4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

Μονογονιδιακά αυτοφλεγμονώδη νοσήματα με εικόνα περιοδικού πυρετού

Παναγιώτης Σκένδρος

Αν. Καθηγητής Παθολογίας

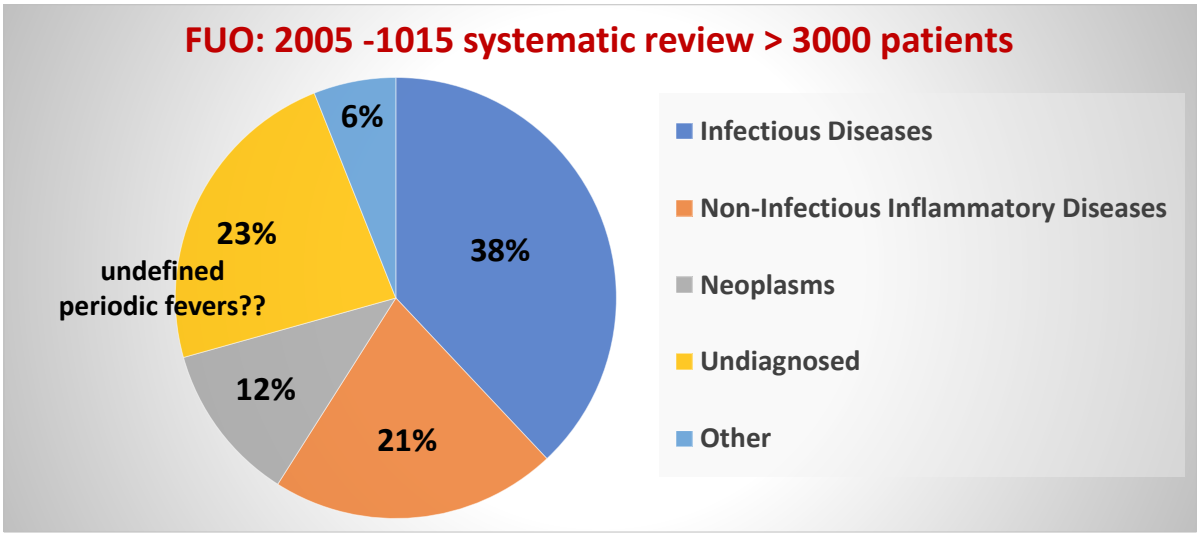
Α' Παθολογική Κλινική

& Εργαστήριο Μοριακής Αιματολογίας,

Πανεπιστημιακό Νοσοκομείο Αλεξανδρούπολης

Δημοκρίτειο Πανεπιστήμιο Θράκης

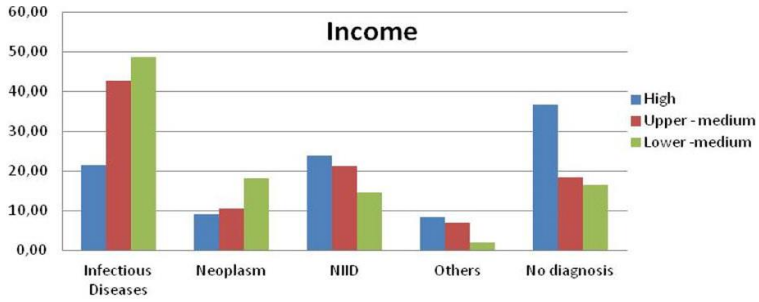
www.inflathrace.gr



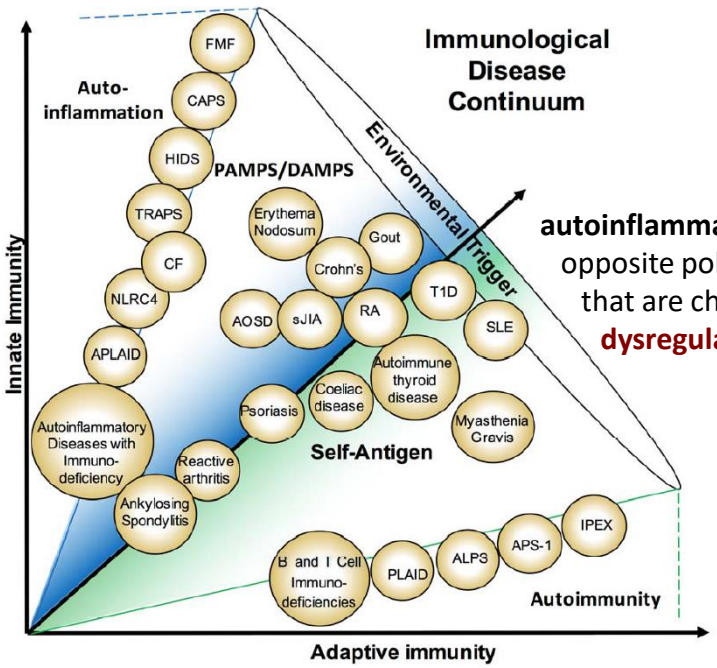
Fusco FM et al. BMC Infect Dis 2019

Non-Infectious Inflammatory Diseases (NIID)
Major causes of inflammation in Internal Medicine

- ✓ ***Autoimmune diseases***
- ✓ ***Autoinflammatory diseases***



Vanderschueren S, et al. Arch Intern Med 2003 - Bleeker-Rovers CP, et al. Medicine (Baltimore) 2007 - Horowitz HW. N Engl J Med 2013 - Fusco FM et al BMC Infect Dis 2019



autoinflammation and **autoimmunity** are the two opposite poles of the same spectrum disorders that are characterized by **immune response dysregulation** and **chronic inflammation**

- McGonagle D, McDermott MF. PLoS Med. 2006
- Peckham et al. J Pathol. 2016

Common characteristics of systemic autoinflammatory diseases (SAIDs)

- **Systemic inflammation/recurrent fever/neutrophilia**
- **Dysregulation of innate immunity**
- **Absence of autoantibodies /autoreactive T-cells**
- **Absence of active infection**
- **Monogenic periodic fever syndromes**
- **Multifactorial diseases or common metabolic disorders**
- **If untreaded, progressive organ damage, morbidity & increased mortality**

IL-1-mediated autoinflammatory diseases: most frequent monogenic periodic fevers (HPFs)

- Characterized by recurrent attacks of **fever**; **rash**; **serositis**; **lymphadenopathy**; and **musculoskeletal involvement**
- In HPFs, genetic mutations lead to **dysregulation of the innate immune system** and to **episodic manifestations of systemic inflammation**
  - **Familial Mediterranean fever (FMF)**
  - **Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS)**
  - **Tumor necrosis factor receptor–associated periodic syndrome (TRAPS)**
  - **Cryopyrin-associated periodic syndromes (CAPS)**

Overlap of Symptoms Can Exist Between The Syndrome Classifications

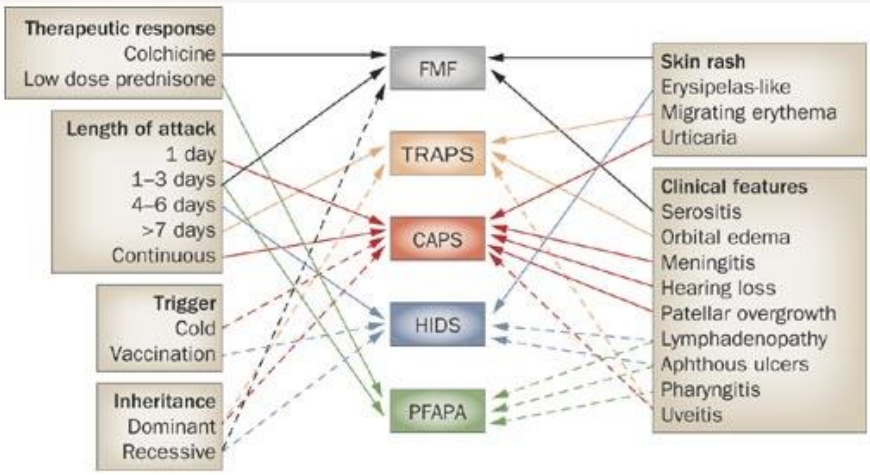
https://www.autoinflammatorydiseases.com/autoinflammatory-diseases

CLINICAL classification criteria for hereditary recurrent fevers

CAPS	FMF	TRAPS	MVK
Presence of *at least two of five**: ▶ Urticarial rash. ▶ Cold/Stress-triggered episodes. ▶ Sensorineural hearing loss. ▶ Chronic aseptic meningitis. ▶ Skeletal abnormalities (epiphysial overgrowth/frontal bossing).	At least *six out of nine*: Presence ▶ Eastern Mediterranean ethnicity. ▶ Duration of episodes, 1–3 days. ▶ Chest pain. ▶ Abdominal pain. ▶ Arthritis. Absence ▶ Aphthous stomatitis. ▶ Urticarial rash. ▶ Maculopapular rash. ▶ Painful lymph nodes.	Score ≥5 points: Presence ▶ Fever ≥7 days (2 points). ▶ Fever 5–6 days (1 point). ▶ Migratory rash (1 point). ▶ Periorbital oedema (1 point). ▶ Myalgia (1 point). ▶ Positive family history (1 point). Absence ▶ Aphthous stomatitis (1 point). ▶ Pharyngotonsillitis (1 point).	Presence of *at least three of six*: ▶ Age at onset <1 years. ▶ Gastrointestinal symptoms. ▶ Painful lymph nodes. ▶ Aphthous stomatitis. ▶ Triggers. ▶ Maculopapular rash.
Sensitivity: 0.80	Sensitivity: 0.91	Sensitivity: 0.87	Sensitivity: 0.91
Specificity: 0.91	Specificity: 0.92	Specificity: 0.92	Specificity: 0.82
Accuracy: 0.85	Accuracy: 0.97	Accuracy: 0.96	Accuracy: 0.92

Gattorno M et al. Ann Rheum Dis. 2019

Diagnostic features and differential diagnosis of recurrent febrile syndromes



Variable disease courses

No fever (especially in adults)

Longer or shorter febrile episodes

nature REVIEWS RHEUMATOLOGY

Hoffman HM and Simon A. Nat Rev Rheumatol 2009

Identification of the "inflammasome": a major breakthrough in the field of innate immunity & autoinflammation

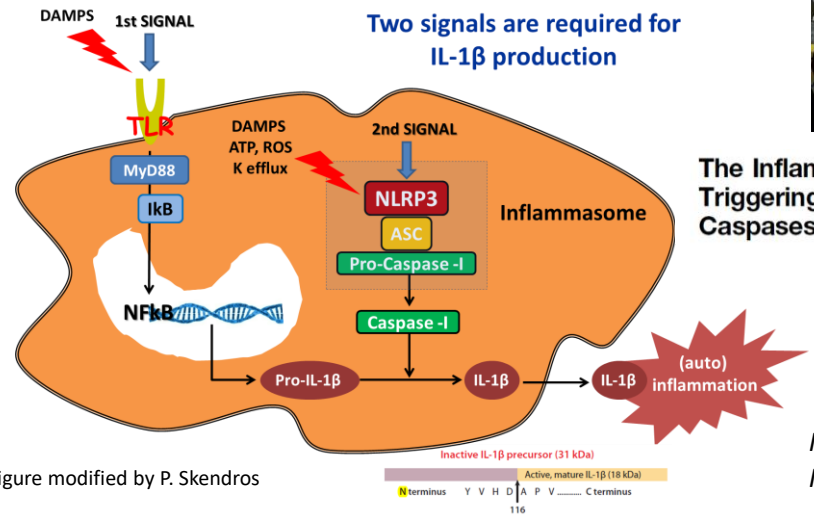
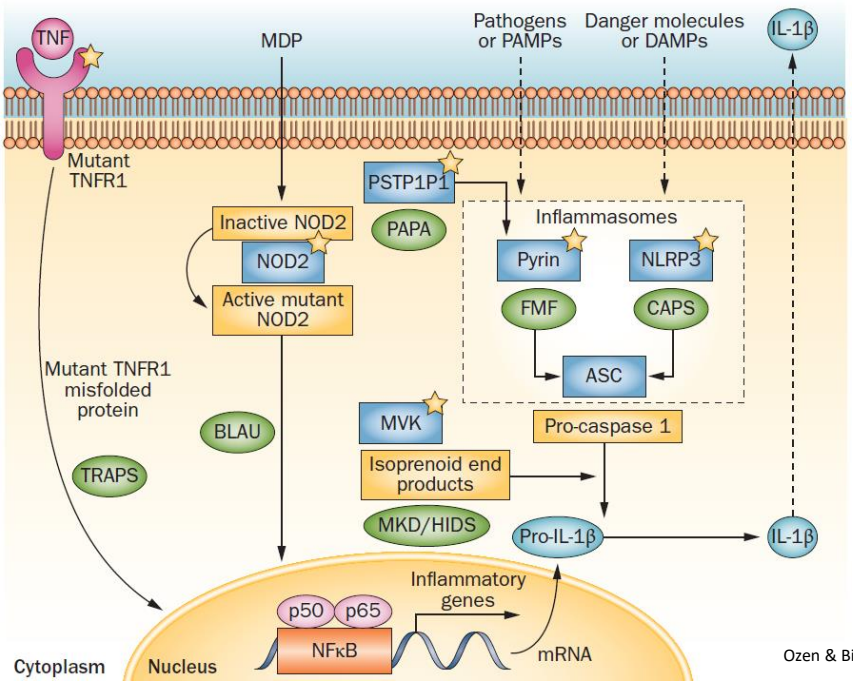


Figure modified by P. Skendros

The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL-β

Martinon F, Burns K, Tschopp J. Mol Cell. 2002



Ozen & Bilginer. *Nat Rev Rheumatol. 2014*

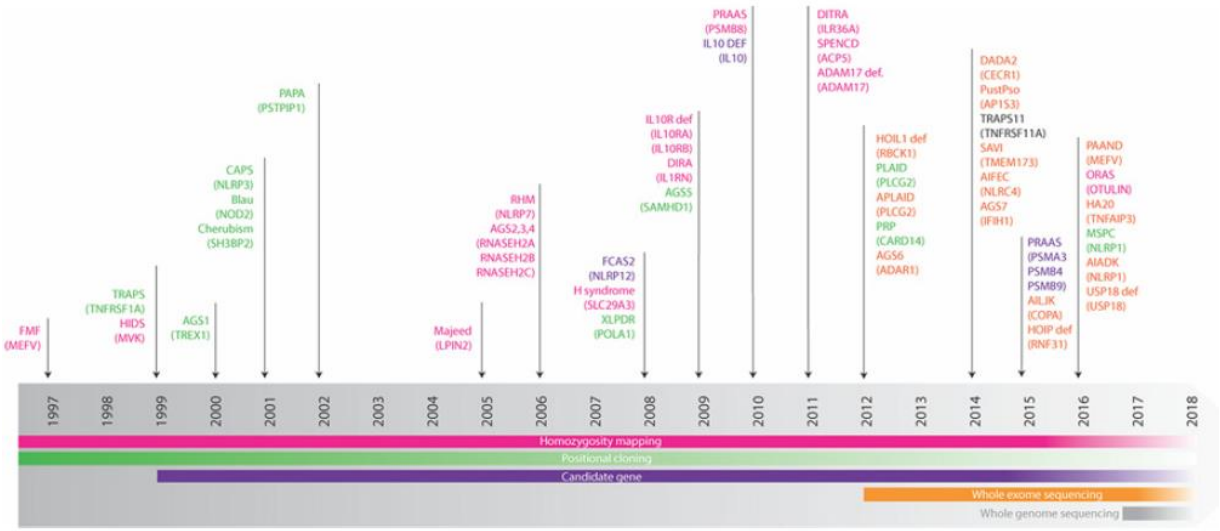
New Eurofever/PRINTO classification criteria for HRFs

CAPS	FMF	TRAPS	MKD
Presence of a *confirmatory NLRP3 genotype** and *at least one* among the following: ► Urticarial rash. ► Red eye (conjunctivitis, episcleritis, uveitis). ► Neurosensorial hearing loss. OR Presence of *not confirmatory NLRP3 genotype*† and *at least two* among the following: ► Urticarial rash. ► Red eye (conjunctivitis, episcleritis, uveitis). ► Neurosensorial hearing loss.	Presence of *confirmatory MEFV genotype** and *at least* one among the following: ► Duration of episodes 1–3 days. ► Arthritis. ► Chest pain. ► Abdominal pain. OR Presence of *not confirmatory MEFV* genotype‡ and *at least two* among the following: ► Duration of episodes 1–3 days. ► Arthritis. ► Chest pain. ► Abdominal pain.	Presence of confirmatory *TNFRSF1A* genotype* and at least one among the following: ► Duration of episodes ≥7 days. ► Myalgia. ► Migratory rash. ► Periorbital oedema. ► Relatives affected. OR Presence of a not confirmatory *TNFRSF1A* genotype† and *at least two* among the following: ► Duration of episodes ≥7 days. ► Myalgia. ► Migratory rash. ► Periorbital oedema. ► Relatives affected.	Presence of a *confirmatory MVK genotype** and *at least one* among the following: ► Gastrointestinal symptoms. ► Cervical lymphadenitis. ► Aphthous stomatitis.
Sensitivity: 1	Sensitivity: 0.94	Sensitivity: 0.95	Sensitivity: 0.98
Specificity: 1	Specificity: 0.95	Specificity: 0.99	Specificity: 1
Accuracy: 1	Accuracy: 0.98	Accuracy: 0.99	Accuracy: 1

- **confirmatory genetic test (<u>pathogenic</u> or <u>likely pathogenic</u> variant)**
- **not confirmatory genetic test (<u>variants of unknown significance</u>-VUS)**

Gattorno M et al. Ann Rheum Dis. 2019

Timeline of monogenic autoinflammatory disorder discovery and genetic sequencing technique used



Moghaddas F, Masters SL. Clin Sci (Lond). 2018

Στοχευμένη Αλληλούχηση Νέας Γενιάς (targeted-NGS)

αλληλούχηση του πλήρους τμήματος των εξονίων (whole exome seq) 16 γονιδίων

Γονίδιο	Σχετιζόμενη Ασθένεια (Ακρωνύμιο)
1. ADA2	Deficiency of adenosine deaminase 2 (DADA2)
2. CARD14	CARD14-mediated psoriasis (CAMPS/PSORS2)
3. ELANE	ELANE-related neutropenia
4. IL36RN	Deficiency of IL-36-receptor antagonist (DITRA)
5. LPIN2	LPIN2 deficiency/ Majeed syndrome
6. MEFV	Familial Mediterranean fever (FMF)
7. MVK	Mevalonate kinase deficiency/Hyper IgD syndrome (MVK/HIDS)
8. NLRC4	NLRC4 macrophage activation syndrome/ familial cold autoinflammatory syndrome 4 (MAS/FCAS4)
9. NLRP3	Cryopyrin-associated periodic syndromes (FCAS, MWS, NOMID/CINCA)
10. NLRP12	Familial cold autoinflammatory syndrome 2 (FCAS2)
11. NOD2	Blau syndrome/early-onset sarcoidosis (Blau syndrome)
12. PSMB8	Proteasome-Associated Autoinflammatory Syndromes (PRAAS)
13. PSTPIP1	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)
14. TNFAIP3	Haploinsufficiency of A20 (HA20)
15. TNFRSF1A	TNFR1-associated periodic syndrome (TRAPS)
16. TRNT1	Sideroblastic anaemia with immunodeficiency, fevers, and developmental delay (SIFD)

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΠΑΘΟΛΟΓΙΚΗ ΦΥΣΙΟΛΟΓΙΑ
ΕΡΓΑΣΤΗΡΙΟ ΣΥΝΔΡΟΜΩΝ ΠΕΡΙΟΔΙΚΟΥ ΠΥΡΕΤΟΥ
Διευθυντής: Καθηγητής Αθανάσιος Γ. Τζιούφας

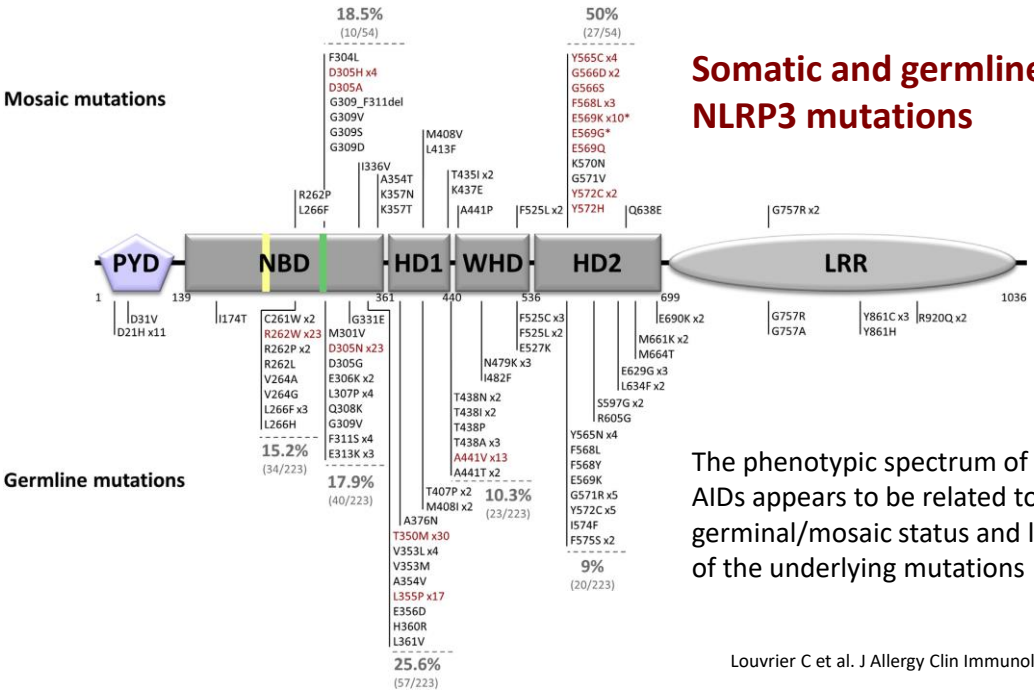
Acquired auto-inflammatory disorders (AAIDs)
Adult-onset autoinflammation

Somatic mutations in myeloid lineage as a cause of later-onset auto-inflammatory disorders

- **NLRP3-associated (somatic CAPS)**
- **VEXAS** (Vacuoles, E1 ubiquitin ligase, X-linked, Auto-inflammatory, Somatic)

Poulter JA and Savic S. Semin Hematol 2021
de Koning HD et al. J Allergy Clin Immunol. 2015

Somatic and germline NLRP3 mutations

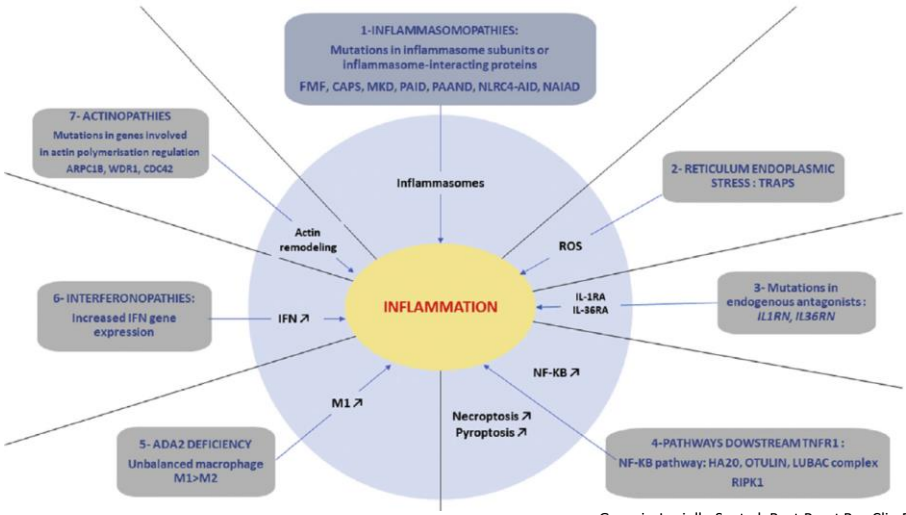


The phenotypic spectrum of NLRP3-AIDs appears to be related to the germinal/mosaic status and localization of the underlying mutations

Louvrier C et al. J Allergy Clin Immunol 2020

Spectrum of systemic autoinflammation today

- ✓ ***Over 40 autoinflammatory diseases***
- ✓ ***Classification according to pathomechanism***

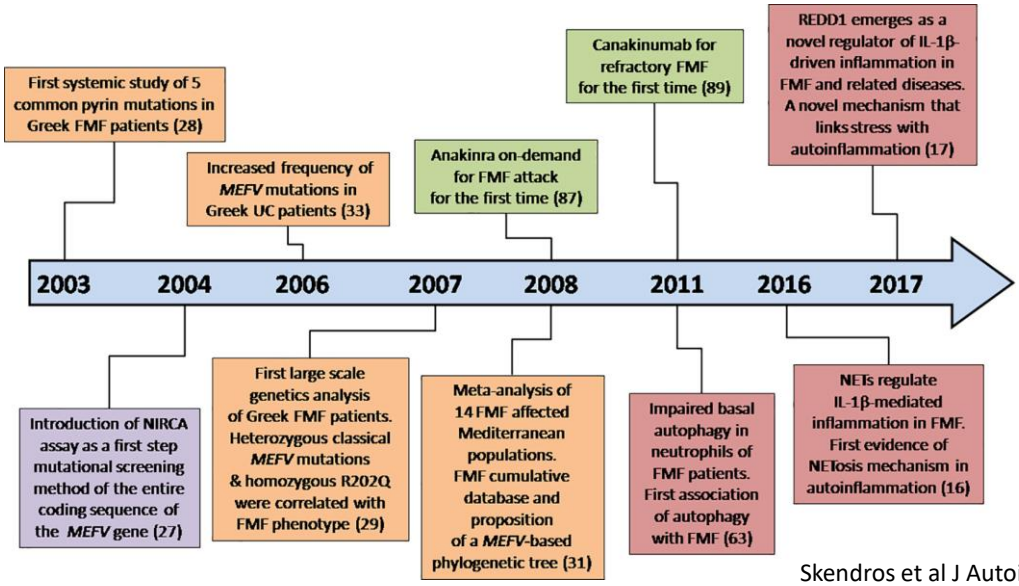


Georgin-Lavialle S, et al. Best Pract Res Clin Rheumatol. 2020

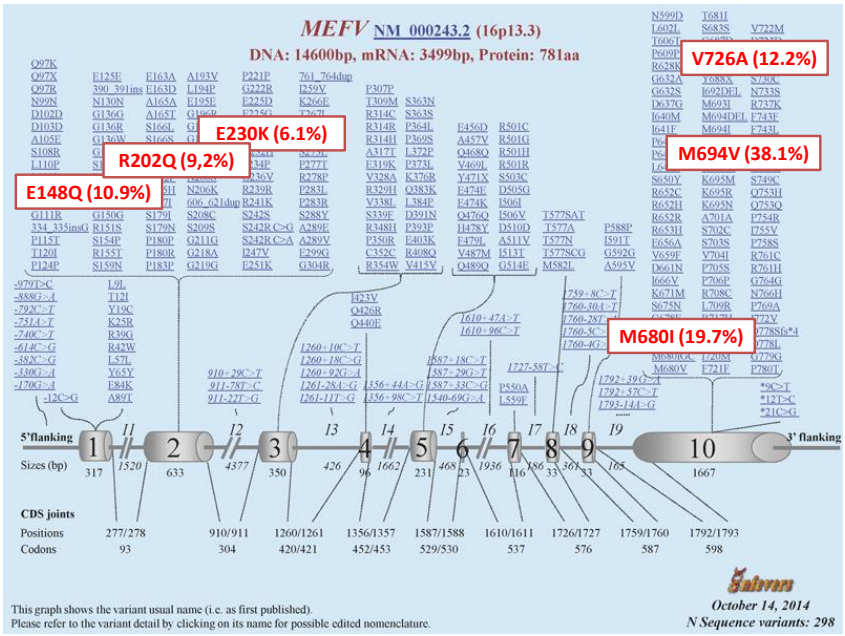
Autoinflammatory diseases
"the model of FMF"

FMF: The prototype autoinfammatory disease

Timeline of the main contribution of Inflammation Research Group DUTH, in the study of FMF



Skendros et al J Autoimmun 2019

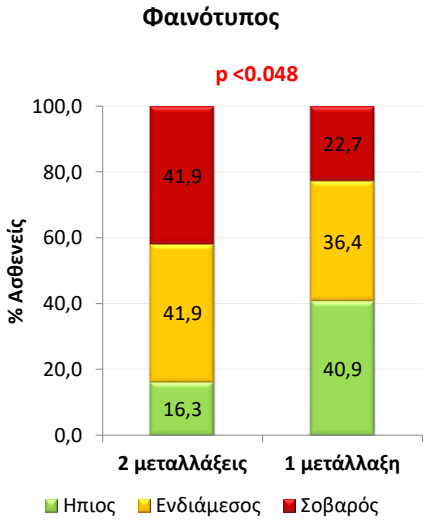


Giaglis S et al. Clin Genet 2007: 71: 458–467

FMF - Γενετικό «φορτίο» και Φαινότυπος

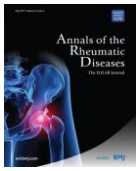
Μεταλλάξεις στο *MEFV*	Ασθενείς (N=152)	Υγιείς (N=140)
Καμία	16.4%	98.6%
1	40.8	1.4%
2	42.8	0

"Genetic dose effect"



Giaglis S et al. Clin Genet 2007: 71: 458–467

ARD Online First, published on September 26, 2014 as 10.1136/annrheumdis-2014-205958
Basic and translational research



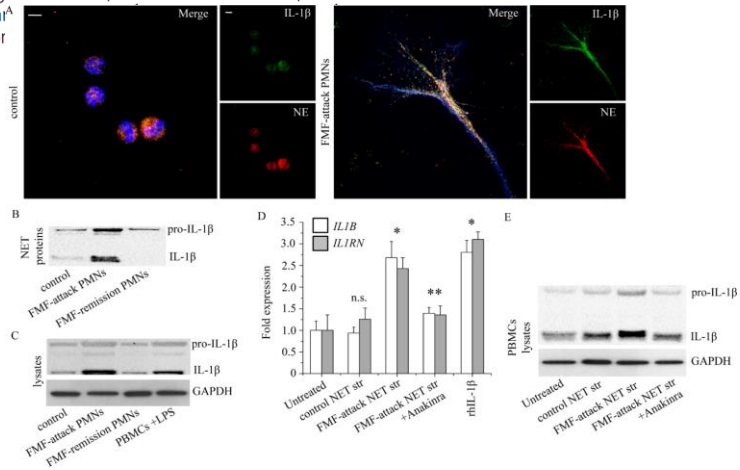
ARD 2014

EXTENDED REPORT

Neutrophil extracellular traps regulate IL-1β-mediated inflammation in familial Mediterranean fever

Eirini Apostolidou,[1,2] Panagiotis Skendros,[1,2] Konstantinos Kambas,[1] Ioannis Mitroulis,[3] Theochari[A] Konstantinos Nakos,[4] Victor Konstantinos Ritis[1,2]

IL-1 positive neutrophils/NETs in FMF episodes



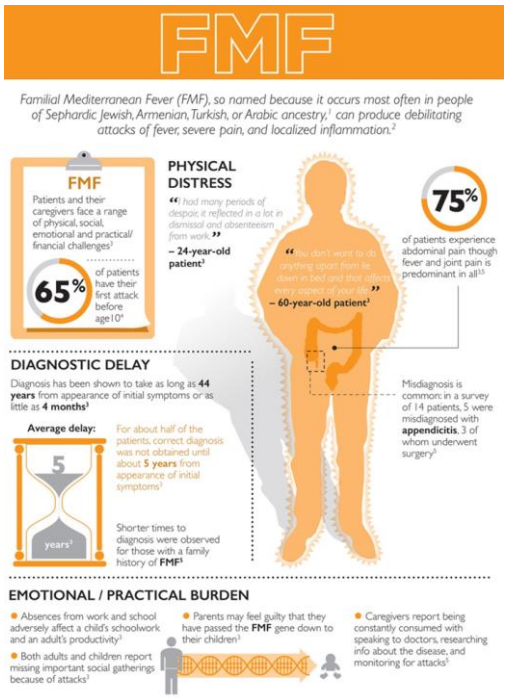
ongoing anti-inflammatory process occurring in both phases. Surprisingly, serum concentrations of IL-1β, the cytokine thought to contribute most to the pathogenesis of FMF, are normal or even decreased in patients with FMF during acute attacks or in remission periods

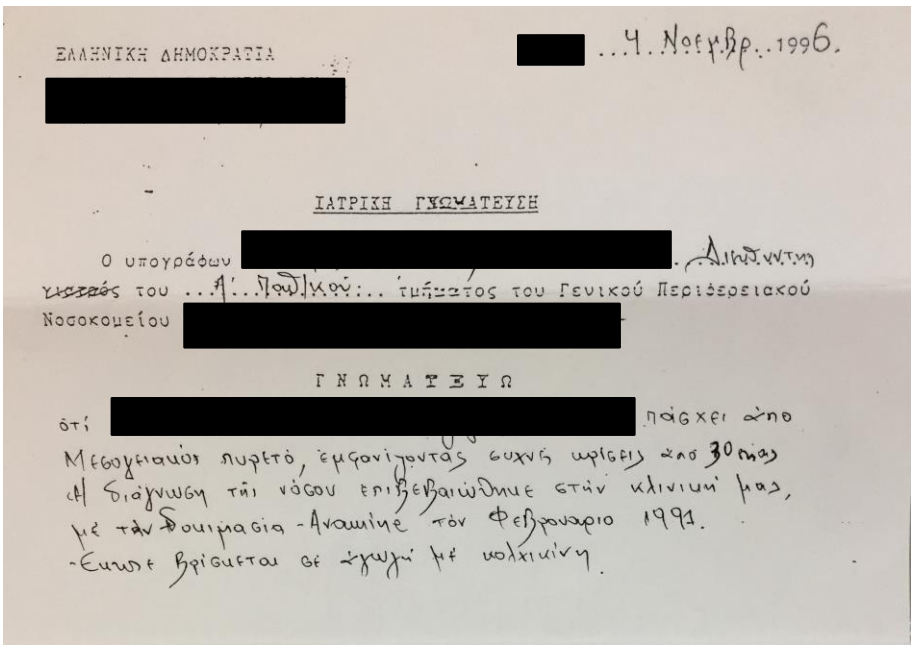
Ben-Zvi I, Livneh A. Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. Nat Rev Rheumatol. 2011

FMF & stress

- ✓Unpredictable, recurrent and self limited **inflammatory attacks** of fever and serositis
- ✓Several factors associated with **emotional and physical stress** are proposed to **trigger FMF attacks**

- Ben-Zvi I, Livneh A. Nat Rev Rheumatol. 2011
- Yenokyan G, Armenian HK. Am J Epidemiol 2012
- Ozen S, et al. Ann Rheum Dis 2016




ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ

[redacted] ...4..Νοεμβρ..1996.

[redacted]

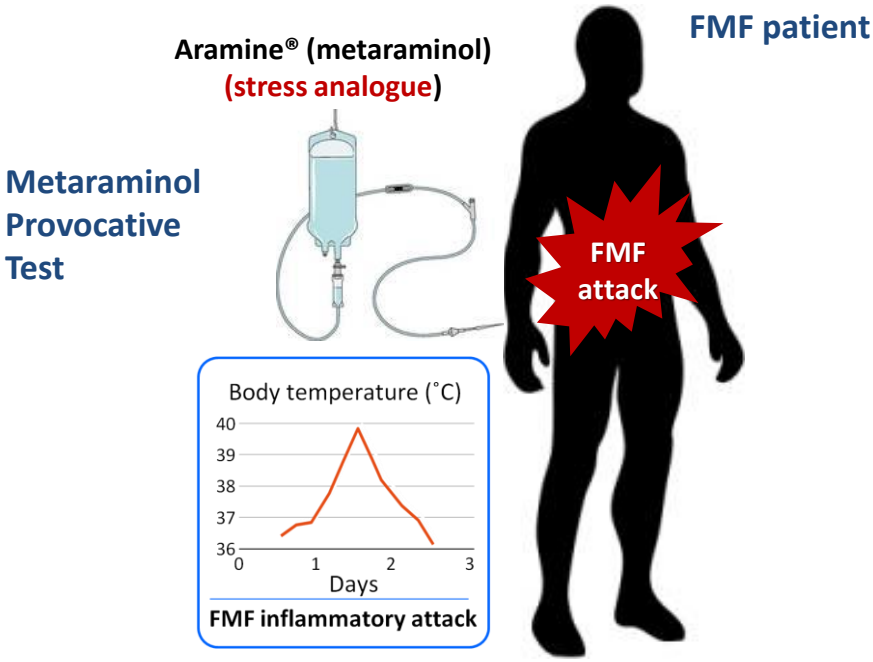
ΙΑΤΡΙΚΗ ΓΝΩΜΑΤΕΥΣΗ

Ο υπογράφων [redacted] ... Διευθυντής

~~Υιατρός~~ του ...Α'..Παθολικού... τμήματος του Γενικού Περιφερειακού Νοσοκομείου [redacted]

Γ Ν Ω Μ Α Τ Ε Υ Ο Υ

ότι [redacted] πάσχει από Μεσογειακό πυρετό, εμφανίζοντας συχνές ωρίγες από 30 ημέρες. Η διάγνωση της νόσου επιβεβαιώθηκε στην κλινική μας, με την δοκιμασία - Ανάπτυξη τον Φεβρουάριο 1993. - Ενώσει βρίσκεται σε έγχυση με κολχικίνη.



ARD Online First, published on January 22, 2016 as 10.1136/annrheumdis-2015-208690

EULAR recommendations for the management of familial Mediterranean fever

Seza Ozen,[1] Erkan Demirkaya,[2] Burak Erer,[3] Avi Livneh,[4] Eldad Ben-Chetrit,[5] Gabriella Giancane,[6] Huri Ozdogan,[7] Illana Abu,[8] Marco Gattorno,[9] Philip N Hawkins,[10] Sezin Yuce,[11] Tilmann Kallinich,[12] Yelda Bilginer,[13] Daniel Kastner,[14] Loreto Carmona[15]

Recommendation 8

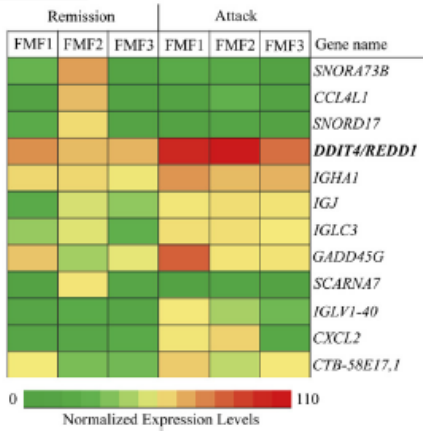
"Periods of physical or emotional stress can trigger FMF attacks, and it may be appropriate to increase the dose of colchicine temporarily"

Translational and clinical immunology

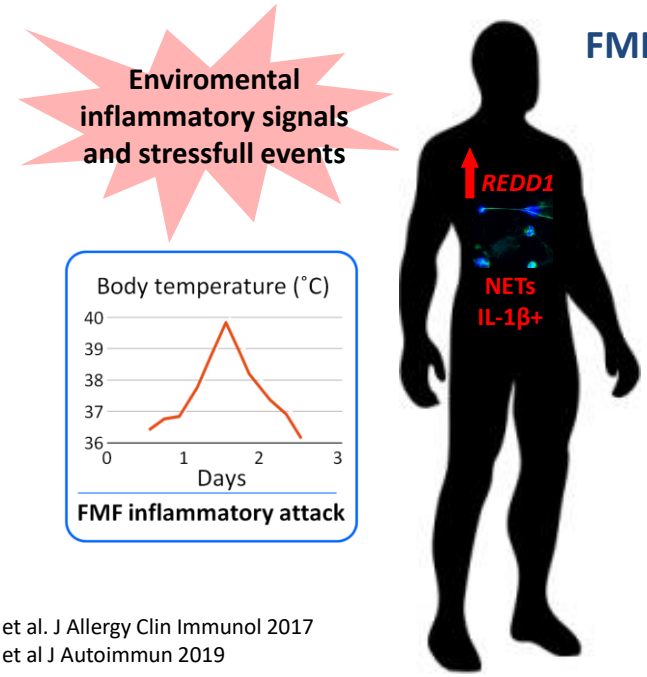
Regulated in development and DNA damage responses 1 (REDD1) links stress with IL-1β–mediated familial Mediterranean fever attack through autophagy-driven neutrophil extracellular traps

J ALLERGY CLIN IMMUNOL
NOVEMBER 2017

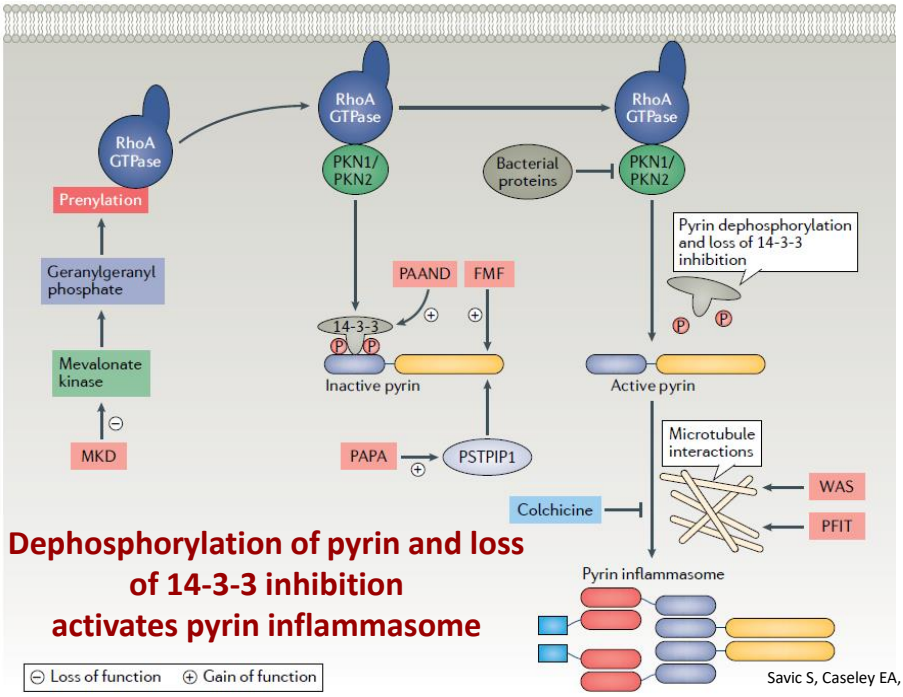
The **stress-related protein REDD1** emerges as a novel regulator of IL-1b–driven inflammation in neutrophils of patients with FMF by both **activating autophagy mediated NET release** and **affecting IL-1β maturation**



Skendros P et al. J Allergy Clin Immunol. 2017



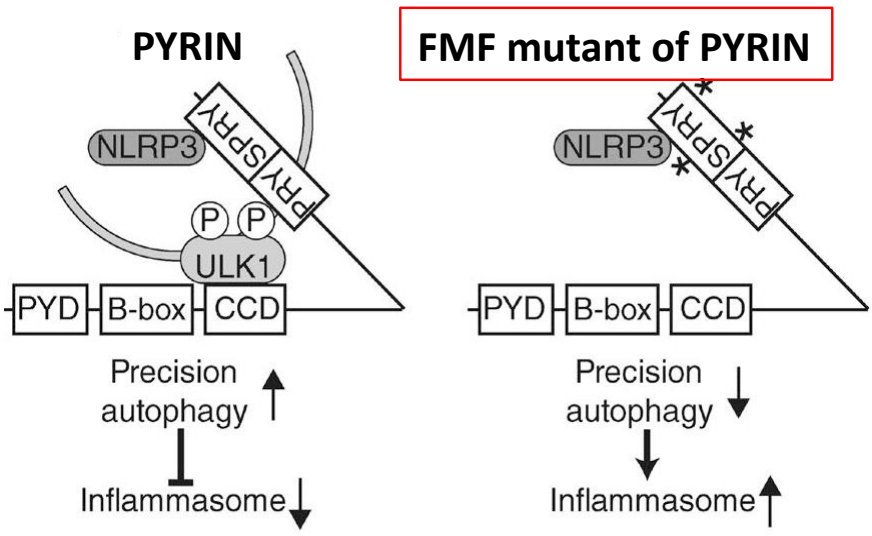
Skendros et al. J Allergy Clin Immunol 2017
Skendros et al J Autoimmun 2019



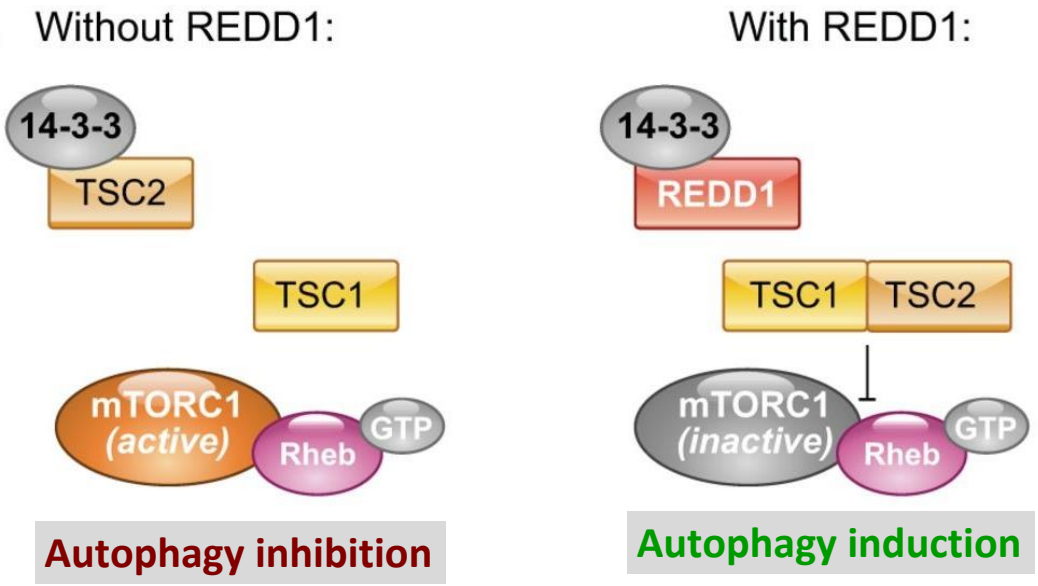
14-3-3 protein " the break of pyrin activation"

Savic S, Caseley EA, McDermott MF. Nat Rev Rheumatol. 2020

Pyrin acts as a receptor for the selective autophagic degradation of inflammasome components, a function that is significantly impaired in mutated protein

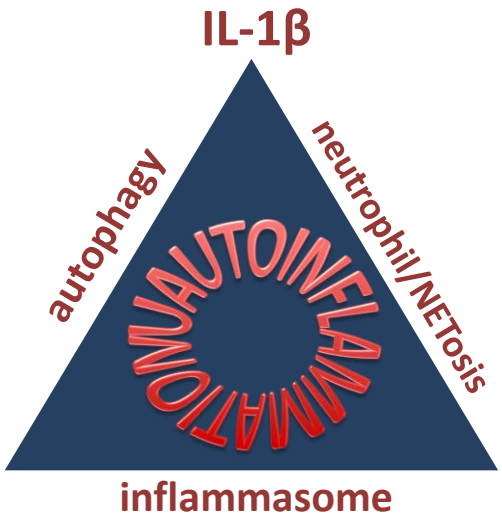


Kimura T et al J Cell Biol 2015



Gordon BS et al. Am J Physiol Endocrinol Metab. 2016

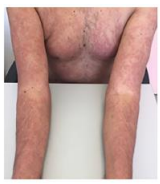
FMF proposed model of autoinflammation

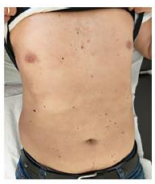


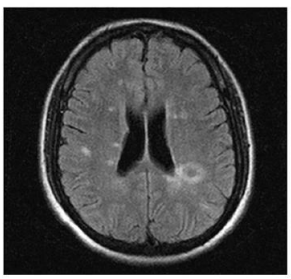
Translation Medicine

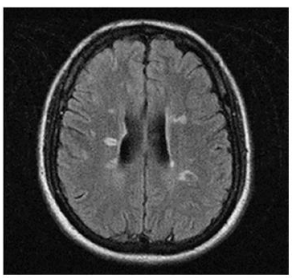
Targeting IL-1α & IL-1β in CAPS

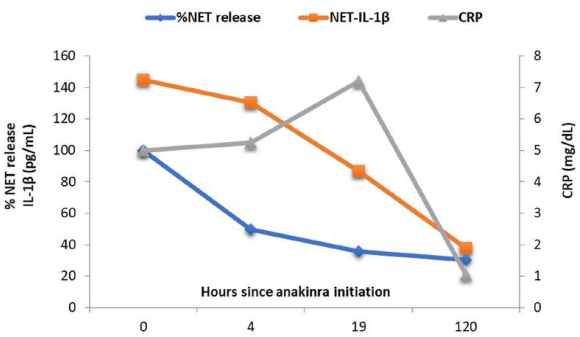
NLRP3 E304K/0











Papagoras C, Lampropoulou V, Mavraki E, Chrysanthopoulou A, Deftereos S, Aróstegui JI, Skendros P, Ritis K. Clin Immunol. 2021

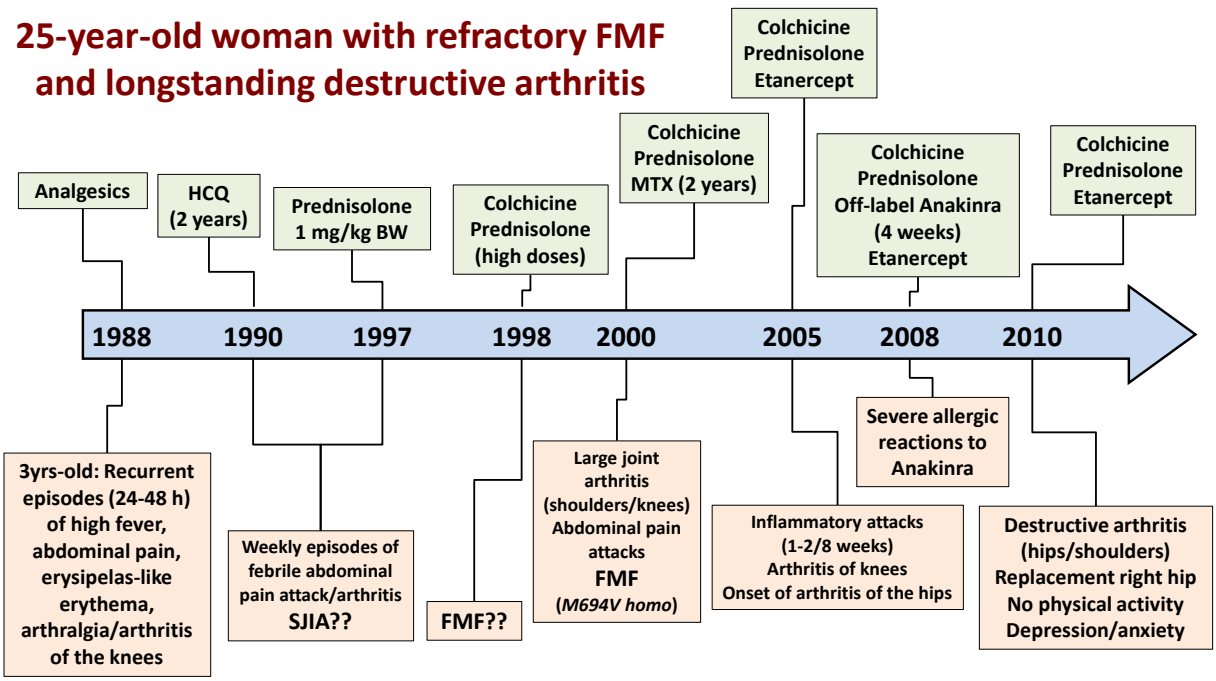
FMF Is Divided Into 3 Phenotypes

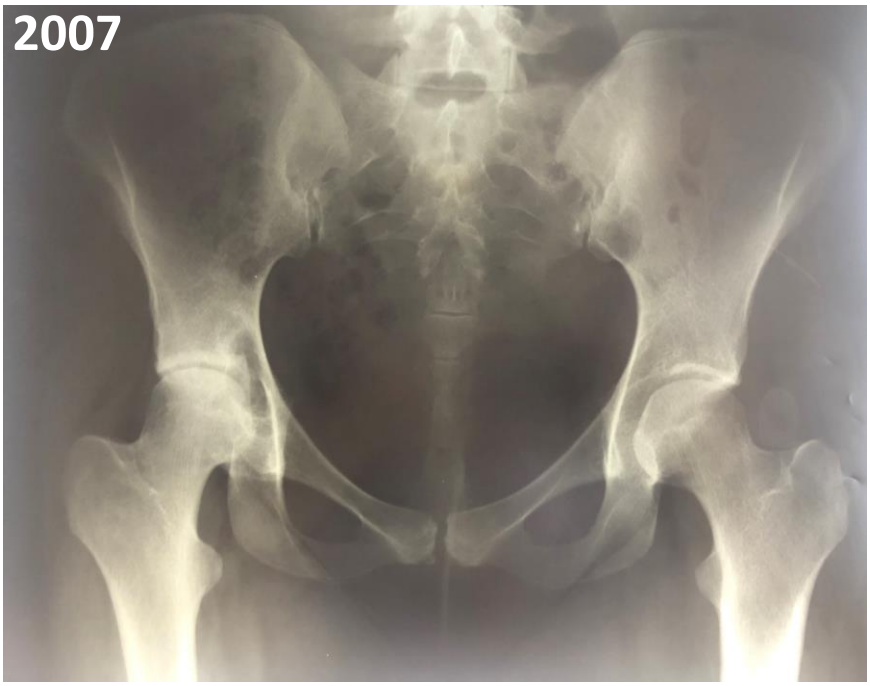
Phenotype I	Phenotype II	Phenotype III
▪ Clinically overt disease ▪ Manifested with episodes of fever and arthritis, or peritonitis, pleuritis, or rash (erysipelas-like erythema); or ▪ Combination of above with AA amyloidosis ▪ Genetic diagnosis is not required*	▪ Only manifestation is AA amyloidosis ▪ Diagnosis based on family history of phenotype I disease, or presence of *MEFV* mutations	▪ Genetic positive (≥2 mutations) ▪ Clinically silent disease†

*__Only 60% of patients bear 2 mutations__ (30% have 1, and 10% have 0); †rates of phenotype III in Israeli population are very high (1:50 vs 1:400 for phenotype I).
Ben-Zvi I, Livneh A. *Nat Rev Rheumatol*. 2011;7:105-12.

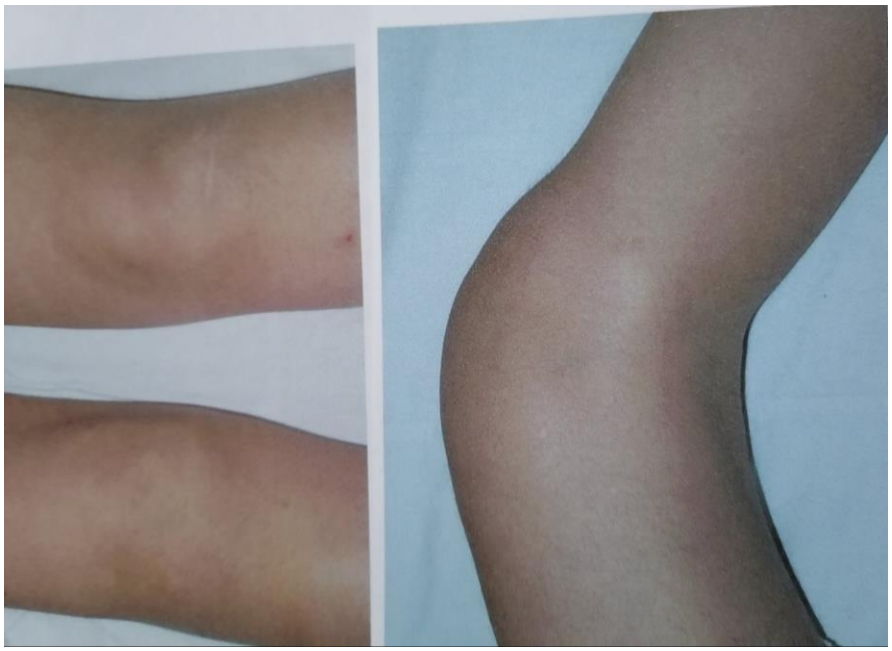
35

25-year-old woman with refractory FMF and longstanding destructive arthritis



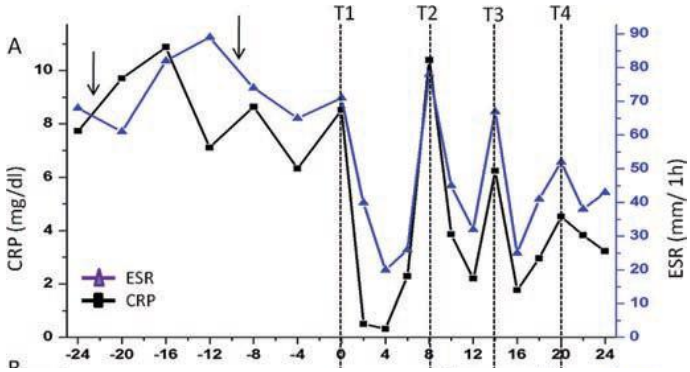


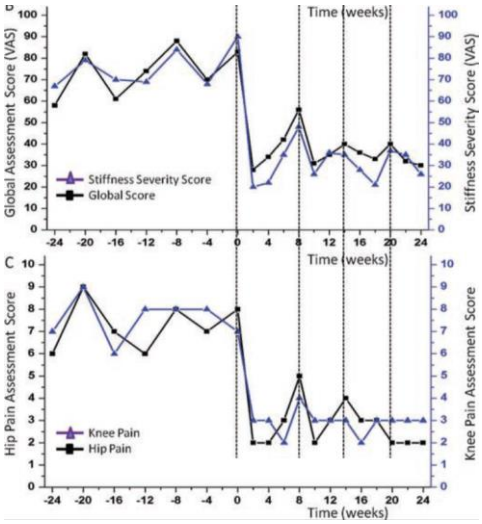
2010



25-year-old woman with refractory FMF and longstanding destructive arthritis

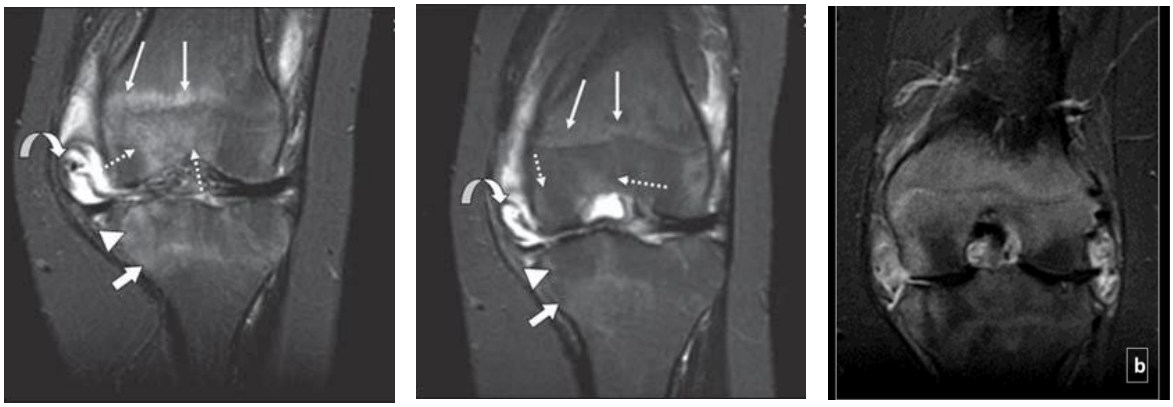
- **2010: Initiation of canakinumab 150 mg/8 weeks, step-up 150 mg/6 weeks**
- **Colchicine 2 mg/day, prednisolone 2.5-5 mg/day**





Mitroulis I, Skendros P, Oikonomou A, et al. Ann Rheum Dis. 2011

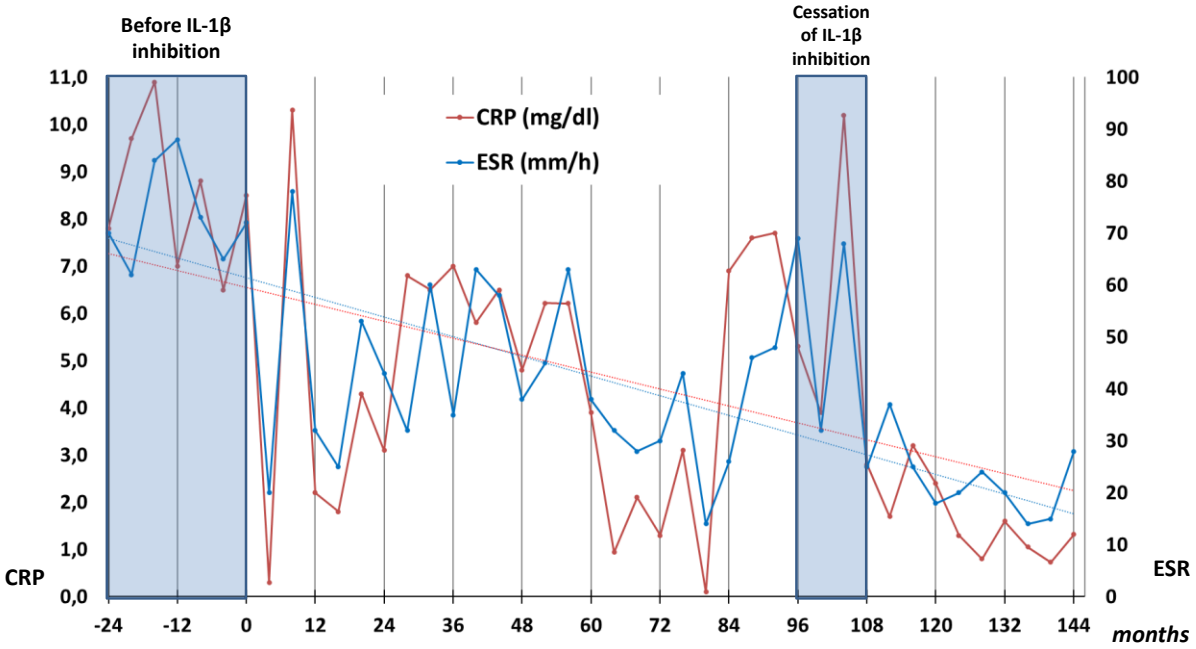
Baseline **Follow-up 6 months** **Follow-up 42 months**



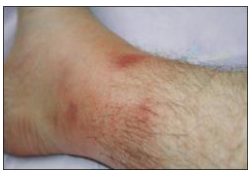
MRI Coronal short tau inversion recovery (STIR) images of the left knee

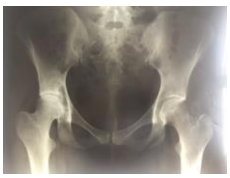
Mitroulis I, Skendros P, Oikonomou A, et al. Ann Rheum Dis. 2011

Skendros P, Papagoras C, Oikonomou A , et al. Ann Rheum Dis. 2014 (suppl 2)



Arthritis in FMF



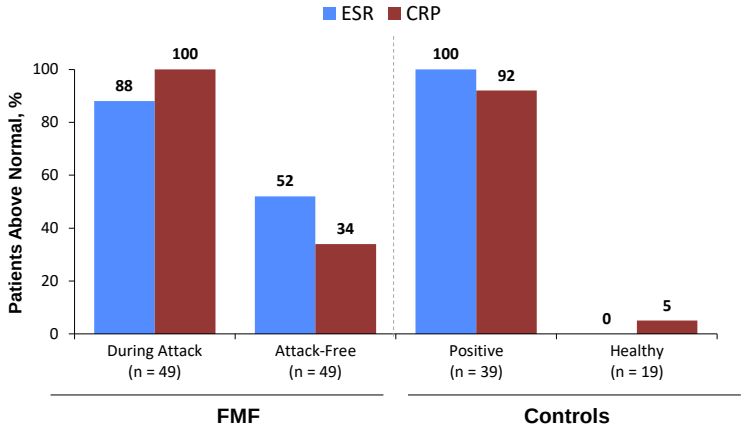


- Up to 45% of FMF patients
- Monoarticular/oligoarticular mainly involving lower limbs (hip, knee, ankle)
- Sacroiliitis up to 14%
- Self-limited, non-erosive
- **Chronic destructive arthritis (mainly hips) 3-5%**
- Association with M694V mutation, erysipelas-like erythema, and protracted febrile myalgia
- Unresponsiveness to colchicine was found in 21% [EULAR 2022]

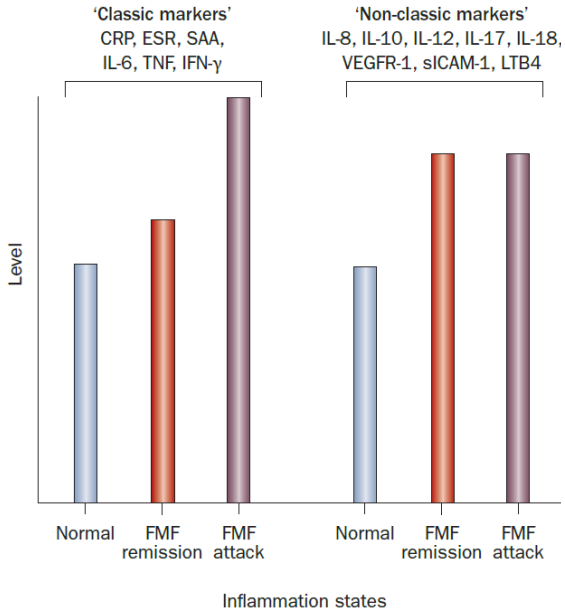
- Garcia-Gonzalez A, Weisman MH. Semin Arthritis Rheum 1992
- Uthman I, et al. Rheumatol Int 2001;20:145–8.
- Yalçinkaya F, et al. Br J Rheumatol 1997;36:1228–30.
- Jarjour RA, Dodaki R. Mol Biol Rep. 2011
- Avar-Aydın PO, et al. Clin Rheumatol. 2022
- Yenigun S, et al Ann Rheum Dis 2022 (suppl 1).

FMF and subclinical inflammation

CRP and ESR may remain high during the attack free periods



Korkmaz C, et al. Ann Rheum Dis. 2002



Box 2 | Clinical sequelae of chronic inflammation in FMF

The chronic inflammation associated with FMF has important deleterious clinical consequences.

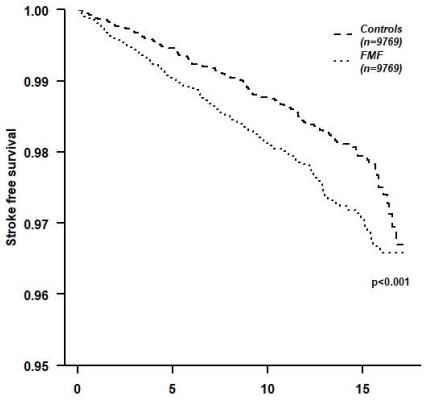
- Normocytic-normochromic anemia
- Splenomegaly
- Growth retardation in children
- Decreased bone density
- Impaired quality of life
- Depression and anxiety
- Female infertility, preterm deliveries
- Increased risk of heart disease
- Amyloid A amyloidosis

Ben-Zvi I, Livneh A. Nat Rev Rheumatol. 2011

› Rheumatology (Oxford). 2023 Apr 2;kead153. doi: 10.1093/rheumatology/kead153.
Online ahead of print.

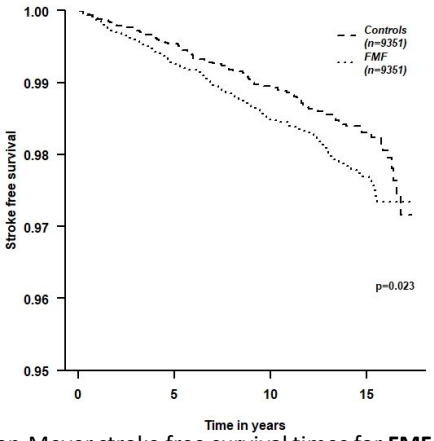
Increased risk for stroke in patients with familial Mediterranean fever: results from a large population-based study

Niv Ben-Shabat [1 2 3], Omer Gendelman [1 2 3], Lior Fisher [1 2 3], Uria Shani [1 2 3], Yonatan Shneor Patt [1 2 3], Abdulla Watad [1 2 3 4], Vita Skuja [5 6], Dennis McGonagle [4 7], Howard Amital [1 2 3]



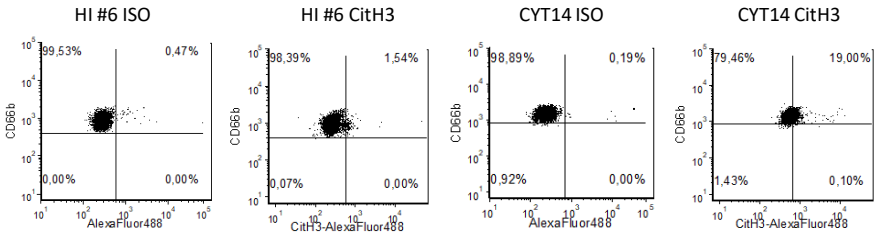
Kaplan-Meyer stroke free survival times for **the entire FMF cohort vs. controls**

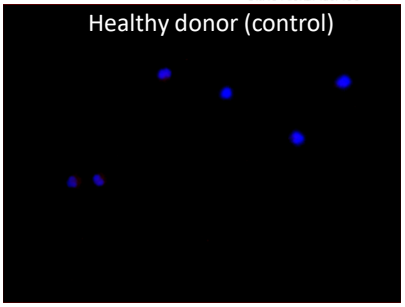
FMF patients have higher stroke incidence and younger stroke onset compared to the general population, regardless of the presence of amyloidosis and renal failure

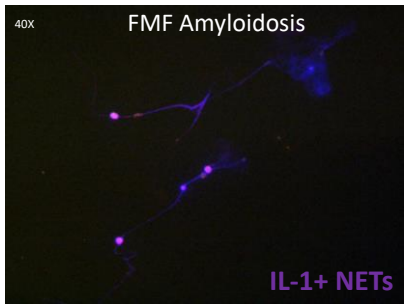


Kaplan-Meyer stroke free survival times for **FMF patients without disease-related comorbidities vs. controls**

52-years-old male with newly diagnosed FMF-Renal Amyloidosis (MEFV 694 +/-)





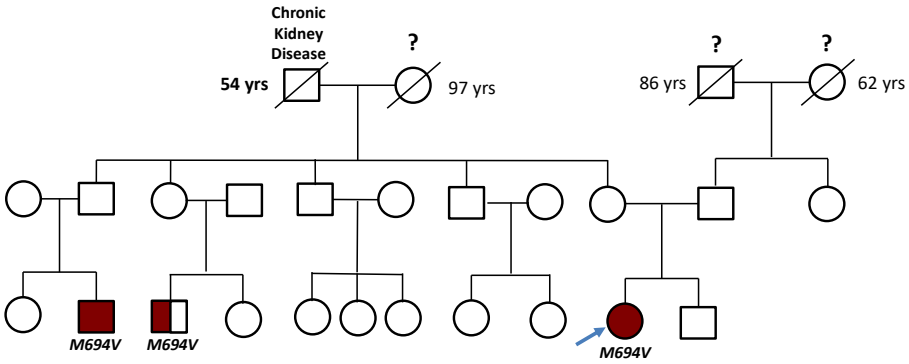


ANC: 7.570/μL
CRP< 0.5 mg/dL
T=36.6°C
Nephrotic syndrome

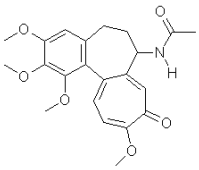
Peripheral blood neutrophils

First Department of Internal Medicine & Laboratory of Molecular Hematology, Democritus University of Thrace
CYTONET project 2018-2022
(unpublished data)

Family pedigree of the patient



Κολχικίνη (Colchicine)



Βάση όλων των θεραπευτικών προσεγγίσεων του FMF από το 1972

Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med. 1972

- **Αποτροπή της κρίσης, μείωση της βαρύτητας της κρίσης**
- **Μη αποτελεσματική στην διάρκεια της κρίσης**
- **Προστασία από εκδήλωση αμυλοείδωσης**
- **Απαιτείται καθημερινή χορήγηση** **1-2 mg 24ωρο/pos**
- **Σημαντικά χαμηλό κόστος**
- **Σημαντική ασφάλεια - εγκυμοσύνη/θηλασμός**

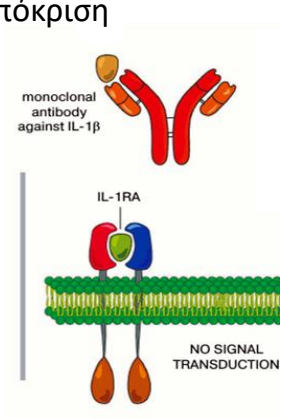
ήπια τρανσαμινασιαμία, περιφερική νευροπάθεια, μυοπάθεια (XNN!)
statins, ketoconazole, ritonavir, clarithromycin, verapamil, diltiazem

Χρήση αναστολέων της IL-1 στη θεραπεία ασθενών με FMF

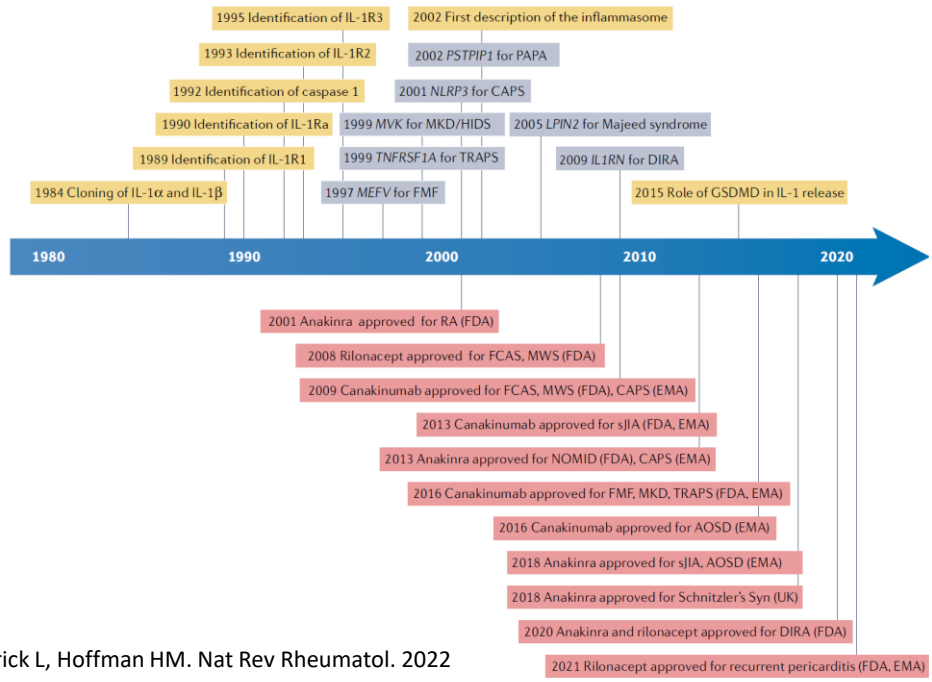
- **Ασθενείς με FMF και κολχικίνη:**

  5% είναι ανθεκτικοί, **5%** δεν την ανέχονται, **30%** μερική απόκριση
- **FMF δύσκολες περιπτώσεις:**

  διαβρωτική αρθρίτιδα, αμυλοείδωση, αγγείτιδα
- ***Anakinra (recombinant IL-RA)***
- ***Canakinumab (humanized anti-IL-1β)***



- Ben-Chetrit E, Aamar S. Clin Exp Rheumatol. 2009
- Ben-Chetrit E, Levy M. Lancet. 1998
- Ozturk MA, et al. Clin Exp Rheumatol. 2011
- Mitroulis I, Skendros P, et al Ann Rheum Dis. 2011
- Hentgen V, et al. Semin Arthritis Rheum. 2013
- van der Hilst JCh et al. Biologics: Targets and Therapy 2016
- Laskari K et al. Rheumatol. 2017
- De Benedetti F et al . N Eng J Med. 2018



Broderick L, Hoffman HM. Nat Rev Rheumatol. 2022

Drugs in development targeting the IL-1 pathway

Drug	Target	Mechanism	Clinical Trial
CE-224535	P2X7	Selective P2X(7) receptor antagonist	NCT00628095
AZD9056	P2X7	Selective P2X(7) receptor antagonist	NCT00520572
BMS-986299	NLRP3	Agonist	NCT03444753
Dapansutrile	NLRP3	Small molecular inhibitor	NCT03595371
IZD334	NLRP3	Small molecule inhibitor	NCT04086602
ZYIL1	NLRP3	Small molecule inhibitor	NCT04731324
IZD174	NLRP3	Small molecule inhibitor, CNS penetrant	NCT04338997
AC-201	NLRP3	Small molecule inhibitor	NCT02287818
VX-765	Caspase 1	Small molecule inhibitor	NCT00205465
Emricasan	Caspase 1	Pan caspase inhibitor	NCT04803227
Disulfiram	GSDMD	Gasdermin D inhibitor	NCT04485130
Bermekimab	IL-1α	Anti-IL-1α monoclonal antibody	NCT03512275
Gevokizumab	IL-1β	Anti-IL-1β monoclonal antibody	NCT01211977
LY2189102	IL-1β	Anti-IL-1β humanized monoclonal immunoglobulin G4	NCT00380744
CYT013-IL1bQb	IL-1β	Vaccine to IL-1β	NCT00924105
Lutikizumab	IL-1α/IL-1β	Dual affinity monoclonal antibody to IL-1α/IL-1β	NCT01668511
MAS825	IL-1β/IL-18	Bispecific IL-1β and IL-18 monoclonal antibody	NCT04641442
sc-rAAV2.5IL-1Ra	IL-1R1	Self-complementing, recombinant AAV carrying IL-1RA cDNA	NCT02790723
EBI-005	IL-1R1	IL-1β and IL-1 receptor antagonist fusion protein	NCT04121442
HL2351	IL-1R1	Human IL-1Ra-hyFc	NCT02853084
MEDI8968	IL-1R1	Anti-IL-1R1 human monoclonal antibody	NCT01838499
AMG108	IL-1R1	Anti-IL-1R1 monoclonal antibody	NCT00110942
EBI-005	IL-1R1	Chimeric IL-1RA- IL-1β	NCT02082899
KT-474	IRAK4	Oral heterobifunctional small molecule IRAK4 degrader	NCT04772885
ATI-450	MK2	Oral small molecule MAPKAPK2 (MK2) inhibitor	NCT04524858

Broderick L, Hoffman HM. Nat Rev Rheumatol. 2022

FMF: Μηνύματα από την καθημερινή κλινική πρακτική

- ✓ Κλινική εικόνα/ιστορικό, επιδημιολογία - αυξημένη κλινική υποψία
- ✓ Η αδυναμία γενετικού ελέγχου δεν πρέπει να καθυστερήσει την έγκαιρη έναρξη κολχικίνης (βασική θεραπεία) στην ανώτερη ανεκτή δόση
- ✓ Εκτός από την πρόληψη των οξέων προσβολών, η θεραπεία πρέπει να στοχεύει στη μείωση της χρόνιας υποκλινικής φλεγμονής και στην παρεμπόδιση της επιβλαβούς κλινικής έκβασής της
- ✓ Η χρόνια διαβρωτική αρθρίτιδα δεν είναι συχνή, μπορεί όμως να οδηγήσει σε σημαντική αναπηρία
- ✓ Οι αναστολείς της IL-1 έχουν αλλάξει το πεδίο, ιδιαίτερα στις δύσκολες και ανθεκτικές στην κολχικίνη περιπτώσεις
- ✓ Τροποποίηση δόσεων (step-up/down) ανάλογα με την πορεία της νόσου και τον φλεγμονώδη φαινότυπο

Autoinflammatory Disorders

Future perspectives

- New AIDs phenotypes and unclassified syndromes
- NGS as a research & diagnostic tool in AIDs
- New diagnostic/prognostic assays to discriminate infectious from sterile inflammation
- Drug repositioning
- New biologics against other members of IL-1 family
- Selective small-molecule inhibitors against NLRP3 inflammasome
- Regulatory mechanisms underlying autophagy/NETs/IL-1β axis
- Autophagy & NETosis-related candidate biomarkers and theurapeutic targets

Η σπάνια μαύρη λεοπάρδαλη που έχει αγαπήσει όλος ο πλανήτης