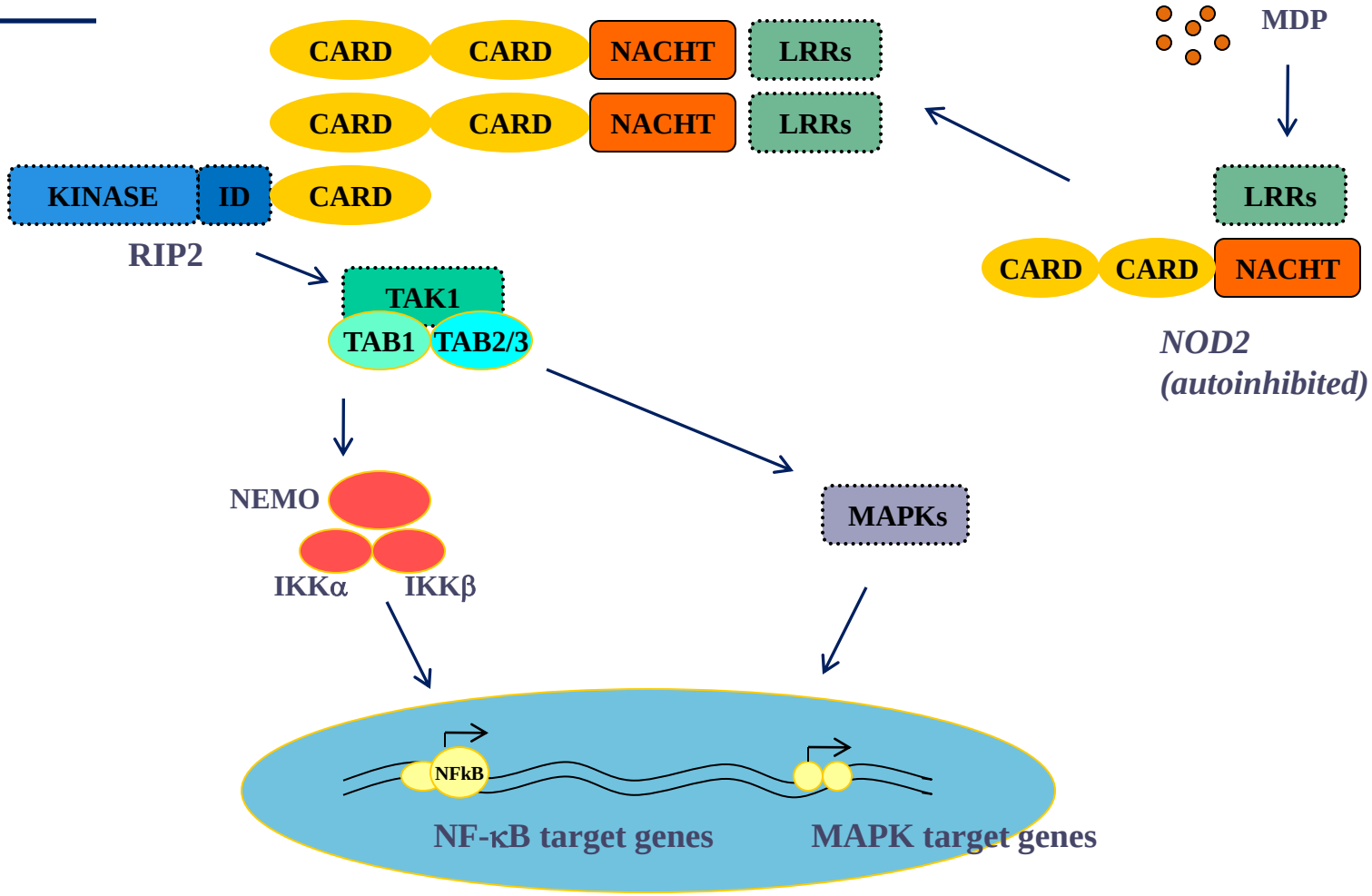
POSTERIOR

- Multifocal chroiditis
- Retinal vasculitis
- Macular edema
- **Persistent vitritis**





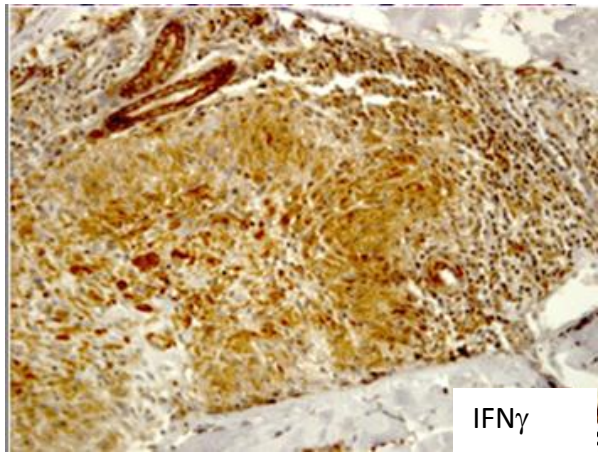
NOD2

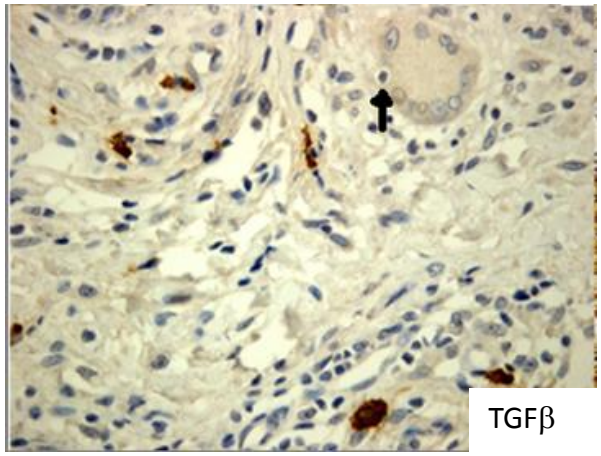


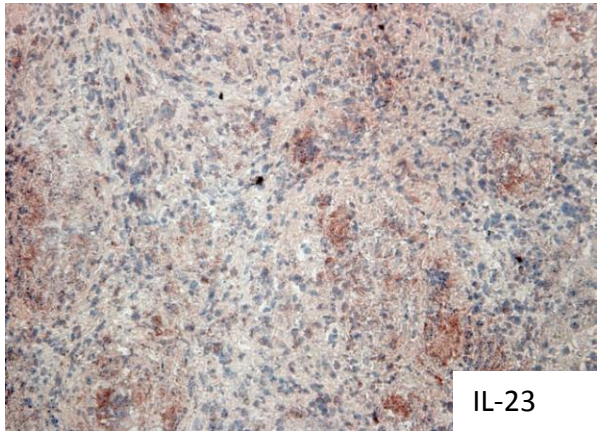
Intracellular pattern recognition receptor of bacterial peptidoglycan molecules
Recruitment of RIP2 kinase protein through CARD-CARD interaction
Activation of transcriptional factors & caspases, secretion of cytokines & chemokines

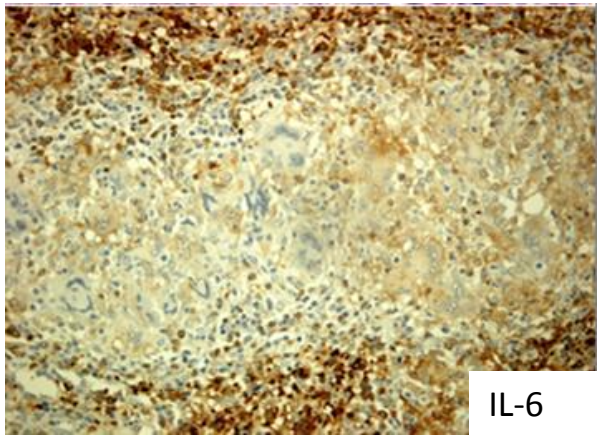
Blau granulomas

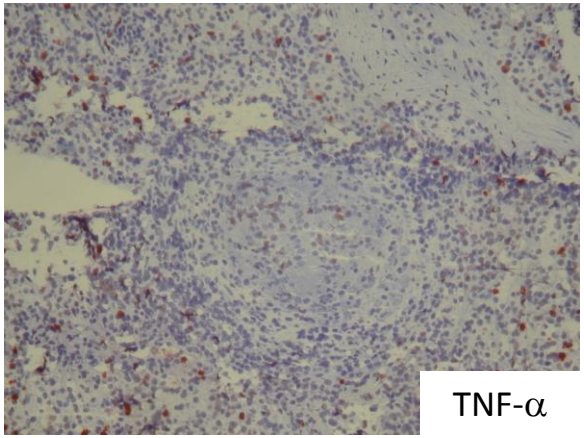
Inflammatory cytokine expression *in situ*

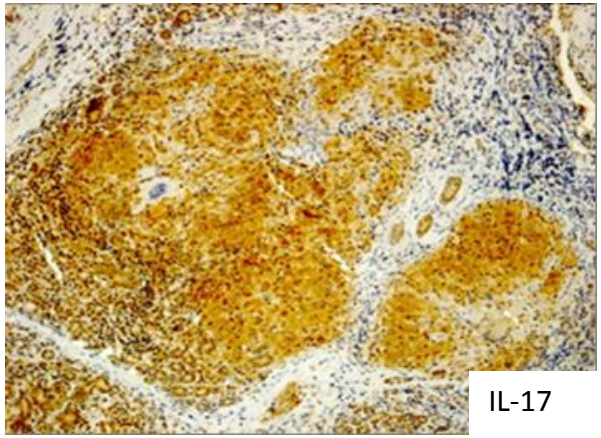

IFNγ

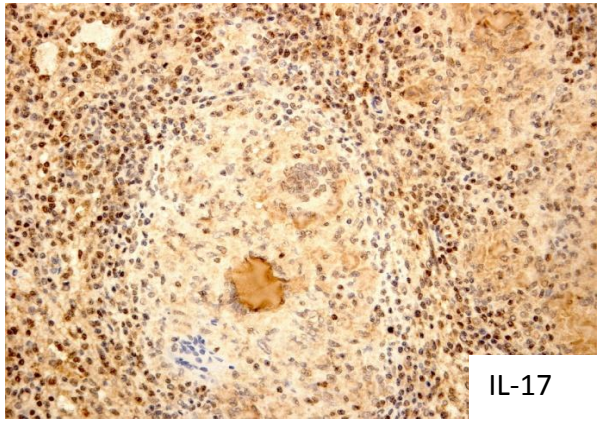

TGFβ

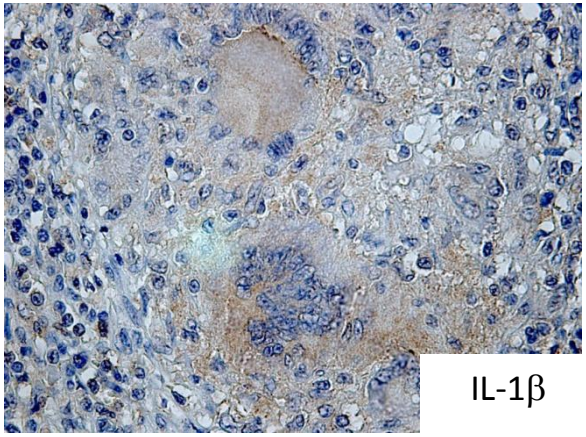

IL-23


IL-6

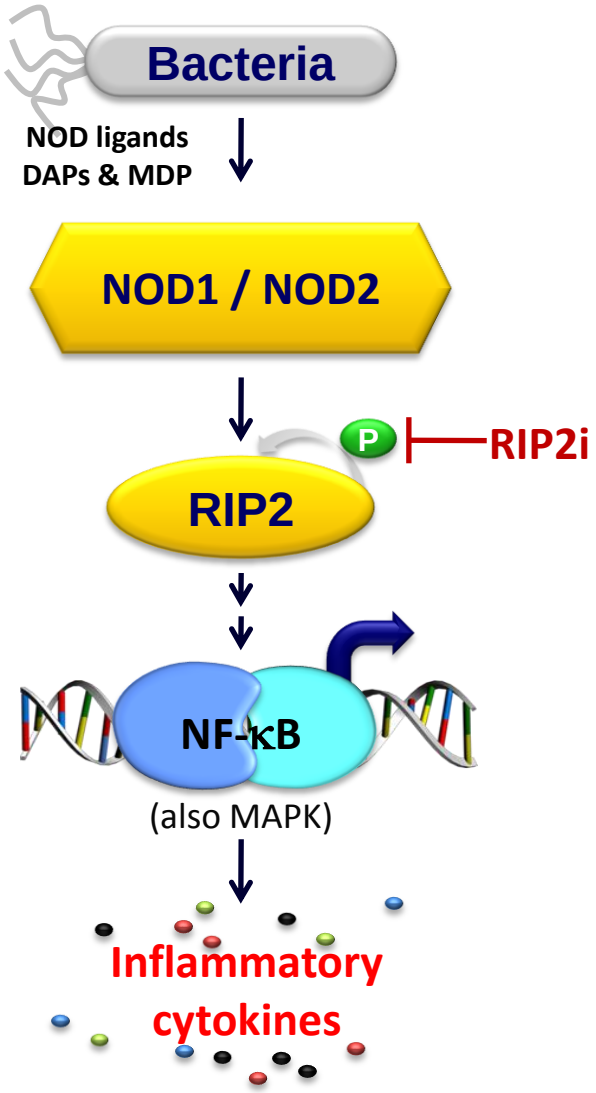

TNF-α

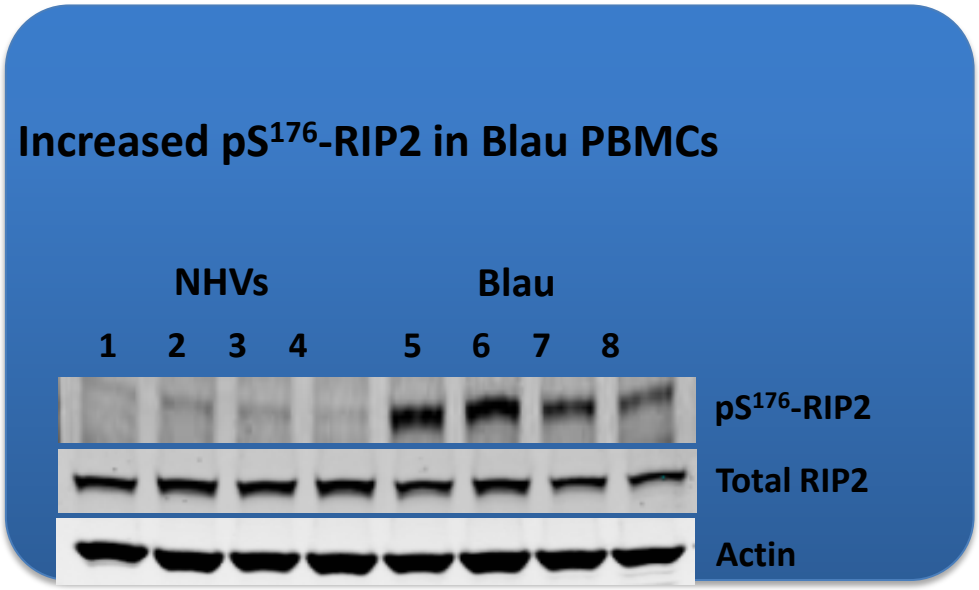

IL-17


IL-17


IL-1β

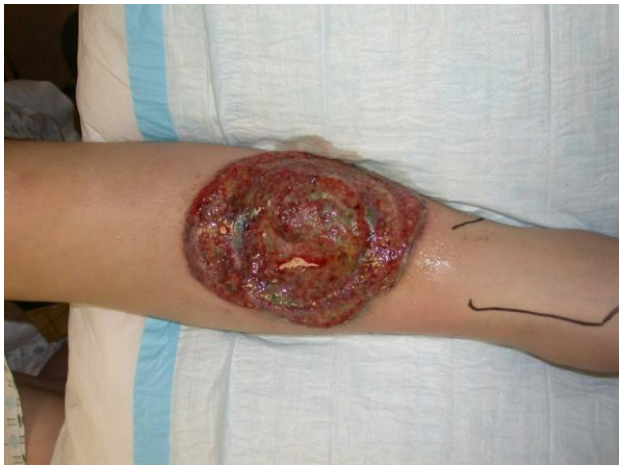
RIP2 Kinase-Mediated Signaling

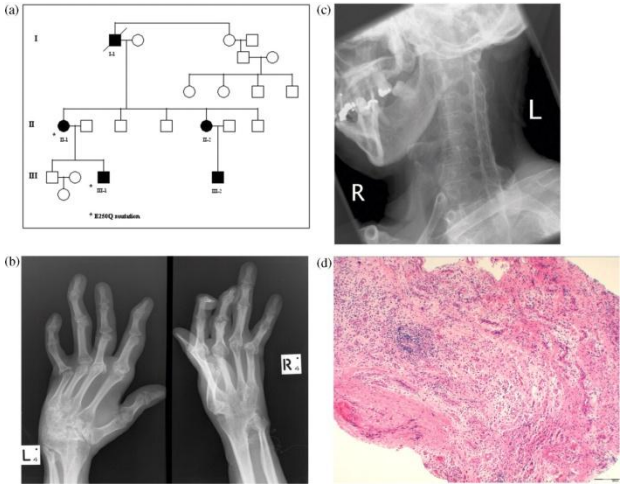




Demonstration of increased pS^{176}-RIP2 levels in Blau patient PBMCs using a GSK's custom rabbit mAb F8

Pyogenic **A**rthritis **P**yoderma gangrenosum and **A**cne



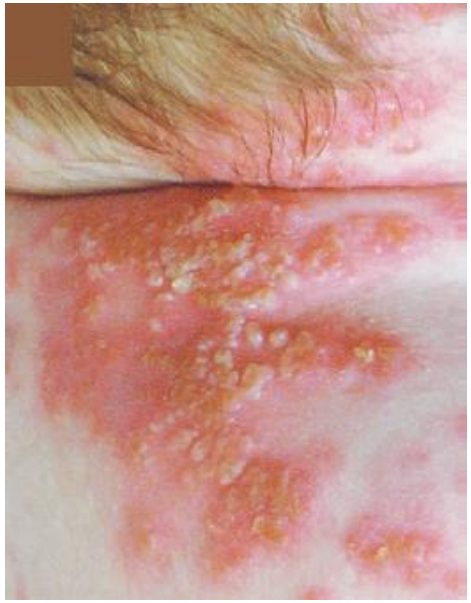


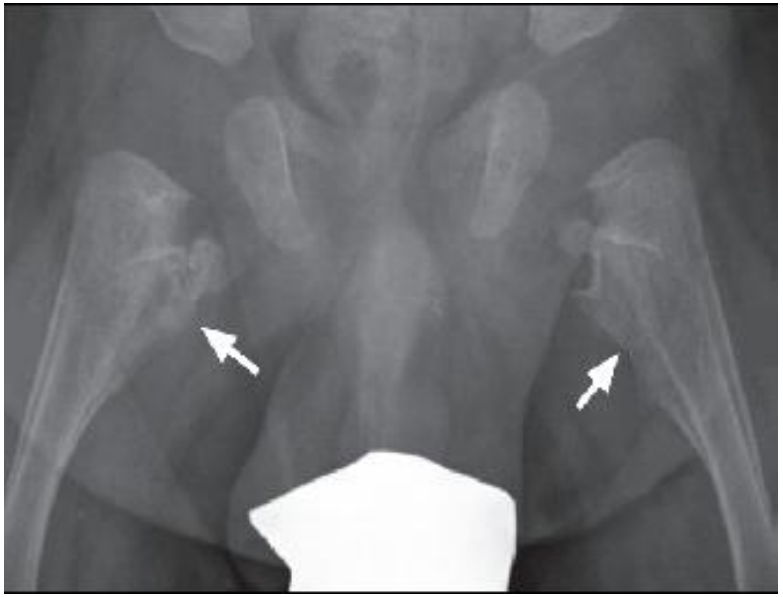
- Episodic large joint pyogenic destructive and ankylosing arthritis with onset in early childhood (1/3 in Eurofever Registry: non episodic)
- Cystic acne and pyoderma gangrenosum/pathergy in adolescence
- Gain of function AD mutation in the PSTPIP1 (exCD2BP), a binder of pyrin with promotion of pyrosome formation

Pattern 4: PUSTULAR PSORIASIS WITH /WITHOUT OSTEITIS

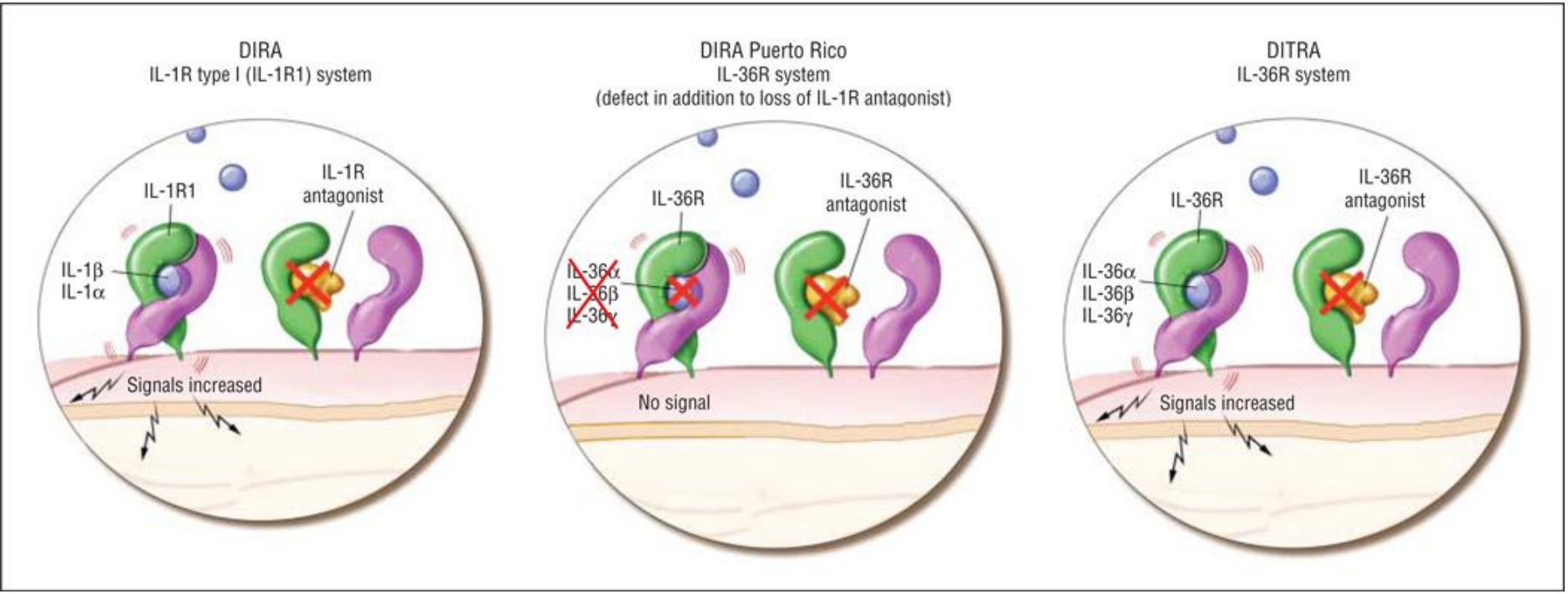
Deficiency of IL-1 Receptor Antagonist (DIRA)

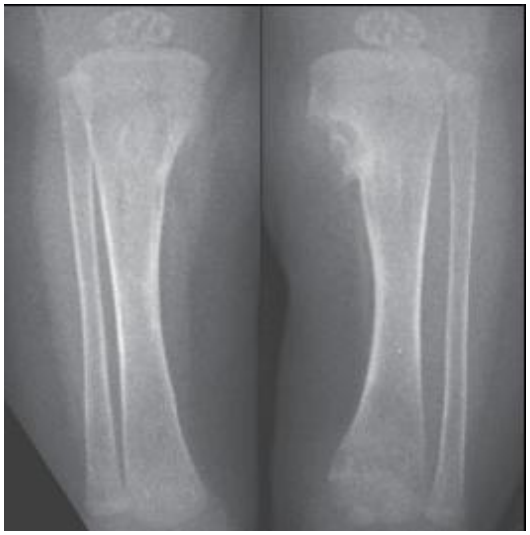
Mutations in IL1RN encoding endogenous IL-1 receptor antagonist

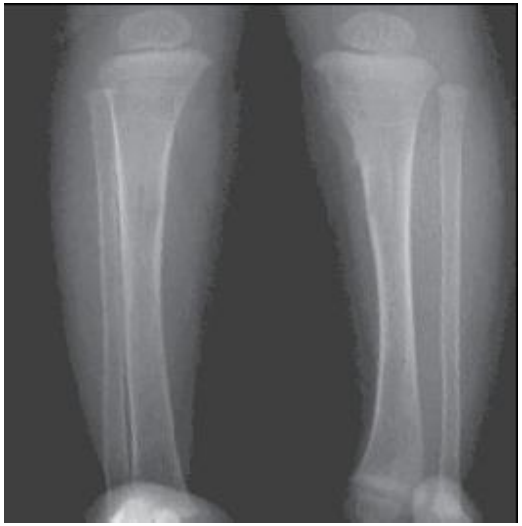




- Systemic inflammation neonatal period
- Pustular skin lesions, generalized pustulosis
- Multifocal osteolytic bone lesions, periostitis


DIRA
IL-1R type I (IL-1R1) system
IL-1R1
IL-1R antagonist
IL-1β
IL-1α
Signals increased
DIRA Puerto Rico
IL-36R system
(defect in addition to loss of IL-1R antagonist)
IL-36R
IL-36R antagonist
IL-36α
IL-36β
IL-36γ
No signal
DITRA
IL-36R system
IL-36R
IL-36R antagonist
IL-36α
IL-36β
IL-36γ
Signals increased





Prompt and dramatic improvement with IL-1 receptor antagonist therapy

N Eng J Med, 2009

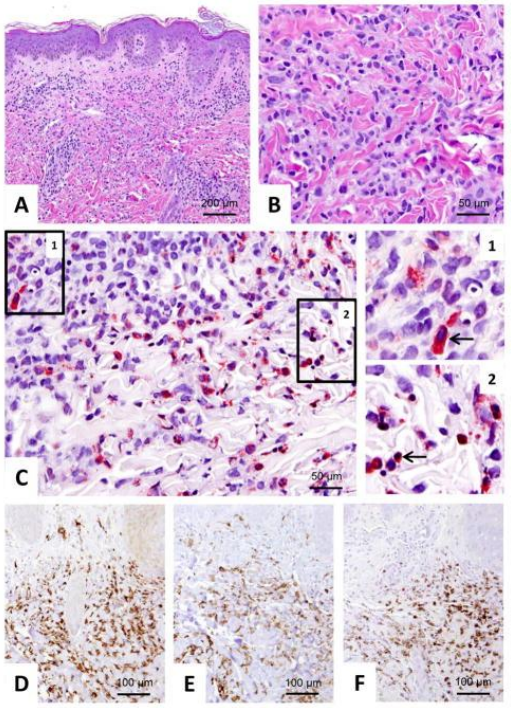
MAJEED

- Severe episodes of sterile osteomyelitis
- Dyserythropoyetic microcytic anemia
- Sweet syndrome
- Autosomic recessive hypomorphic mutation of LPIN2 (mouse model is PTSPIP2)

PANNICULITIS/LIPOATROPHY

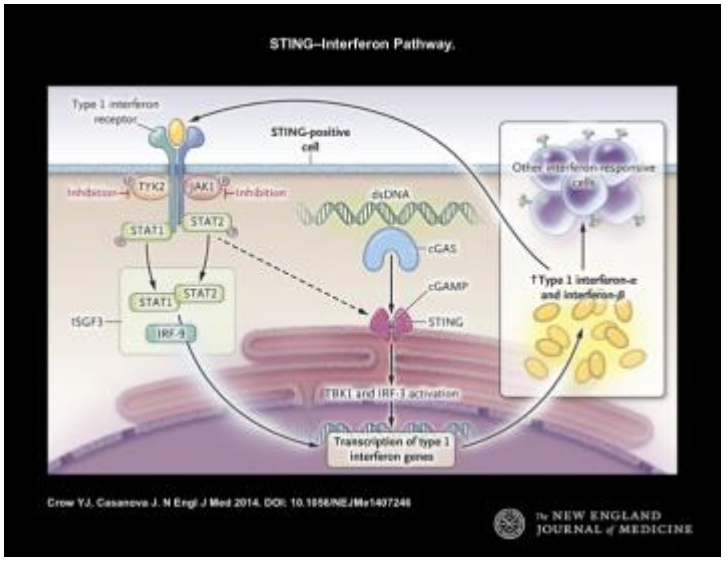
Chronic **A**typical **N**eutrophilic **D**ermatosis with **L**ipodystrophy and **E**levated temperature

- Younger than 6 months
- Periodic fever with purpuric annular plaques
- Later orbital erythema and lipodystrophy
- FTT
- **Interferon signature**
- Autoantibodies +/-
- Proteosome dysfunction due to mutation of PSMB8 gene



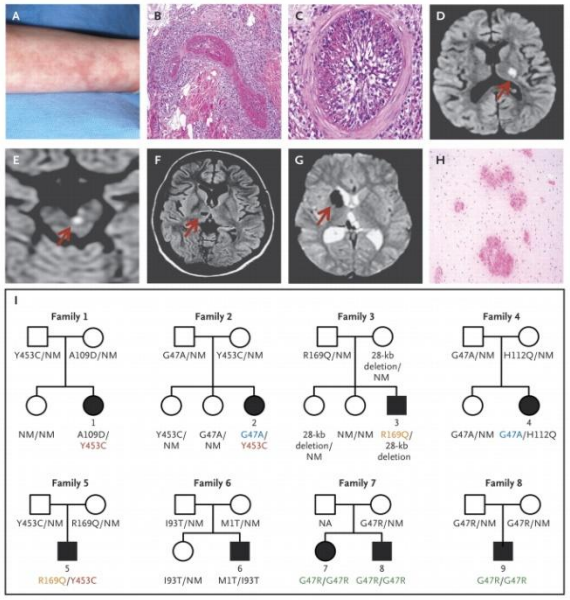
VASCULAR

STING **A**ssociated **V**asculopathy with onset in **I**nfancy

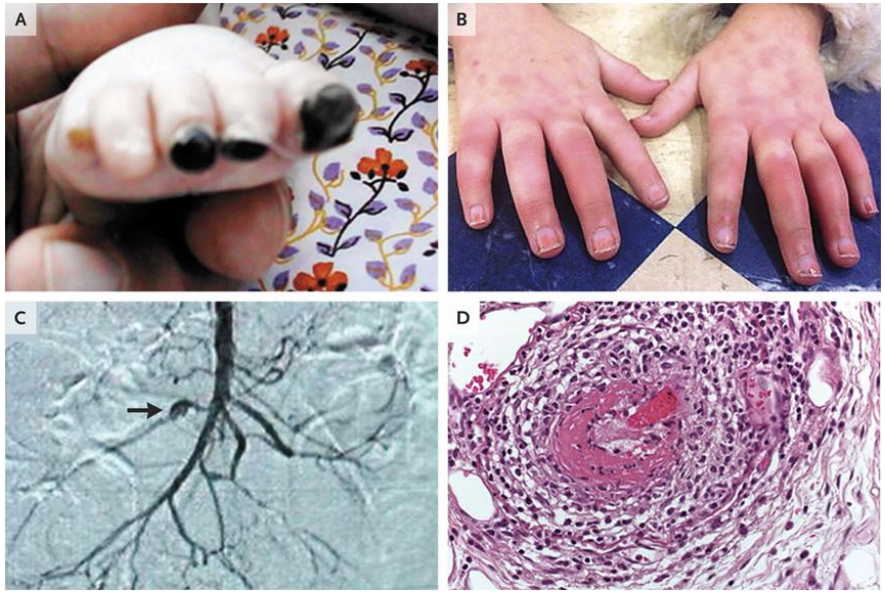


- Neonatal onset of inflammatory syndrome
- Fever and rash (blisters, pustules, telangiectasia) in face, ears and dorsum of hands. Vasculitic looking plaques.
- Capillary tortuosity and vasculitis with acroosteolysis and autoamputation
- Interstitial lung disease
- Gain of function mutation of TMEM173 encoding STING (Stimulator of interferon genes) leading to oversecretion of Interferon beta

ADA2 (CERC1)



Zhou Q et al. N Engl J Med 2014;370:911-920.



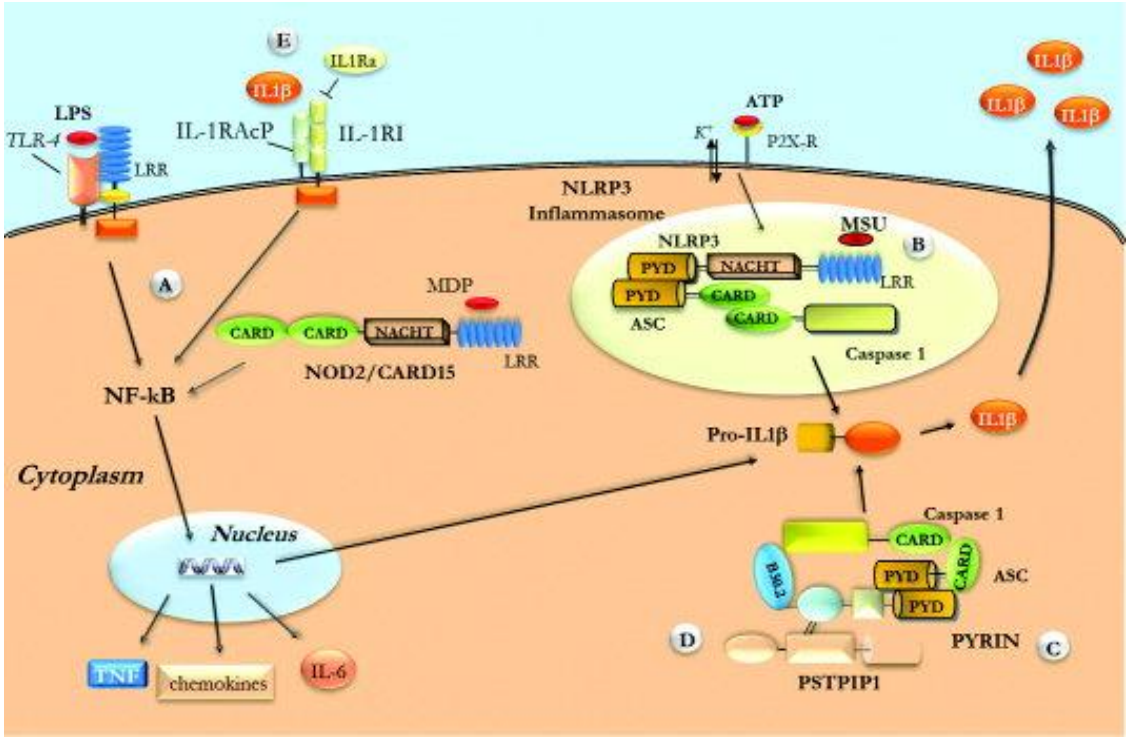
Navon Elkan P et al. N Engl J Med 2014;370:921-931.

- Inflammatory events with pernio (Bx perivascular or vasculitic)
- Sub cortical stroke with inflammation and hemorrhage on recurrence
- Pericyte function, discovered by exome sequencing and proven on zebra fish
- New phenotype associated with Castleman's

- 5 pedigrees AR inheritance
- Caucasian (Georgian jews and german)
- Typical PAN pattern with more pernio and CNS involvement

Management

- If you don't know what it is try colchicine for the "periodics" and anti-IL-1 for the persitent febrile diseases (CAPS)
- If you know what it is **pray** that iIL-1 is involved (TRAPS, HIDS, DIRA)(good luck)
- NFkB mediated: anti TNF is a good start. Consider Toci
- Methotrexate works for arthritic diseases. PAPA is a nightmare
- Interferonopathies (CANDLE, SAVI) may respond to JAK inhibitors: the "ibs"



Gattorno & Martini. A&R 2013; 65: 1137