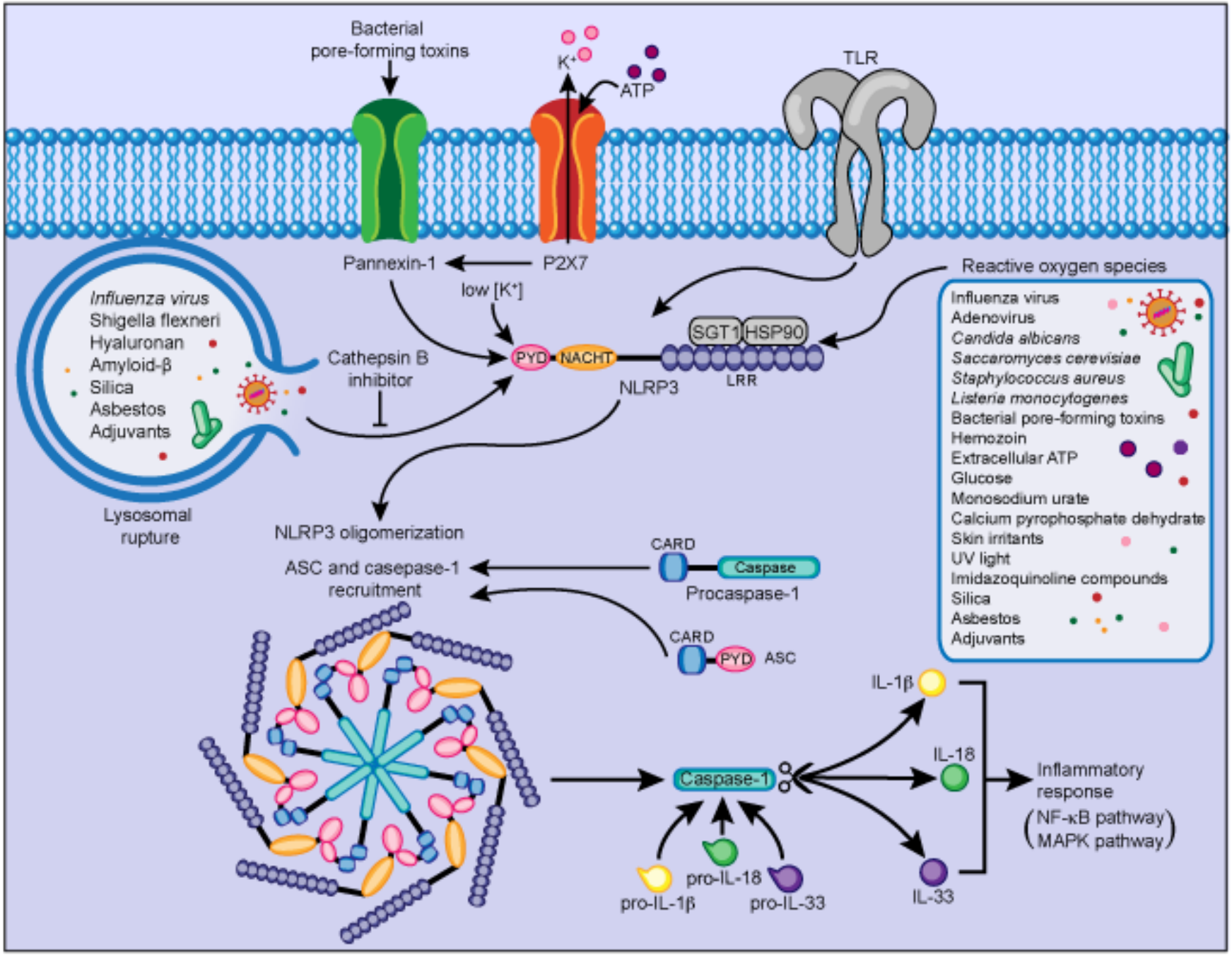
The Role of Q703K in the NLRP3 Gene in Patients with Autoinflammatory Syndromes

Yael Brantz
Elon Pras


Bacterial
pore-forming toxins
K+
ATP
TLR
Pannexin-1
P2X7
low [K+]
Reactive oxygen species
Influenza virus
Shigella flexneri
Hyaluronan
Amyloid-β
Silica
Asbestos
Adjuvants
Cathepsin B
inhibitor
PYD
NACHT
SGT1
HSP90
LRR
NLRP3
Influenza virus
Adenovirus
Candida albicans
Saccaromyces cerevisiae
Staphylococcus aureus
Listeria monocytogenes
Bacterial pore-forming toxins
Hemozoin
Extracellular ATP
Glucose
Monosodium urate
Calcium pyrophosphate dehydrate
Skin irritants
UV light
Imidazoquinoline compounds
Silica
Asbestos
Adjuvants
Lysosomal
rupture
NLRP3 oligomerization
ASC and casepase-1
recruitment
CARD
Caspase
Procaspase-1
CARD
PYD
ASC
IL-1β
IL-18
Caspase-1
Inflammatory
response
(NF-κB pathway
MAPK pathway)
pro-IL-18
pro-IL-1β
pro-IL-33
IL-33

Skin:
Cold-induced: Fever
Urticaria
Arthralgia
Conjunctivitis

Normal life span

FCAS
Familial cold autoinflammatory syndrome

Skin:
Fever
Abdominal pain
Urticaria
Conjunctivitis

Musculoskeletal:
Arthritis
Hearing loss

Hearing loss (2nd-4th decade of life)
amyloidosis up to 30%

MWS
Muckle Wells syndrome

Skin:
Fever
Urticaria

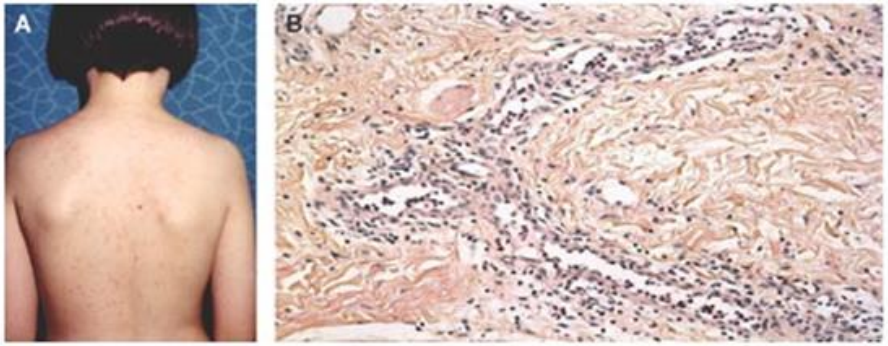
Musculoskeletal:
Arthropathy
Hearing loss

CNS involvement:
Headaches
Meningitis, papilledema

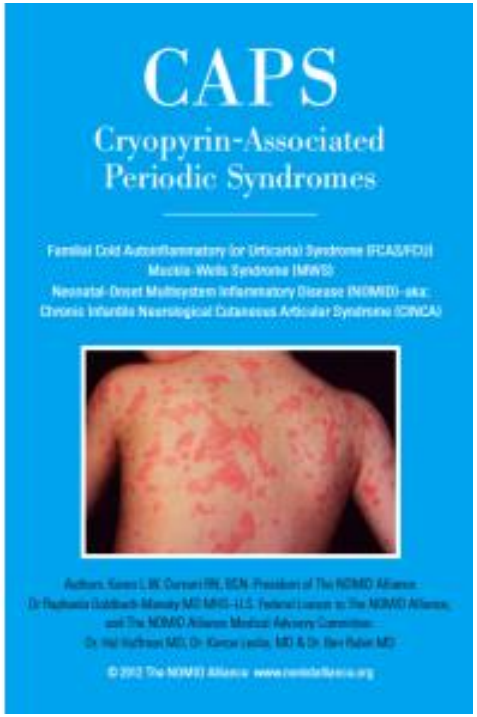
Mental retardation,
hearing loss (1st decade of life),
short statue, vision loss, joint contractures, unable to reproduce

NOMID/CINCA
Neonatal-onset multisystem inflammatory syndrome
Chronic infantile neurological, cutaneous and arthritis

Figure 1 Skin rash in a patient with cryopyrinopathy.



Neven B *et al.* (2008) Cryopyrinopathies: update on pathogenesis and treatment *Nat Clin Pract Rheumatol* doi:10.1038/ncprheum0874



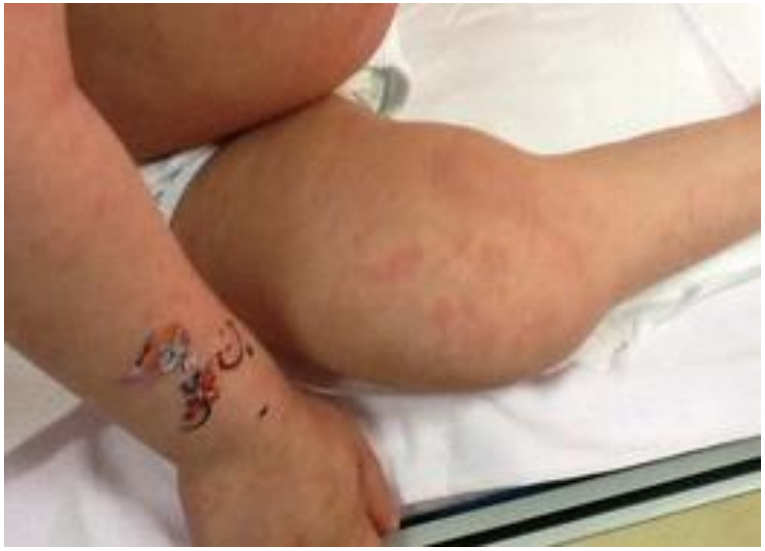
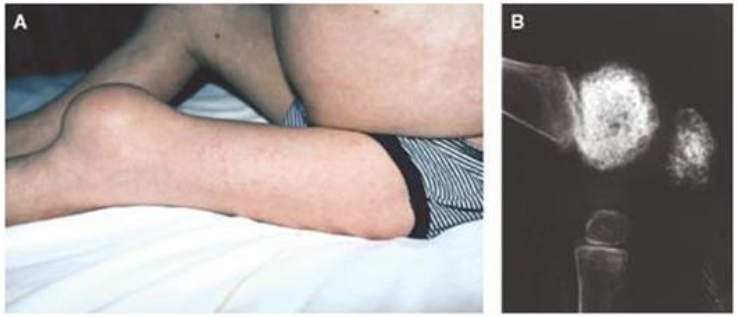


Figure 2 Overgrowth arthropathy in a patient with CINCA (NOMID).



- Autoinflammatory diseases (AIDs), also called periodic fever syndrome, refer to a group of rare hereditary recurrent unprovoked inflammation without high titres of autoantibodies or antigen-specific T lymphocyte in the absence of infection

Syndrome	Gene	Inheritance	Age at onset	Distinctive Features	Treatment
FMF	MEFV Chr. 16	Recessive ΔM694 is dominant	Childhood	Attacks < 3 days Abdominal pain 85% Chest pain 15%	Colchicine
TRAPS	TNFRSF1A Chr. 12	Dominant	Childhood	Attacks > 7days	Int. corticosteroids Anakinra
MKD	MVK Chr .12	Recessive	Infancy	Vaccination induced attacks, Gut upset, attacks ~ 7 days	Int. corticosteroids Anakinra Etanercept
CAPS	NLRP3 Chr. 1	Dominant or Sporadic	Birth	Cold induced attacks Worse later in day Nettle rash Headaches Deafness in 40%	Anakinra Rilonacept Canakinumab
NALP12 associated periodic syndrome	NALP12 Chr.19	Dominant	Infancy	Cold induced attacks Nettle rash Deafness	None reported
DIRA	IL1RN	Recessive	Infancy	Looks like bone infection, Pustular rash	Anakinra
PAPA	PSTPIP1(CD2BP1) Ch.15	Dominant	Childhood	Looks like joint infections, Deep scarring rash	Etanercept
Blau Syndrome	NOD2(CARD15) Ch.6	Dominant	Childhood	Arthritis, inflammation in the eyes, rashes	Corticosteroids ? Biologics
Majeed Syndrome	LPIN2 Ch.18	Recessive	Infancy	Looks like bone infection, problems making blood cells, rashes	NSAIDS & Corticosteroids
DITRA	IL36RN Chr. 2	Recessive	Childhood to 6th decade	Recurrent episodes of pustular rash & fever	
CANDLE /JMP	PSMB8 Chr.6	Recessive	Birth	Rash, joint aches and swelling and Loss of fat under facial skin.	

Mutation

Polymorphism

VOUS

Q703K – Benign polymorphism or a disease causing mutation?

PROS

CONS

- FCAS like clinical phenotype in small case series of Q703K carriers
- Associated with increased IL-1β secretion
- Somewhat increased prevalence in cases>controls (7% vs. 3%-5%)

- Located outside of the NACHT domain
- Same prevalence in cases and controls according to some studies

Q703K in NLRP3

80 patients with various autoinflammatory symptoms were checked

10 were found positive (12.5%)

Frequency in the databases between 2-9% (average 3-5%)

	Cold induced	Fever	Arthralgia	Conjuctivitis	Rash	Deafness	Amyloidosis
1	√	√	√	√	√		
2	√	√	√		√		
3		√	√		√		
4		√			√		
5							
6		√			√		
7			√		√	√	
8		√			√		
9		√			√		
10		√					

Hypothesis

- Q703K is over represented in patients with periodic fever and rash suspected of suffering from an autoinflammatory syndrome

Methods (1)

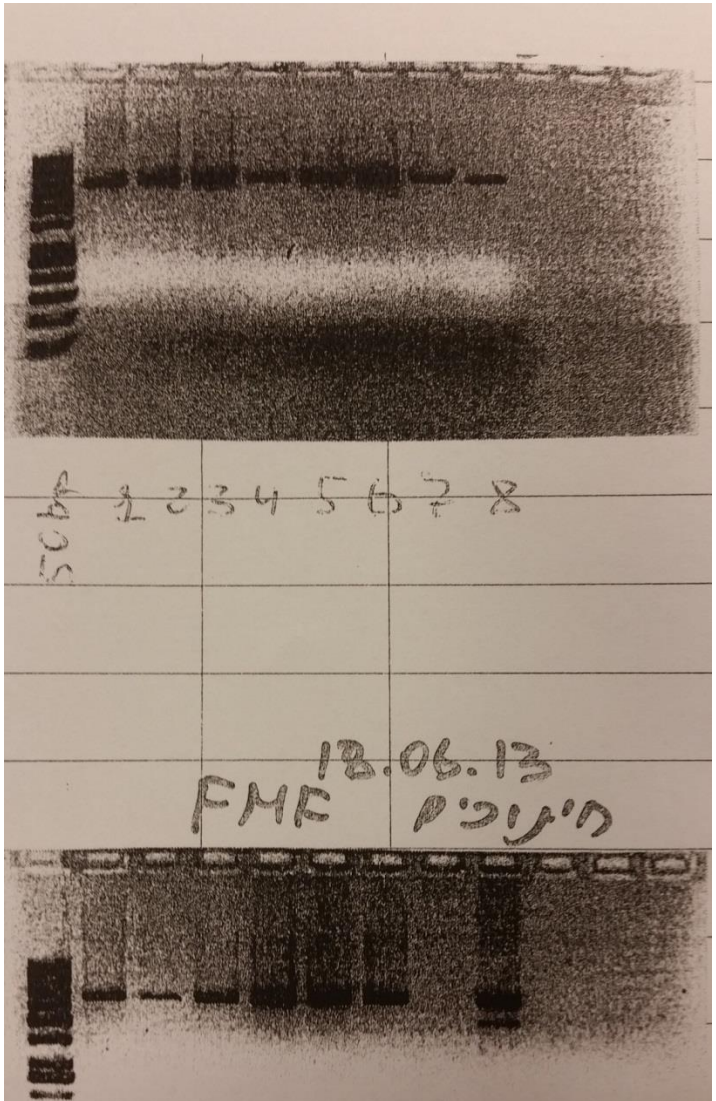
Isolate from the 80 patients checked for Q703K those with recurrent fever and rash

create a control group which will fit the ethnic origin of the positive patients and check the frequency of the Q703K missense change

Methods (2)

- Collect 10 control DNA's for each positive patient in concordance with his/her ethnic origin
- All together 70 samples
- Check them for the Q703K change
- Perform statistical analysis

Q703K Restriction Assay



PubMed nlrp3 multiple sclerosis

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☐ [**NLRP3** inflammasome and **multiple sclerosis**/EAE].

1. Inoue M, Shinohara ML.
Nihon Rinsho. 2015 Sep;73 Suppl 7:835-41. Japanese. No abstract available.
PMID: 26480802

☐ The pathogenic role of the inflammasome in neurodegenerative diseases.

2. Freeman LC, Ting JP.
J Neurochem. 2015 Jun 27. doi: 10.1111/jnc.13217. [Epub ahead of print]
PMID: 26119245

☐ Fumaric acid esters prevent the **NLRP3** inflammasome-mediated and ATP-triggered pyroptosis of

3. differentiated THP-1 cells.
Miglio G, Veglia E, Fantozzi R.
Int Immunopharmacol. 2015 Sep;28(1):215-9. doi: 10.1016/j.intimp.2015.06.011. Epub 2015 Jun 18.
PMID: 26096886

☐ Expanding spectrum of neurologic manifestations in patients with **NLRP3** low-penetrance

4. mutations.
Schuh E, Lohse P, Ertl-Wagner B, Witt M, Krumbholz M, Frankenberger M, Gerdes LA, Hohlfeld R, Kümpfel T.
Neurol Neuroimmunol Neuroinflamm. 2015 May 14;2(4):e109. doi: 10.1212/NXI.0000000000000109. eCollection 2015 Aug.
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