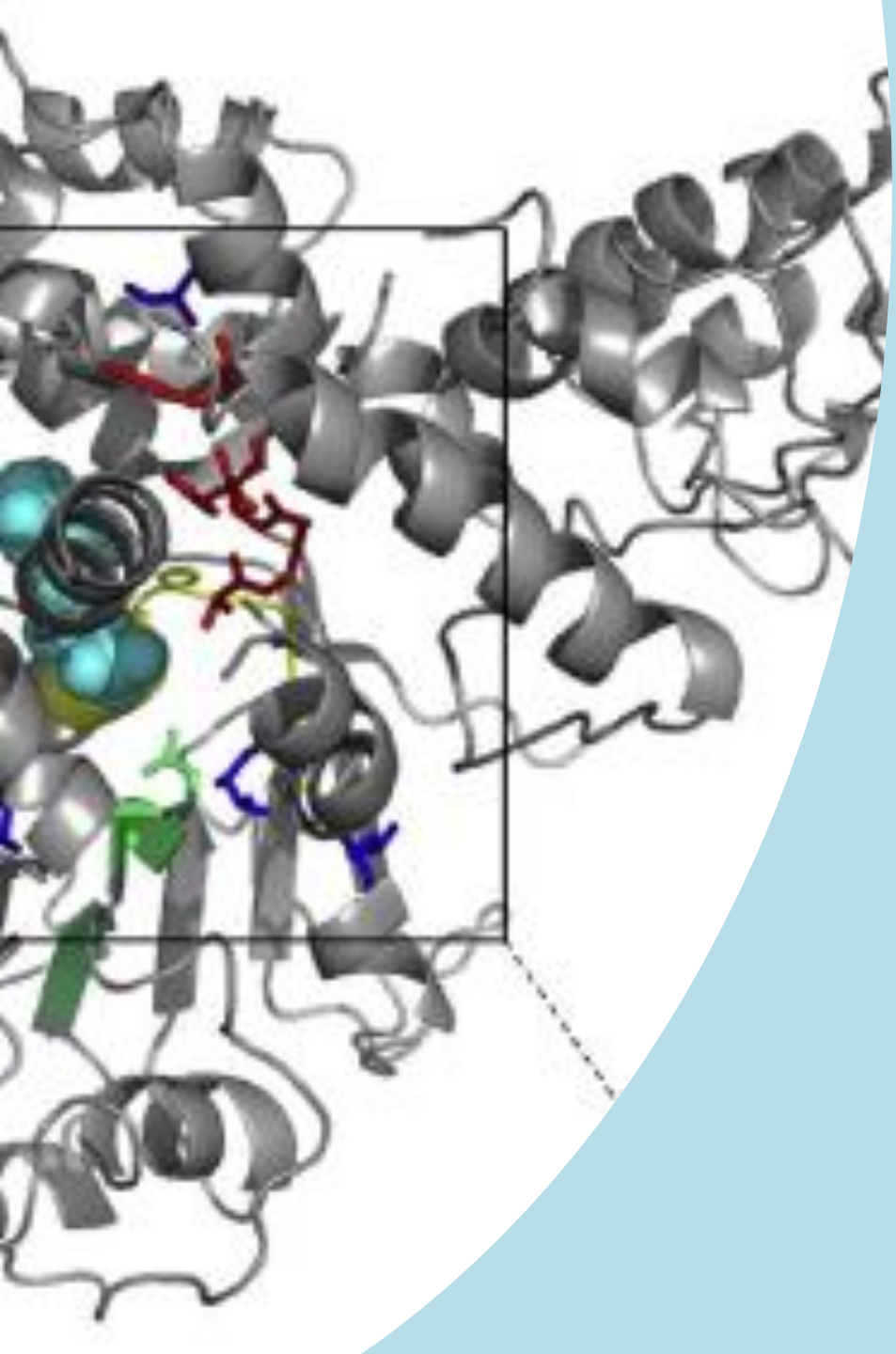


Adult Autoinflammatory Disorders:

Which signs and symptoms should altert clinicians, and how to confirm the diagnosis?

Ahmet Gül

Istanbul University

Istanbul Faculty of Medicine

Talk Plan


Concept of Autoinflammation


Genetic Basis of Autoinflammatory Disorders

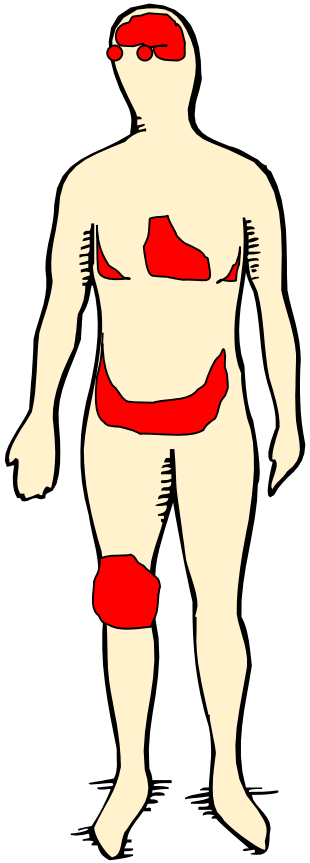

Familial Mediterranean Fever


Treatment Approaches

Hereditary Periodic Fever Syndromes

"**Recurrent episodes**" of

- Fever
- Self limited "sterile inflammation" at specific locations



Monogenic disorders

Ethnic predilection

Familial Mediterranean Fever

Familial Hibernian Fever

Familial Dutch Fever

…

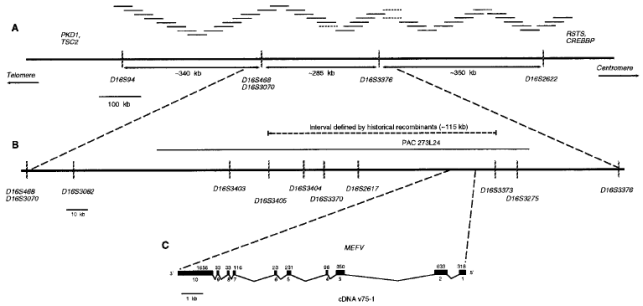
Familial Mediterranean Fever

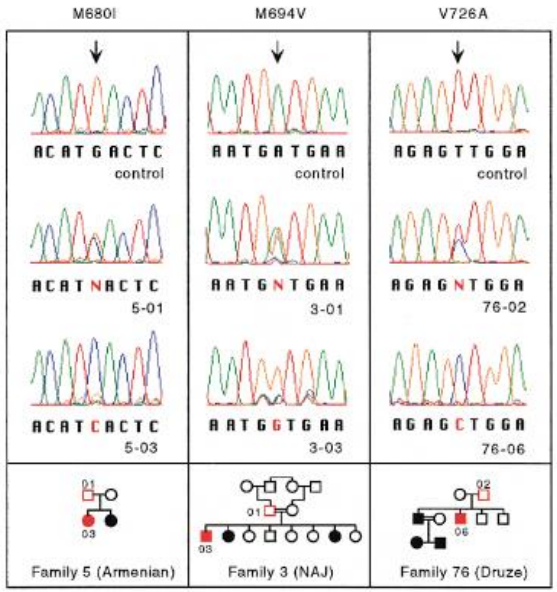
article

A candidate gene for familial Mediterranean fever

The French FMF Consortium

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by attacks of fever and serositis. In this paper, we define a minimal co-segregating region of 60 kb containing the FMF gene (*MEFV*) and identify four different transcript units within this region. One of these transcripts encodes a new protein (marenostrin) related to the ret-finger protein and to butyrophilin. Four conservative missense variations co-segregating with FMF have been found within the *MEFV* candidate gene in 85% of the carrier chromosomes. These variations, which cluster at the carboxy terminal domain of the protein, were not present in 308 control chromosomes, including 162 validated non-carriers. We therefore propose that the sequence alterations in the marenostrin protein are responsible for the FMF disease.



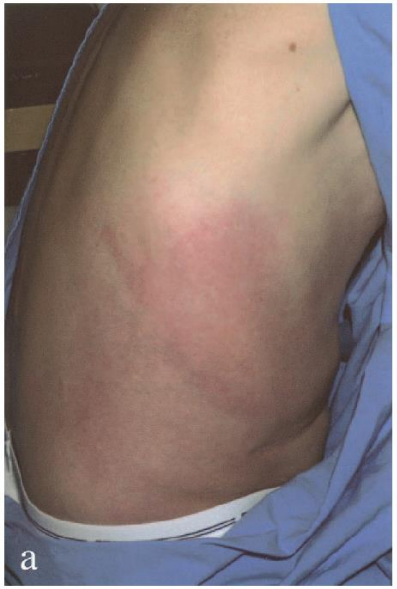


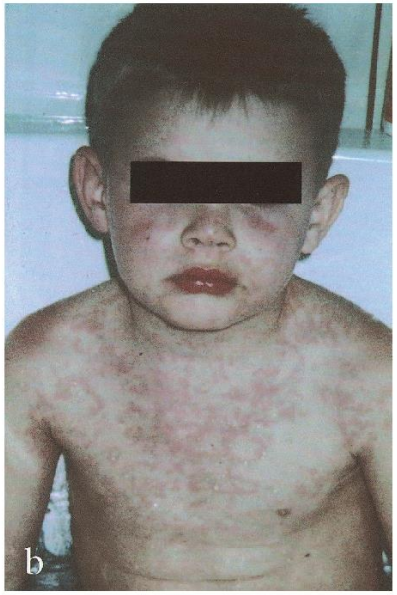
Cell, Vol. 90, 797–807, August 22, 1997, Copyright ©1997 by Cell Press

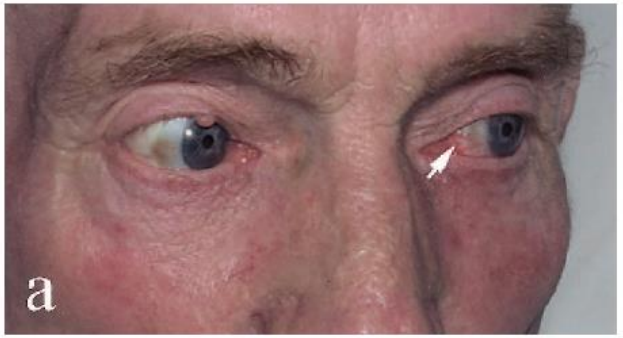
Ancient Missense Mutations in a New Member of the *RoRet* Gene Family Are Likely to Cause Familial Mediterranean Fever

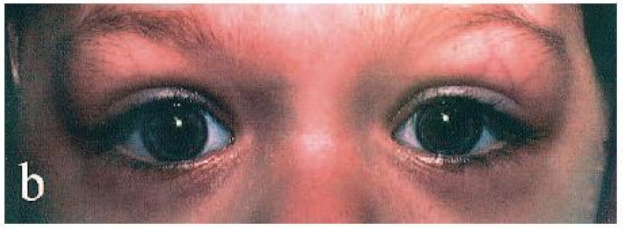
Familial Hibernian Fever

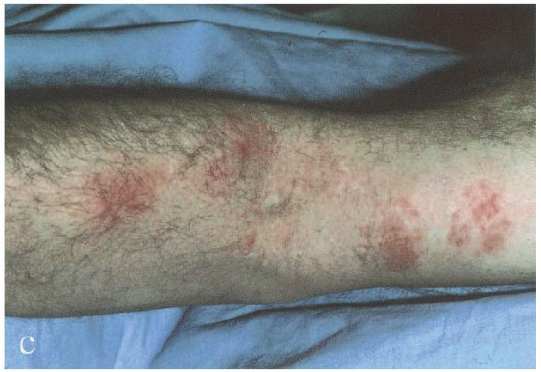
(TNF Reseptor Associated Periodic Syndrome)

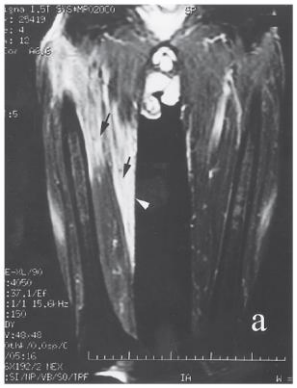


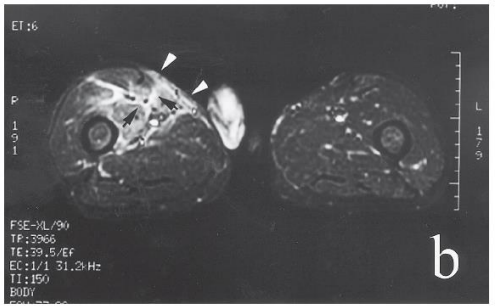












Hull et al. Medicine 2002; 81: 349-68

Autoinflammatory Disorders

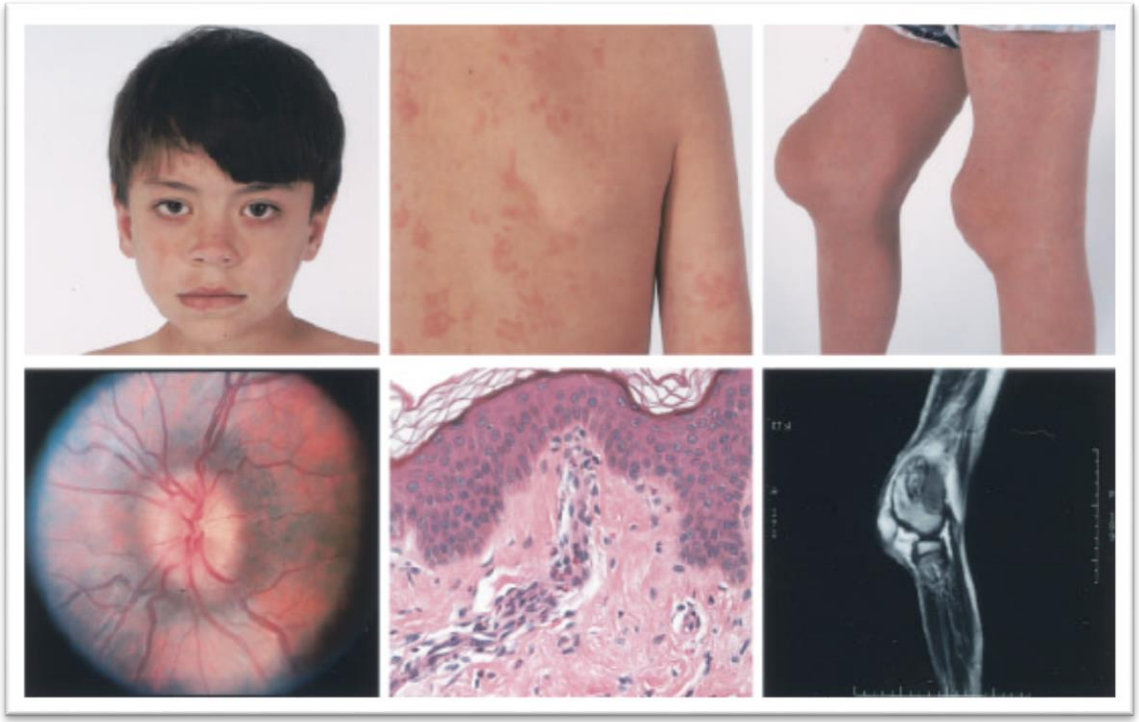
Cell, Vol. 97, 133–144, April 2, 1999, Copyright ©1999 by Cell Press

Germline Mutations in the Extracellular Domains of the 55 kDa TNF Receptor, TNFR1, Define a Family of Dominantly Inherited Autoinflammatory Syndromes

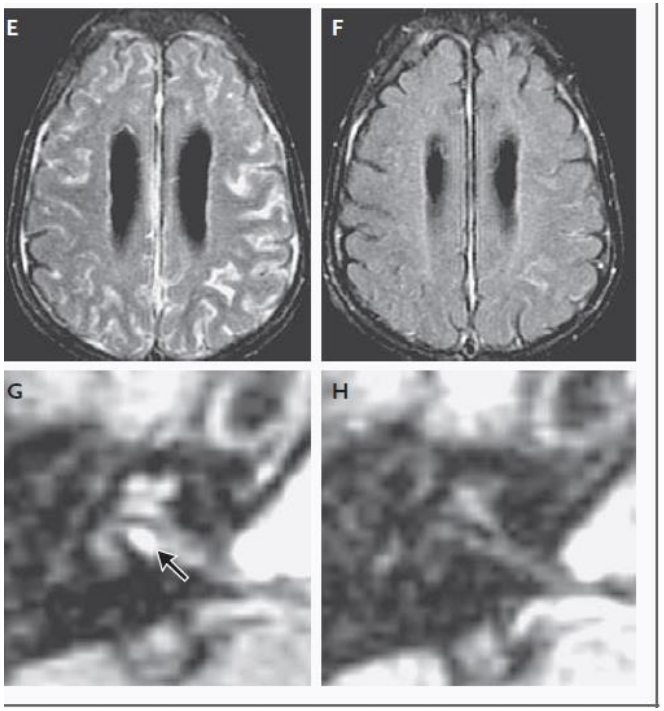
The autosomal dominant periodic fevers therefore represent a class of human disease shown to be caused by mutations in TNF receptors. Autoantibodies are not a general feature of these illnesses or the recessively inherited FMF, and for this reason the term *autoinflammatory* is preferable to *autoimmune* in describing these disorders. Variation in ethnic background, pattern of cutaneous involvement, and presence of systemic amyloidosis have created uncertainty about the etiology and classification of the dominantly inherited periodic fevers.

- *An emerging family of clinical disorders characterized by*
  - episodes of seemingly unprovoked inflammation
  - without high-titer autoantibodies or antigen-specific T lymphocytes
  - inborn errors of the innate immune system

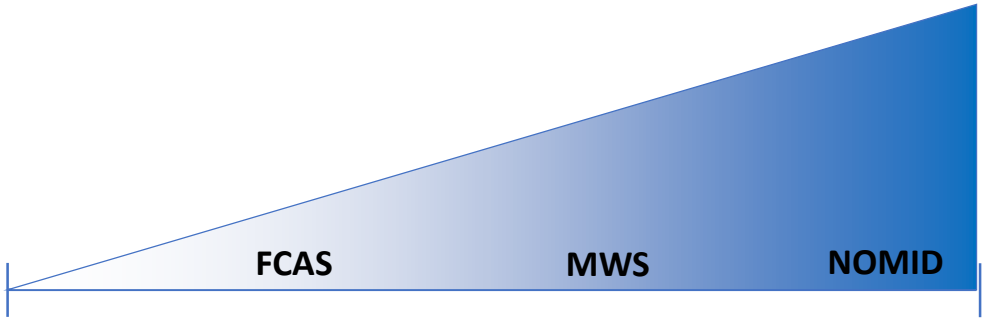
NLRP3 Associated Autoinflammatory Disorder



Aksentijevich et al. Arthritis Rheum 2002; 46: 3340-8



Goldbach-Mansky et al. NEJM 2006; 355: 581-92



Monogenic Autoinflammatory Disorders

- Autosomal recessive
  - Familial Mediterranean fever
  - Hyper-IgD and periodic fever syndrome (HIDS)
    - Deficiency of IL-1 receptor antagonist (DIRA), Deficiency of IL-36 receptor antagonist (DITRA), Deficiency of ADA2 (DADA2), mutations affecting LPIN2, PSMB8 (JMP/NNS/CANDLE), SLC29A3 (H syndrome), IL10RA, IL10RB, RIPK1 deficiency, ...
- Autosomal dominant
  - TNF receptor-associated periodic syndrome (TRAPS)
  - Cryopyrin-associated periodic syndrome
    - Muckle-Wells syndrome
    - Familial cold urticaria syndrome (FCAS)
    - Neonatal onset multisystem inflammatory disorder (NOMID or CINCA)
  - Others: PAPA (pyojenic arthritis, pyoderma gangrenosum and acne) syndrome, Blau syndrome, mutations affecting CARD14 (PSORS2), NLRP12 (NAPS12), PLCG2 (APLAID), SH3BP2 (Cherubism), TMEM173 (SAVI), cleavage-resistant RIPK1 induced autoinflammatory disorder (CRIA), …

Autoinflammatory Disorders

- Episodes of seemingly unprovoked inflammation
  - *Vaccinations, infections, trauma, cold, exercise, stress, ...*
- Lack of obvious (primary) autoimmune pathology
  - High titer pathogenic autoantibodies, and
  - Antigen-specific autoreactive T cells in some patients (secondary)
    - *T cell activation*
    - *Polyclonal hypergammaglobulinemia*

Clinical disorders marked by

- abnormally increased inflammation
- mediated predominantly by the cells and molecules of the innate immune system
- with a significant host predisposition.

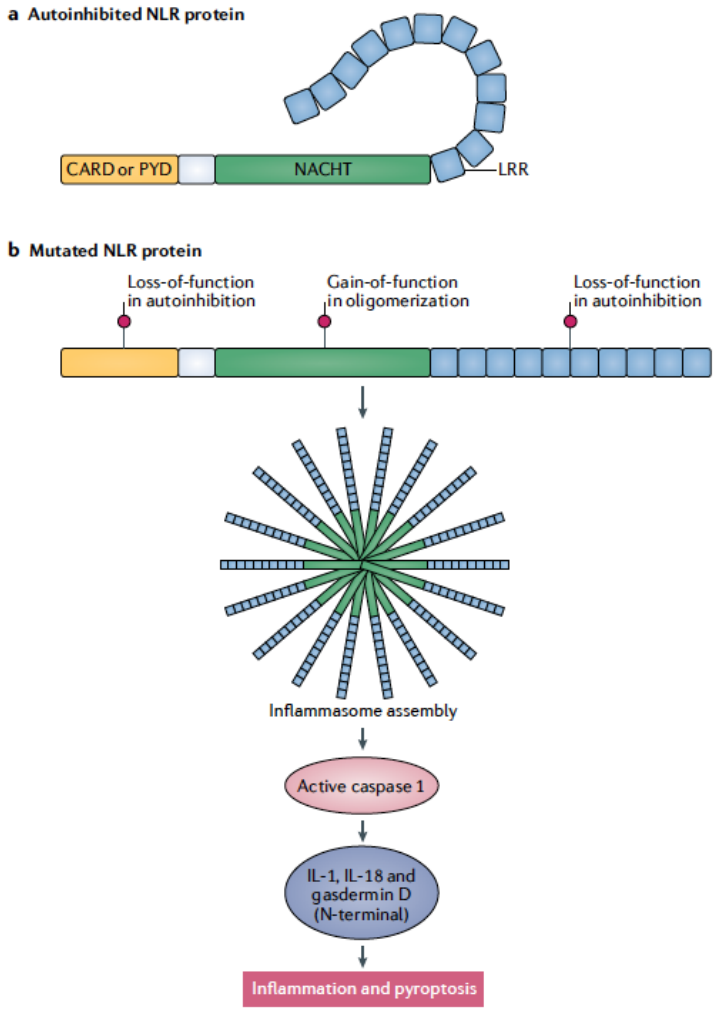
Kastner et al. Cell 2010;140:784-90.

Autoinflammatory Disorders

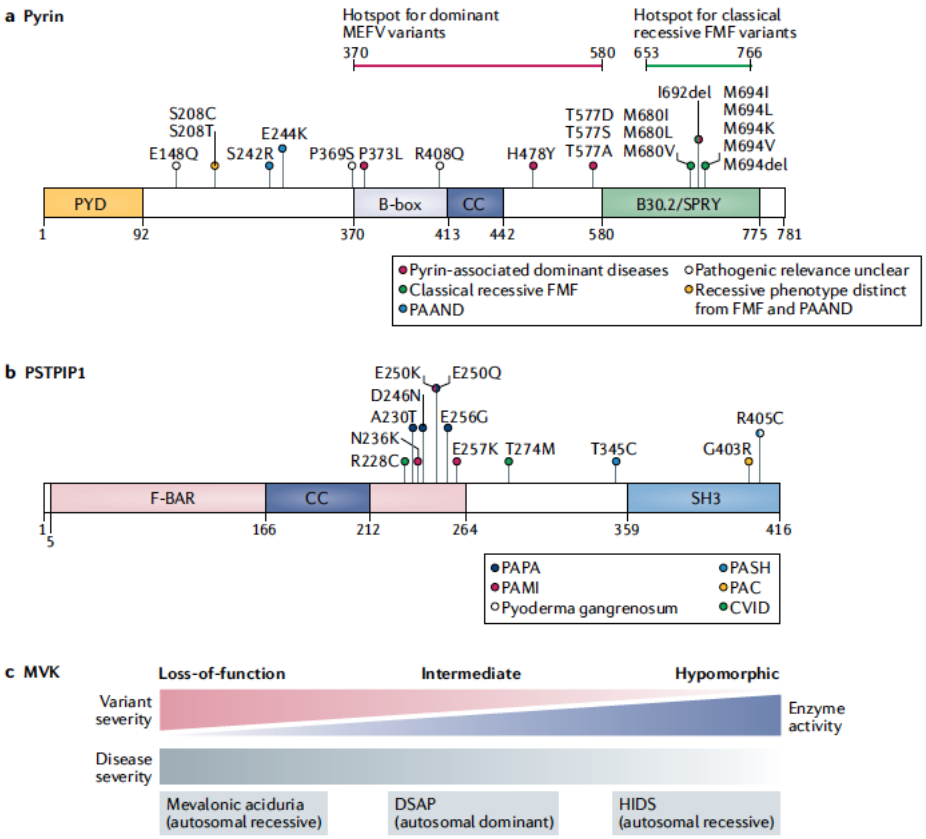
- Autoinflammatory disorders
  - Abnormally increased inflammation mediated predominantly by the cells and molecules of the innate immune system
- Autoinflammatory disorders with autoimmune features
  - Interferonopathies, …
- Autoinflammatory disorders with features of immunodeficiency
  - PLCG2 associated antibody deficiency and immune dysregulation (PLAID), DADA2, RIPK1 deficiency, …

Autoinflammatory Disorders

- Inflammasomopathies



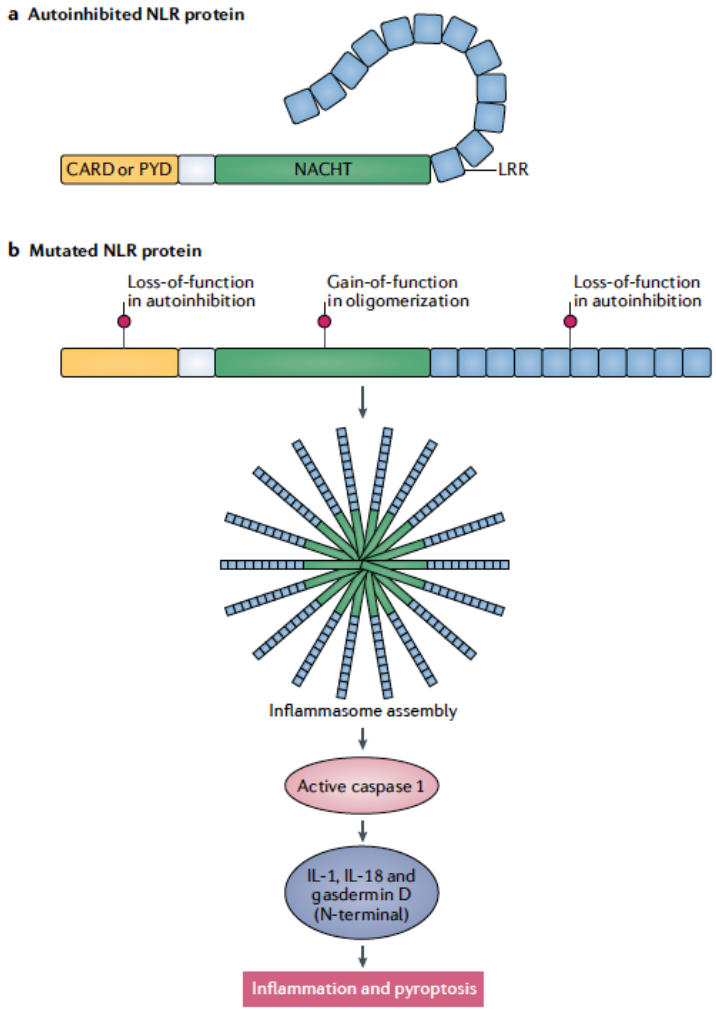
Pyrin-associated autoinflammatory diseases



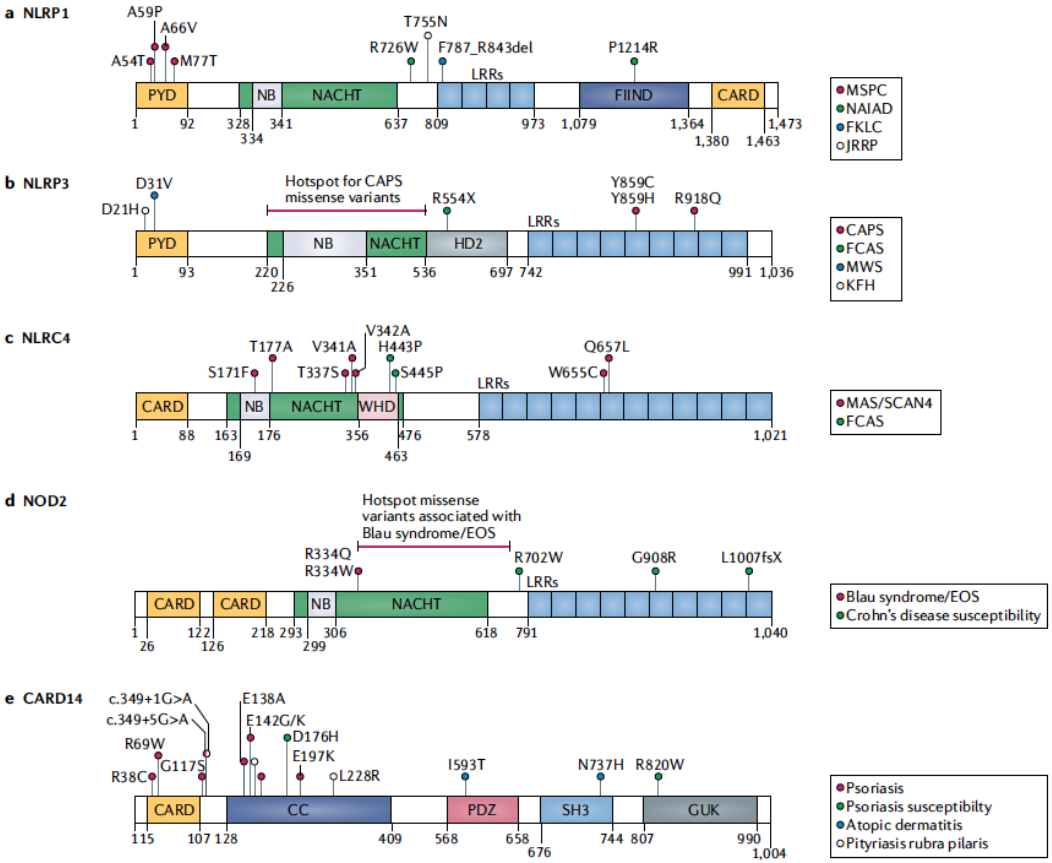
Aksentijevich I, Schnappauf O. Nat Rev Rheumatol 2021;17:405-25.

Autoinflammatory Disorders

- Inflammasomopathies



NOD-like receptor-associated diseases



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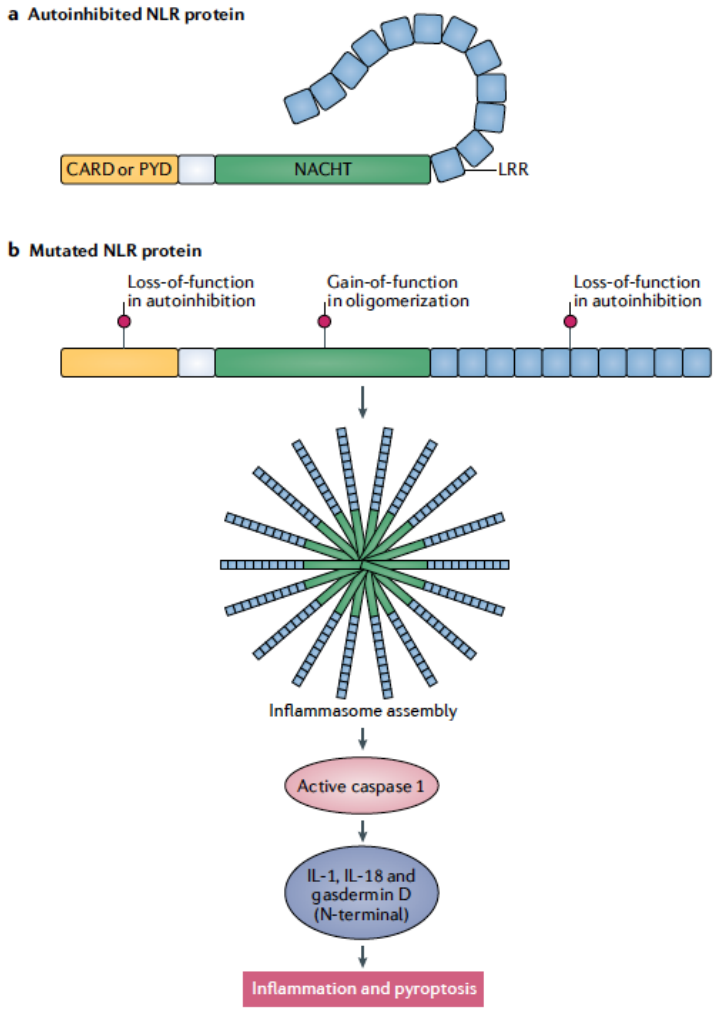
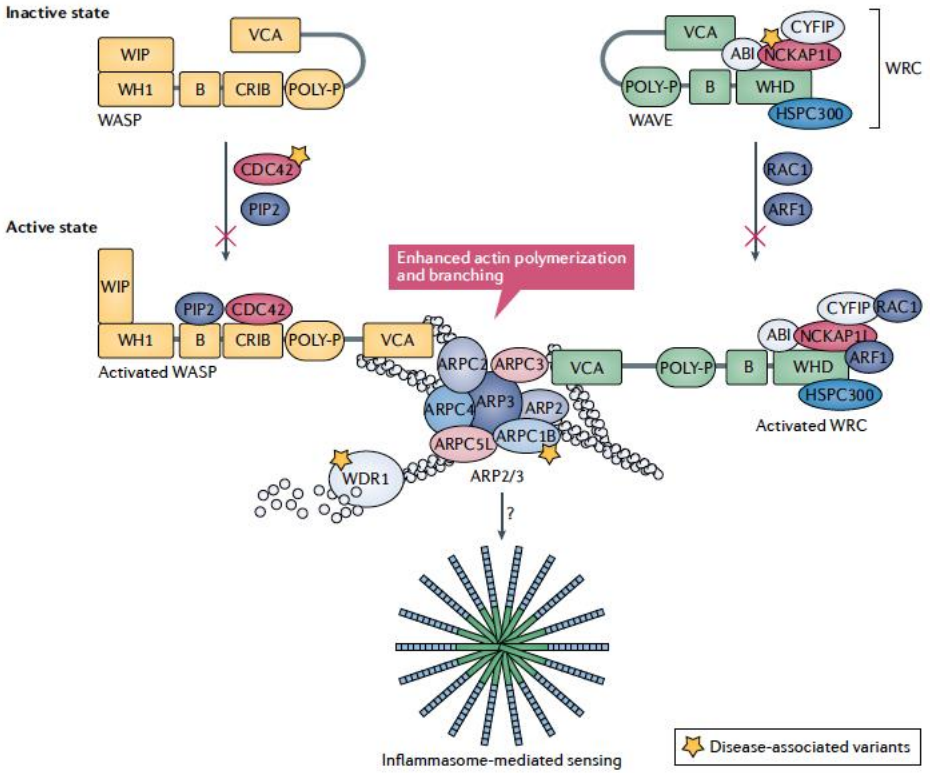
Autoinflammatory Disorders

- Inflammasomopathies



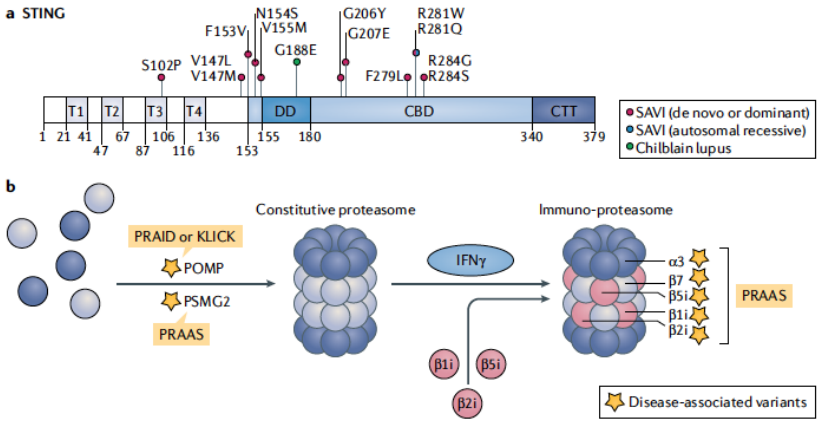
Inflammatory actinopathies



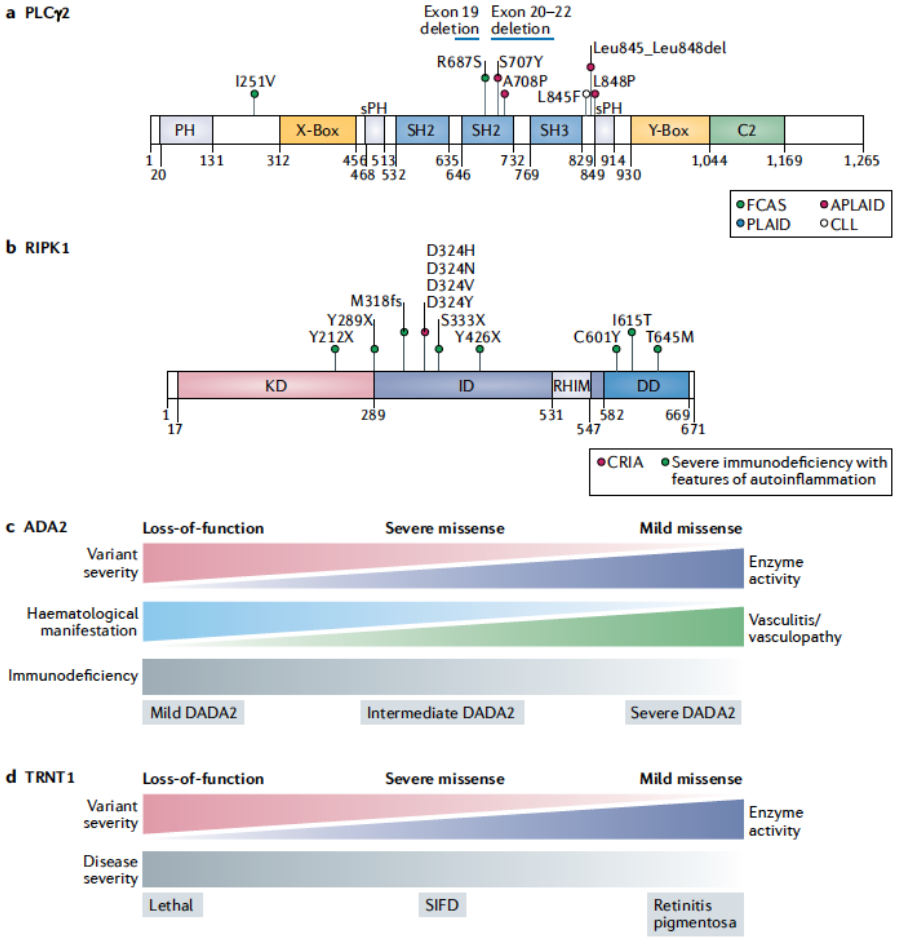
Aksentijevich I, Schnappauf O. Nat Rev Rheumatol 2021;17:405-25.

Autoinflammatory Disorders

Interferonopathies



Autoinflammatory diseases associated with enzyme deficiencies



Aksentijevich I, Schnappauf O. Nat Rev Rheumatol 2021;17:405-25.

Journal of Clinical Immunology (2020) 40:66–81
https://doi.org/10.1007/s10875-020-00758-x

ORIGINAL ARTICLE

Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification

Aziz Bousfiha[1,2] · Leila Jeddane[3] · Capucine Picard[4,5] · Waleed Al-Herz[6] · Fatima Ailal[1] · Talal Chatila[7] · Charlotte Cunningham-Rundles[8] · Amos Etzioni[9] · Jose Luis Franco[10] · Steven M Holland[11] · Christoph Klein[12] · Tomohiro Morio[13] · Hans D. Ochs[14] · Eric Oksenhendler[15] · Jennifer Puck[16] · Troy R. Torgerson[14] · Jean-Laurent Casanova[17,18,19,20] · Kathleen E. Sullivan[21] · Stuart G. Tangye[22,23]

VIIa. Auto-inflammatory disorders

Recurrent inflammation

Recurrent fever

Familial Mediterranean Fever (FMF) * ***MEFV.*** AR or AD (Usually M694del variant)

DA: 1–4 days **FA :** Variable.

Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis and inflammatory bowel disease .

Colchicine-responsive +++.

Mevalonate kinase def* (Hyper IgD sd). ***MVK.*** AR

DA: 3–7 days **FA:** 1–2 monthly.

Cervical adenopathy. Oral aphtosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.

TNF receptor-associated periodic syndrome; TRAPS. ***TNFRSF1A.*** AD.

DA: 1-4 weeks **FA:** Variable

Prolonged fever. Serositis, rash, Periorbital edema and conjunctivitis.

Amyloidosis. Joint inflammation.

Systemic inflammation with urticaria rash

Familial Cold Autoinflammatory Syndrome (CAPS) * . ***NLRP3, NLRP12.*** AD GOF **DA:** 24-48H

Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure.

Muckle Wells syndrome (CAPS) * ***NLRP3.*** AD GOF.

Ethnic group : North European

Continuous fever. Often worse in the evenings. Urticaria, Deafness (SNHL), Conjunctivitis, Amyloidosis.

Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) *. ***NLRP3.*** AD GOF.

Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.

A20 haploinsufficiency ***TNFAIP3.*** AD LOF. Arthralgia,

mucosal ulcers, ocular inflammation.

PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID*. ***PLC2G.*** AD GOF.

Cold Urticaria. Impaired humoral immunity. Hypogammaglobulinemia, autoinflammation.

NLRP1 deficiency*. ***NLRP1.*** AR.
Dyskeratosis, autoimmunity and arthritis.

Others

CANDLE sd (chronic atypical neutrophilic dermatitis with lipodystrophy).
PSMB8, AR and AD. Contractures, panniculitis, ICC, fevers.
PSMG2, AR. Panniculitis, lipodystrophy, AIHA.
(Variants in PSMB4, PSMB8, PSMA3, and POMP have been proposed to cause a similar CANDLE phenotype in compound heterozygous monogenic , digenic, and AD monogenic models).

COPA defect. ***COPA. AD***
Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production

NLRC4-MAS (macrophage activating syndrome)*. ***NLRC4.***
AD GOF. Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure.

NLRP1 GOF. ***NLRP1.*** AD GOF.
Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.

ALPI deficiency*. ***ALPI.*** AR.
TRIM22 def*. ***TRIM22.*** AR
Inflammatory bowel disease.

T-cell lymphoma subcutaneous panniculitis-like (TIMB deficiency). ***HAVCR2.***
AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma

VIIb. Auto-inflammatory disorders

Sterile inflammation (skin / bone / joints)

Predominant on the bone / joints

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hyper-calprotectinemia. ***PSTPIP1*** *(C2BP1).* AD

DA : 5 days **FA:** Fixed interval : 4-6 weeks

Destructive arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks

Chronic recurrent multifocal osteomyelitis and congenital dyserythropoieticanemia (Majeed syndrome). ***LPIN2.*** AR

DA : Few days **FA :** 1-3 / month

Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders

DIRA (Deficiency of the Interleukin 1 Receptor Antagonist) ***IL1RN.*** AR
Continuous inflammation.
Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.

Cherubism. ***SH3BP2.***

AR.

Bone degeneration in jaws

Predominant on the skin

Blau syndrome. ***NOD2*** (CARD15). AD.
Continuous inflammation.

Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response.

CAMPS ***CARD14.*** AD. Psoriasis.

DITRA. (Deficiency of IL-36 receptor antagonist). ***IL-36RN.*** AR .

Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis.

ADAM17 deficiency*. ***ADAM17*** . AR.

Early onset diarrhea and skin lesions. Severe bacteremia.
Defective TNFα production.

SLC29A3 mutation. ***SLC29A3*** . AR.

Hyperpigmentation hypertrichosis, histiocytosis-lymphadenopathy plus syndrome

Otulipenia/ORAS*. ***OTULIN.*** AR.
Neonatal onset of recurrent fever, Arthralgia, lipodystrophy. Dermatitis, diarrhea, Neutrophilia

AP1S3 deficiency*. ***AP1S3.*** AR.

Pustular psoriasis

Type 1 Interferonopathies

Progressive encephalopathy, ICC, Cerebral atrophy, HSMG, leukodystrophy , Thrombocytopenia, Elevated hepatic transaminases . Chronic cerebrospinal fluid (CSF) lymphocytosis

Aicardi-Goutieres Syndromes :
TREX1 AR-AD (+SLE, FCL), ***RNASEH2A, RNASEH2B*** (+SP), ***RNASEH2C, SAMHD1*** (+ FCL), ***ADAR1*** (+BSN, SP), ***IFIH1 GOF*** AD (+ SLE, SP, SMS), ***DNASE2***

Spondyloenchondro-dysplasia with immune dysregulation (SPENCDI). ***ACP5.***
Short stature, SP, ICC, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, Inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, possibly recurrent bacterial and viral infections.

STING-associated vasculopathy, infantile-onset. ***TMEM173.***
Early-onset inflammatory disease, Skin vasculopathy, Inflammatory lung disease, systemic autoinflammation and ICC, FCL.

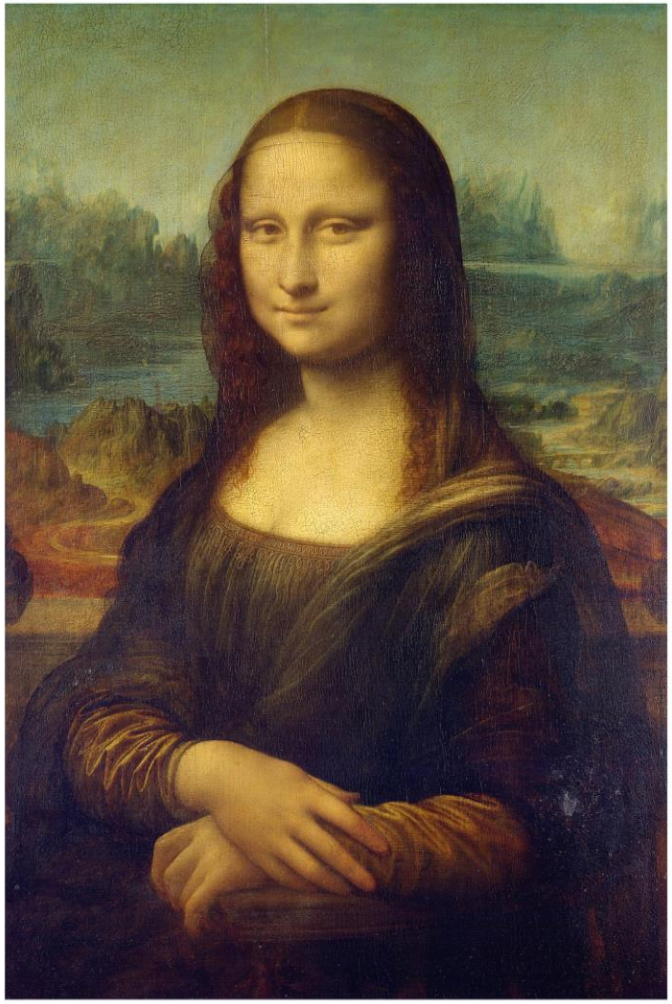
ADA2 deficiency. ***CECR1.*** Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, some patients develop hypogammaglobulinemia

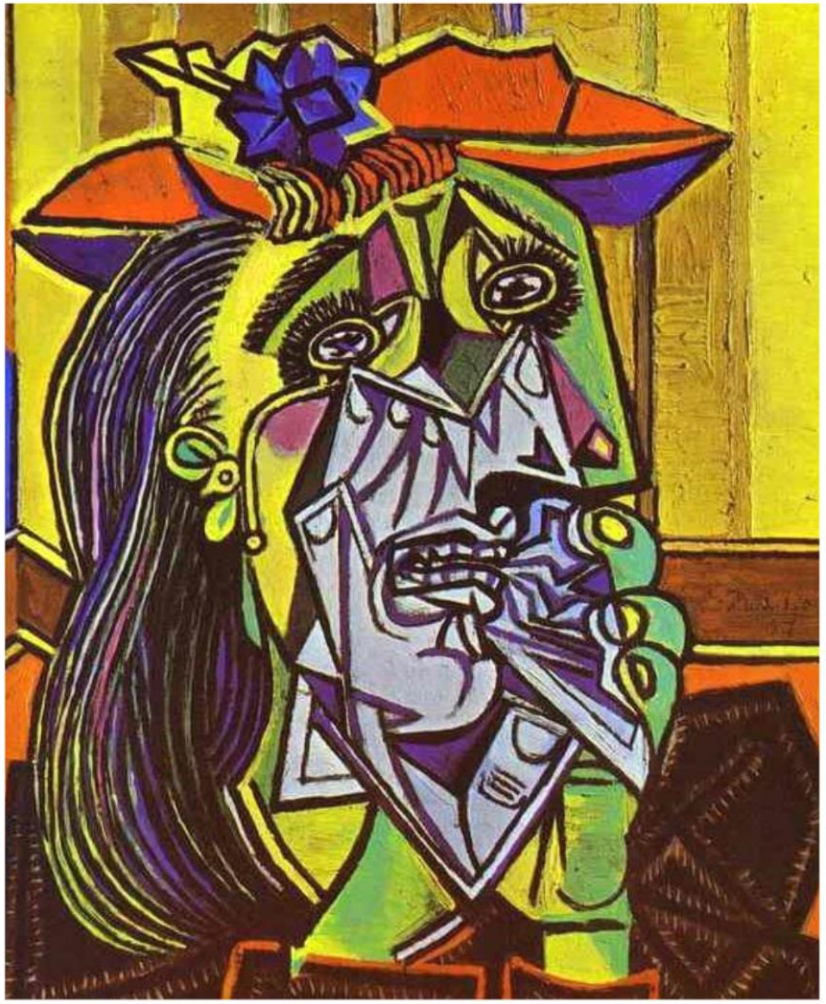
XL reticulate pigmentary disorder. ***POLA1.*** Hyper-pigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies

USP18 def*. ***USP18.*** TORCH like syndrome.

Pediatric systemic lupus erythematosus. ***DNASE1L3.*** Very early onset SLE, reduced complement levels, autoantibodies (dsDNA, ANCA), lupus nephritis, hypocomplementemic urticarial vasculitis syndrome.

OAS1 def*. ***OAS1.*** AD GOF. Pulmonary alveolar proteinosis, skin rash.





TRAPS

Presence of confirmatory *TN*
and at least one among the
- Duration of episodes ≥7
- Myalgia.
- Migratory rash.
- Periorbital oedema.
- Relatives affected.

OR

Presence of a not confirmat
genotype† and *at least two*
following:
- Duration of episodes ≥7
- Myalgia.
- Migratory rash.
- Periorbital oedema.
- Relatives affected.

Sensitivity: 0.95

Specificity: 0.99

Accuracy: 0.99

CAPS

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.

Sensitivity: 1

Specificity: 1

Accuracy: 1

MVK

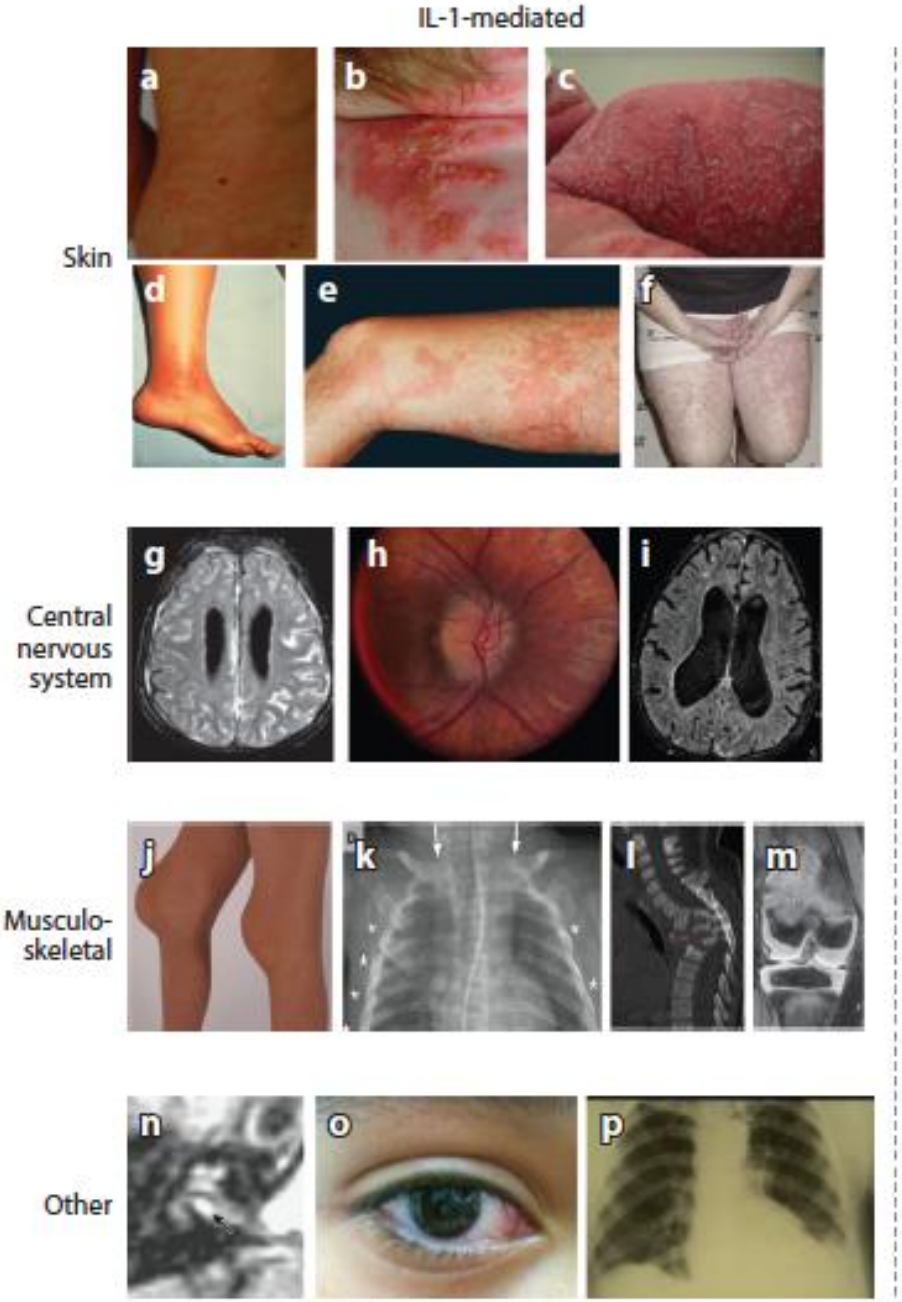
of a *confirmatory MVK*
* and *at least one* among the

ointestinal symptoms.
tal lymphadenitis.
ous stomatitis.

: 0.98

: 1

1



de Jesus A, et al. Annu Rev Immunol 2015; 33:823–74

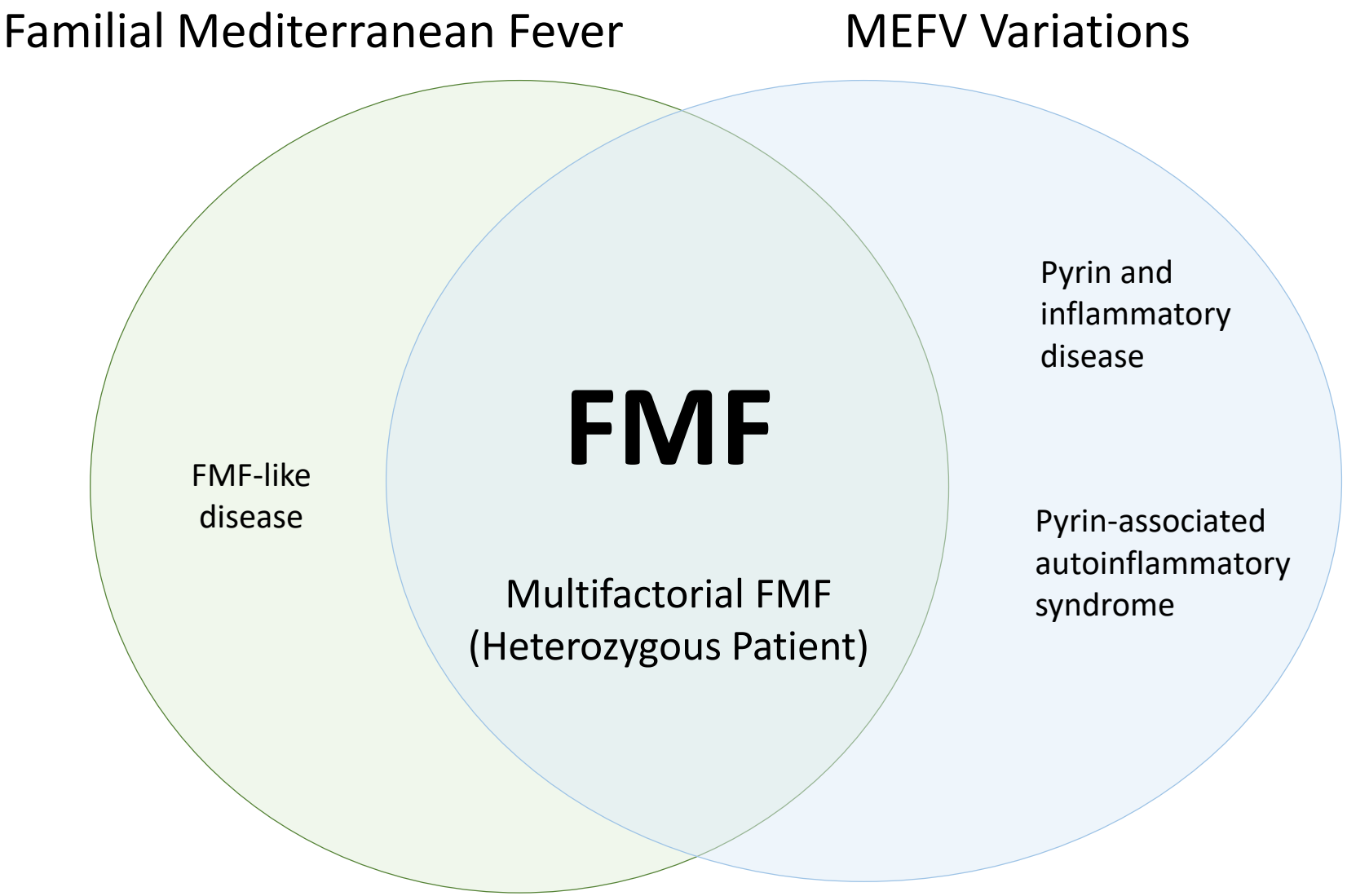
Autoinflammatory Disorders - Clinical Features

- Age at the disease onset
  - Usually starts during childhood

  - **Adult patients**
    - Late diagnosis ?
    - Variable expressivity and incomplete penetrance of disease- causing variants
    - Low penetrance variations and combinations

      MEFV, MVK, TNFRSF1A, NLRP3, …
    - Atypical features / new disorders
    - Somatic variations
    - Multifactorial (complex) disorders

Familial Mediterranean Fever



Gül A. LER (Clin Exp Rheumatol) 2014

FMF and Other Clinical Presentations

- MEFV p.Pro369Ser / p.Arg408Gln

Table 3 Clinical features of symptomatic individuals bearing P369S and R408Q variants in *MEFV* not reaching the Tel-Hashomer criteria

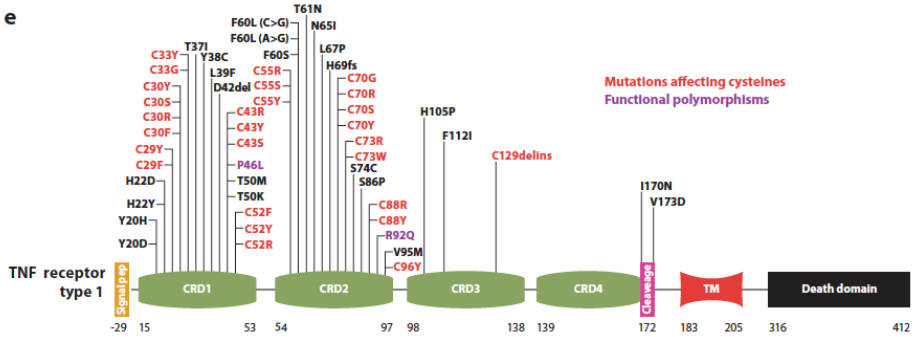
Patient ID	Age at onset	Fever	Biological	Clinical features	Additional *MEFV* variants	*TNFRSF1A*	*MVK*
'PFAPA-like' symptoms							
980	4 years	Y	N	Aphthous ulcers, pharyngitis, cervical lymphadenopathy.	E148Q+E148Q	Negative	Negative
1110	2 years	Y	N	Aphthous ulcers, pharyngitis, cervical lymphadenopathy	E148Q(+) I591T	Negative	Negative
1874	1 month	Y	Y	Aphthous ulcers, pharyngitis, cervical lymphadenopathy		Negative	Negative
Predominantly serositis symptoms							
1300	6 months	Y	N	Pleuritis, lower limb arthralgia	E148Q	Negative	Negative
1688	14 years	N	Y	Pericarditis: tamponade, pleuritis, erysipeloid erythaema		Negative	Negative
1818	12 years	Y	N	Single episode pleuritis			
1880	14 years	N	N	Pleuritis, arthralgia, nausea, vomiting			
Joint symptoms							
83	Adulthood	N	N	Recurrent knee synovitis		Negative	Negative
945	5 years	Y	N	Arthralgia: upper limb and jaw, abdominal pain, rash with fever			
Uveitis							
122	50 years	Y	Y	Panuveitis, inflammatory bowel disease, lethargy	E148Q	Negative	Negative
1408	20 years	N	Y	Uveitis, dactylitis, abdominal pain	E148Q		
Other							
172	30 years	N	N	Unilateral eyelid amyloidosis following conjunctivitis		Negative	Negative
1569	59 years	Y	Y	Profound fatigue, arthralgia		Negative	Negative
1793	11 years	Y	N	Arthralgia, myalgia, abdominal pain, oral ulcers	E148Q	Negative	Negative
1827	35 years	Y	N	Diarrhoea, cervical lymphadenopathy	E148Q	Negative	Negative
1879	18 months	N	N	Large joinst arthralgia and myalgia			
1883	Infancy	N	N	Abdominal discomfort, arthralgia	E148Q		

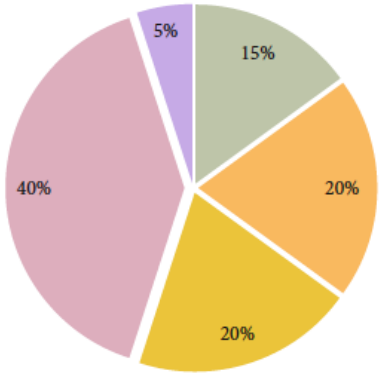
Ryan et al. ARD 2010

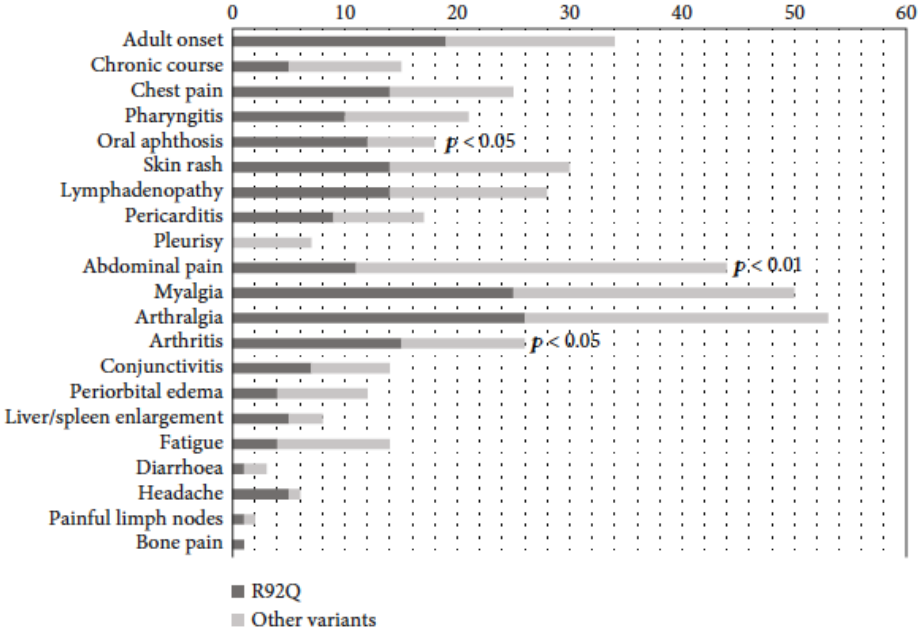
TNFRSF1A - TRAPS and Other Clinical Findings

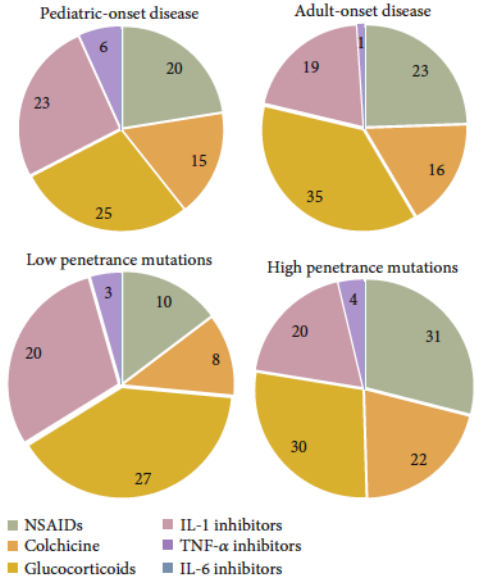
- p.Arg121Gln (R92Q)

Annu Rev Immunol 2009; 27: 621-68







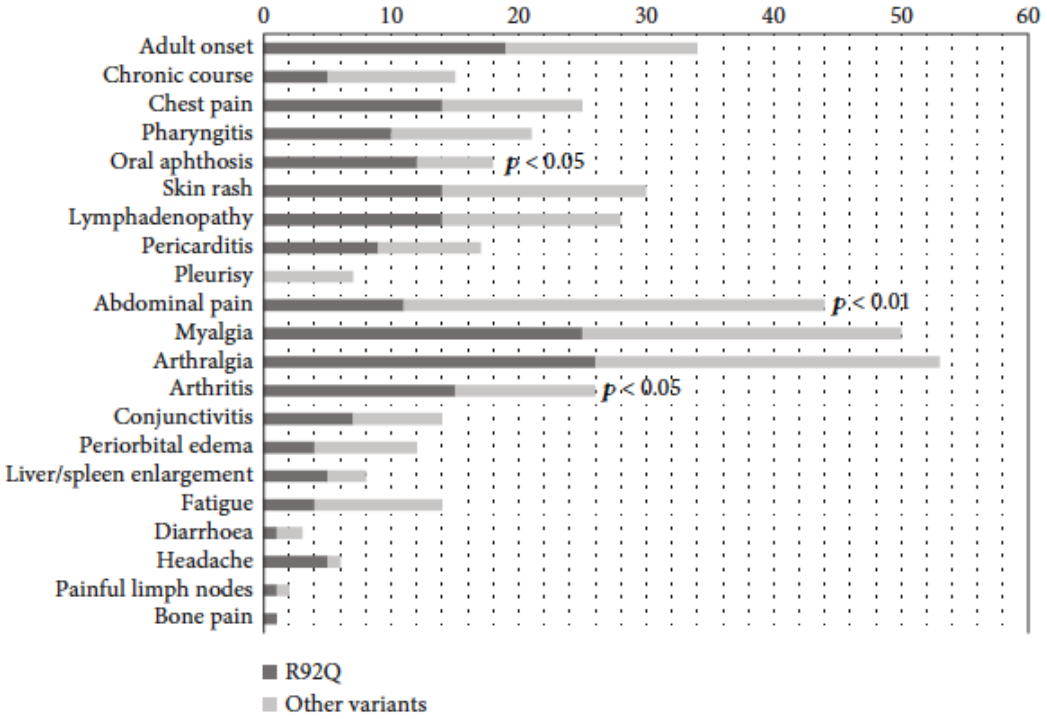


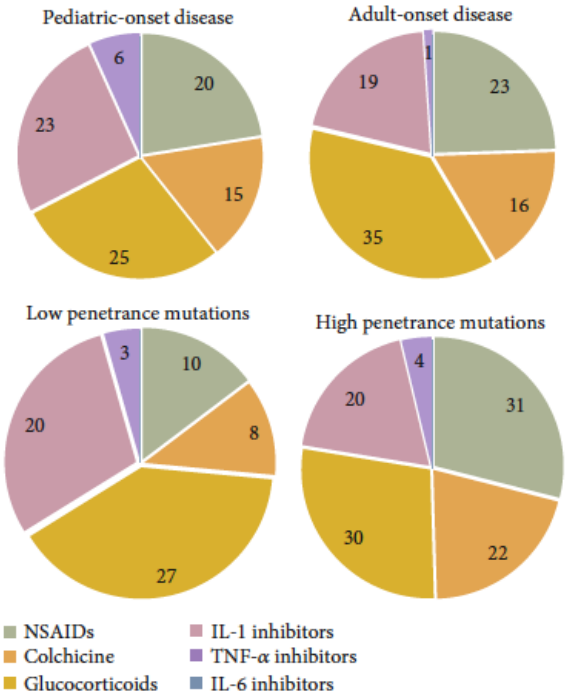
Gaggiano C, et al. Mediators Inflamm. 2020 Aug 7;2020:8562485

TNFRSF1A - TRAPS and Other Clinical Findings

Research Article

Clinical Features at Onset and Genetic Characterization of Pediatric and Adult Patients with TNF-α Receptor—Associated Periodic Syndrome (TRAPS): A Series of 80 Cases from the AIDA Network

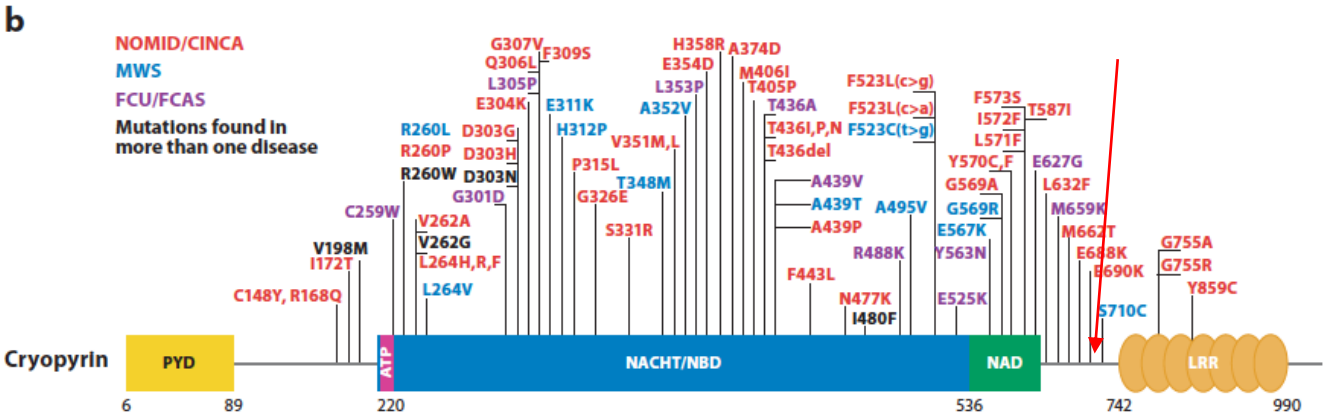




Gaggiano C, et al. Mediators Inflamm. 2020 Aug 7;2020:8562485

NLRP3 - CAPS and Other Clinical Findings

- p.Gln703Lys (Q703K veya Q705K)



Annu Rev Immunol 2009; 27: 621-68

Clinical Characteristics of Patients Carrying the Q703K Variant of the *NLRP3* Gene: A 10-year Multicentric National

Clinical and Molecular Phenotypes of Low-Penetrance Variants of *NLRP3*: Diagnostic and Th

Aldo Naselli, F
Alberto Tomma
Sara Signa, Ors
Anna Rubartell

J. B. Kuemmerle-Deschn
K. Krause,[5] C. Rietschel,[6]
S. M. Benseler[10]

Increased Prevalence of *NLRP3* Q703K Variant Among Patients With Autoinflammatory Diseases: An International Multicentric Study

NLRP3 - CAPS and Other Clinical Findings

- NLRP3 p.Gln703Lys (Q703K veya Q705K)

Table 1. Demographic features of the patients at the time of molecular analysis.

Patient	Sex	Age at Onset, yrs	Age at Molecular Analysis, yrs	Mutations in *NLRP3* or in Other Genes
S1	F	30	41	Q703K
S2	F	45	60	Q703K
S3	F	22	26	Q703K
S4	F	7	11	Q703K
S5	F	4	21	Q703K
S6	M	17	25	Q703K
S7	F	15	19	Q703K
S8	F	57	58	Q703K
S9	F	28	28	Q703K
S10	F	57	64	Q703K
S11	M	33	43	Q703K
S12	F	10	23	Q703K
S13	F	33	38	Q703K
S14	M	15	45	Q703K
S15	M	6	41	Q703K
S16	M	8	8	Q703K
S17	F	1	6	Q703K
S18	F	1	8	Q703K
S19	F	1	7	Q703K
S20	M	1	9	Q703K
S21	F	3	16	Q703K
S22	F	4	7	Q703K
S23	M	3	3	Q703K
S24	M	1	1	Q703K
S25	M	1	1	Q703K
S26	M	2	4	Q703K-M406I
S27	F	29	37	Q703K
S28	F	14	16	Q703K
S29	M	3	11	Q703K
S30	M	1	1	Q703K
S31	M	21	23	Q703K
S32	F	1	1	Q703K
S33	M	5	6	Q703K/V726A (*MEFV*)
S34	M	1	5	Q703K
S35	F	1	2	Q703K
S36	F	1	1	Q703K-D303N + V198M

Naselli A, et al. J Rheumatol 2016;43:1093-100.

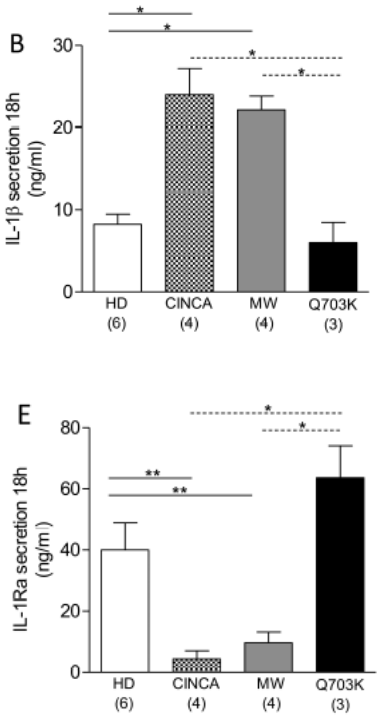


TABLE 4 | Comparison table of clinical characteristics between Q703K-positive vs. -negative uAID patients.

	Q703K+ (n: 12)	Q703K- (n: 5)	*P*-value
Median age at onset (years.months)	2.9	3.8	
Median age at diagnosis	5.3	5.8	
Sex ratio (M/F)	2.3/1	1/4	0.1189
Positive familial history	2/5	2/2	1
Recurrent Fever	10	3	0.5378
Pharyngitis	1	1	0.5147
Abdominal pain	5	2	1
Neurologic symptoms	0	0	1
Adenopathy	1	1	0.5147
Urticaria	1	3	0.0525
Headache	2	1	1
Myalgia	0	1	0.2941
Arthralgia	1	3	0.0525
Rash	1	0	1
Diarrhea	0	0	1
Conjunctivitis	0	0	1
Oral aphthosis	3	2	0.6
Disease Complications	1*	0	1

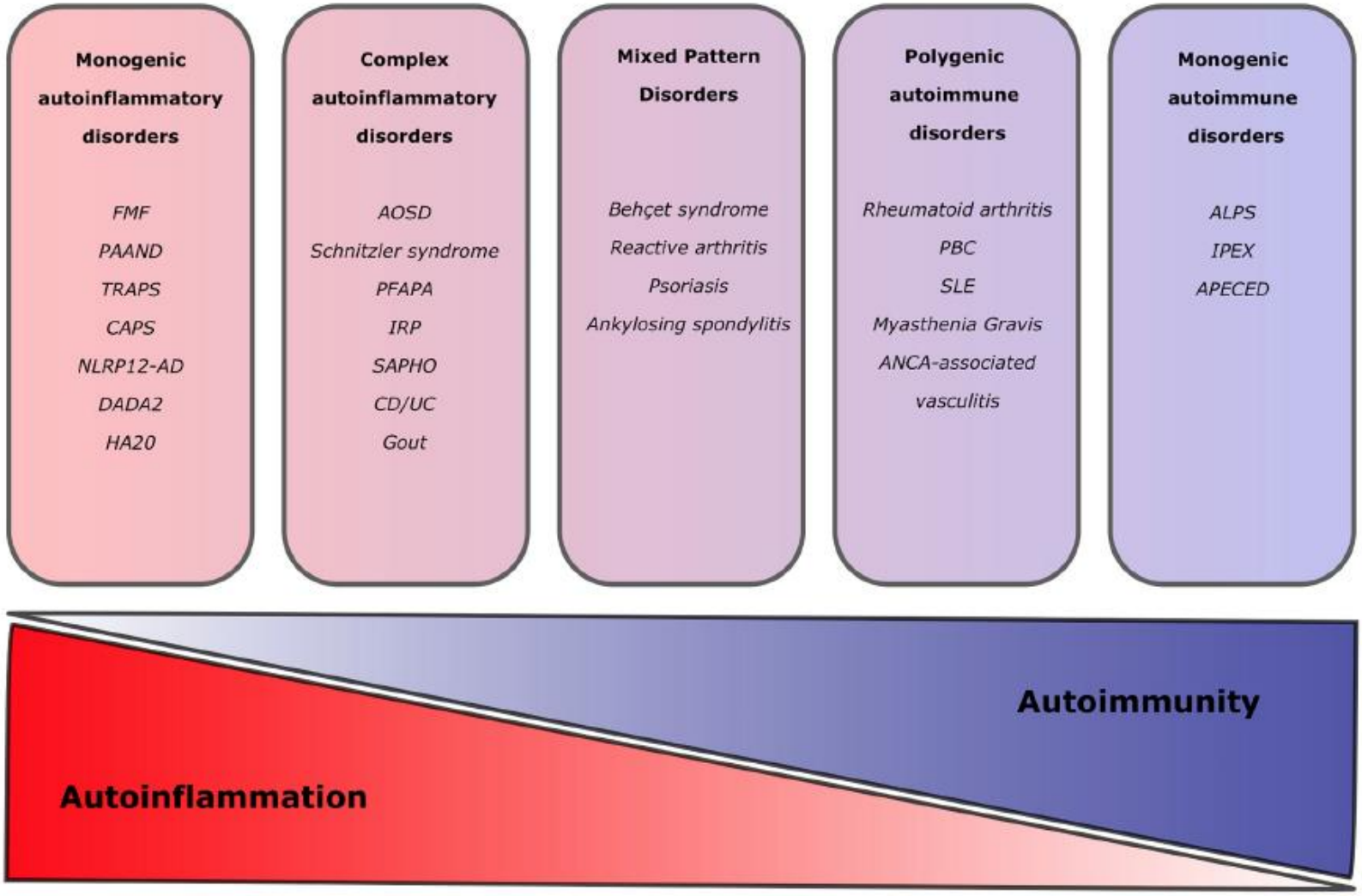
**severe proteinuria in the context of chronic glomerulonephritis.*

Theodoropoulou K, et al. Front Immunol. 2020 May 14;11:877.

Low Penetrance Variants

- Recurrent inflammatory attacks starting during childhood or adulthood
  - Fever, fatigue
  - Arthralgia/myalgia
  - Aphthous stomatitis / cervical lymphadenopathy
  - Pericarditis
  - Arthritis, uveitis, vasculitis, rash, …

Complex Autoinflammatory Disorders



Betrains A, et al. Autoimmun Rev 2021;20:102774

Recurrent Acute Pericarditis

- Acquired autoinflammatory disorder

Box 1 Major causes of pericarditis

Idiopathic

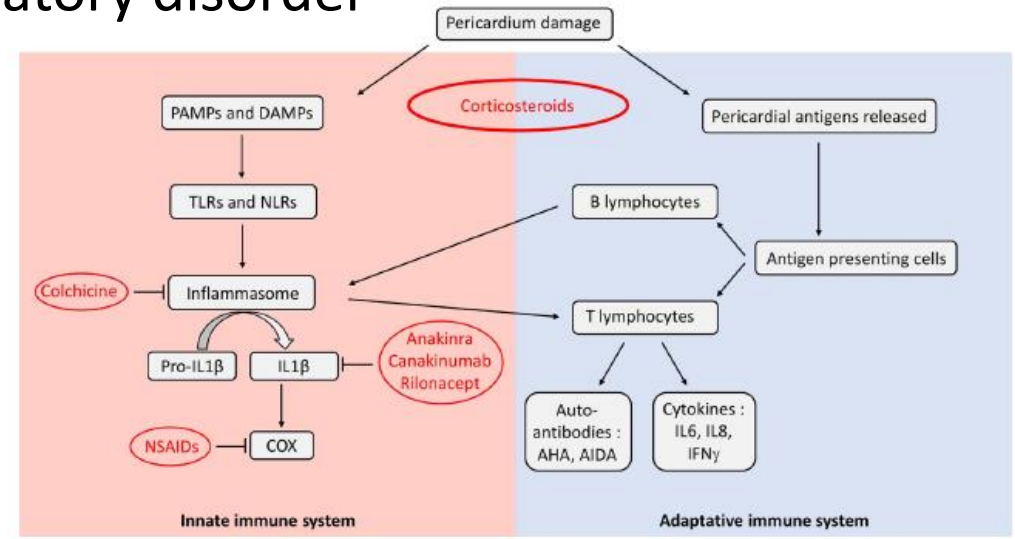
Malignancy

Post-cardiac injury syndrome
- ► Post-myocardial infarction
- ► Post-pericardiotomy
- ► Post-traumatic

Infectious diseases
- ► Viral, including HIV
- ► Bacterial and mycobacterial
- ► Fungal

Radiation

Systemic disorders
- ► Connective tissue diseases
  - – Systemic lupus erythematosus
  - – Rheumatoid arthritis
  - – Systemic sclerosis
  - – Sjögren's syndrome
  - – Myositis
- ► Granulomatous diseases
  - – Sarcoidosis
- ► Vasculitis
  - – Behçet syndrome
  - – Small vessels: eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis
  - – Medium-sized vessels: polyarteritis nodosa, Kawasaki disease
- ► Autoinflammatory diseases
  - – Familial Mediterranean fever
  - – Tumour necrosis factor receptor 1–associated periodic syndrome



Acute pericarditis
- Pericardial pain
- Pericardial friction rub
- ECG changes
- Pericardial effusion
- Elevation of CRP

Free interval of 4-6 weeks

Recurrent pericarditis

Pericardial pain + ≥ 1 sign among :
- Fever
- Pericardial friction rub
- ECG changes
- Pericardial effusion
- Biomarkers of inflammation

Cacoub P, Marques C. Heart 2020;106:1046–1051.

Complex Autoinflammatory Disorders

- Recurrent pericarditis
- Syndrome of Undifferentiated Recurrent Fever (SURF)

  Broderick L, Hoffman HM. J Allergy Clin Immunol 2020
  Papa et al. J Clin Med 2021

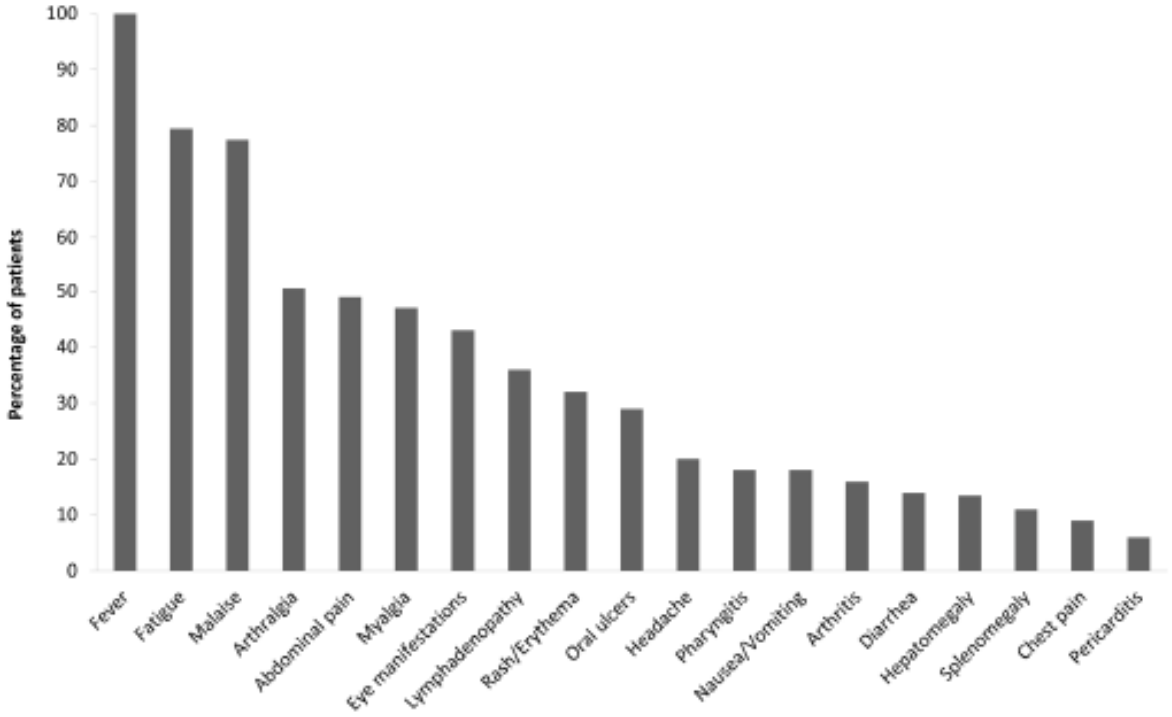
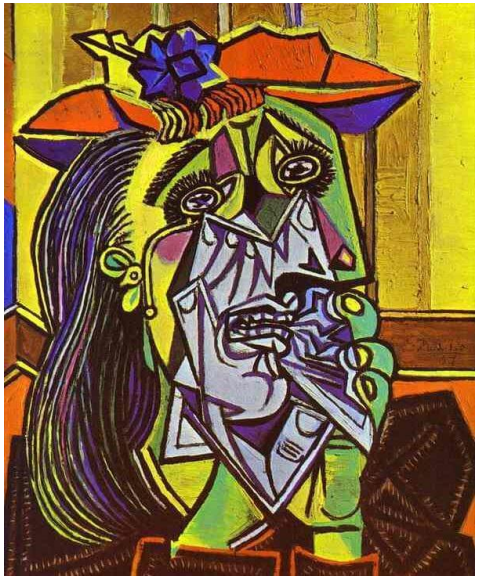


Figure 6. Clinical manifestations of SURF patients reported by at least two studies of Table 2. SURF, syndrome of undifferentiated recurrent fever.

Adult Autoinflammatory Disorders



- Low penetrant variants and combinations…
  - *MEFV, MVK, TNFRSF1A, NLRP3, …*
- Multifactorial (complex) disorders
- Somatic variations

VEXAS

Vacuoles
E1 enzyme
X-linked
Autoinflammatory
Somatic

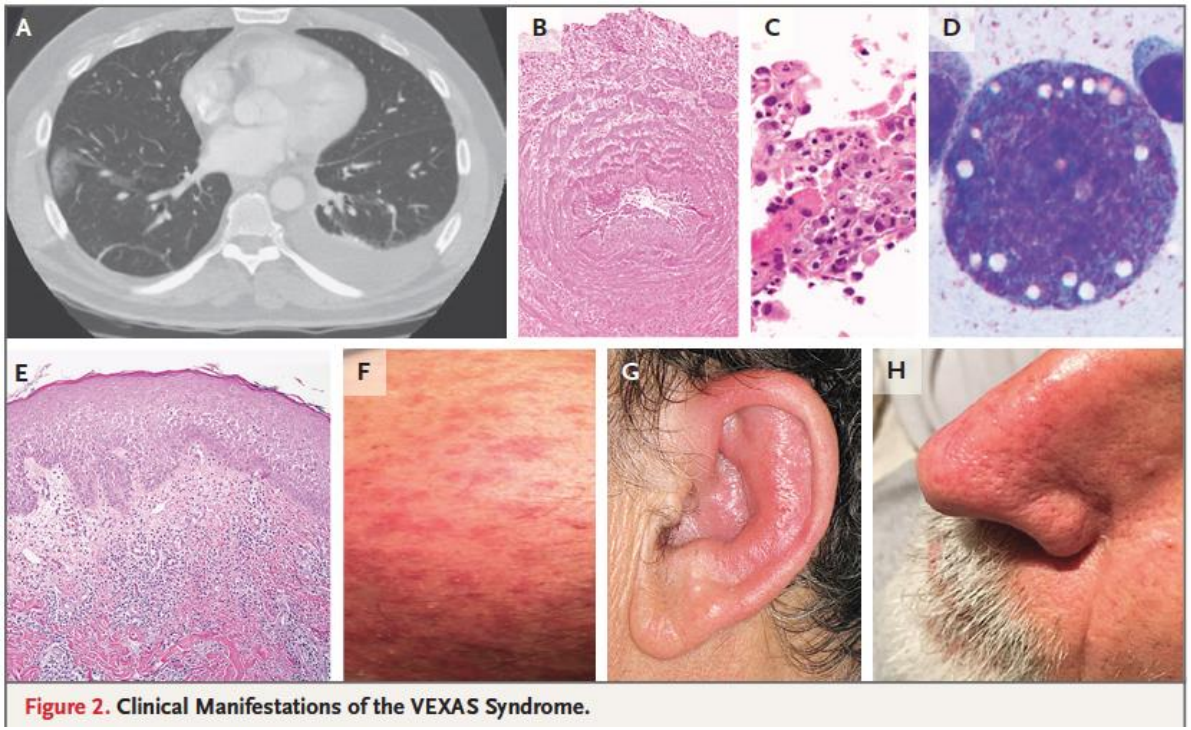
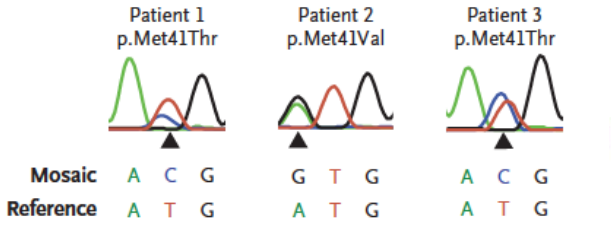
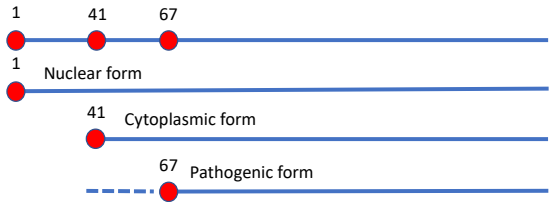
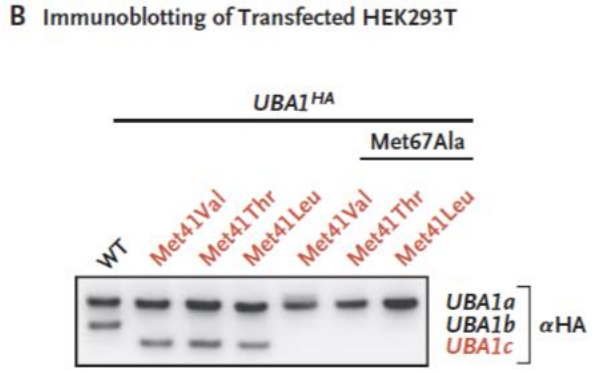


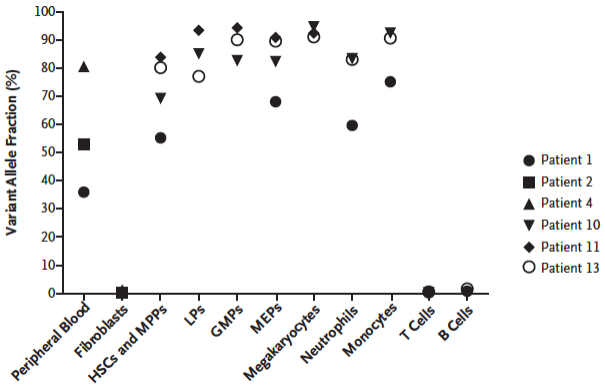
Figure 2. Clinical Manifestations of the VEXAS Syndrome.

Beck et al. N Engl J Med 2020



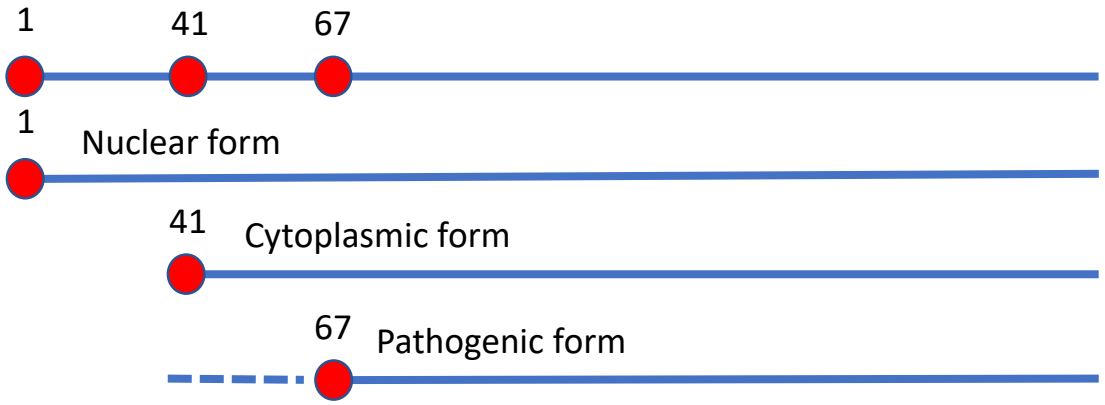


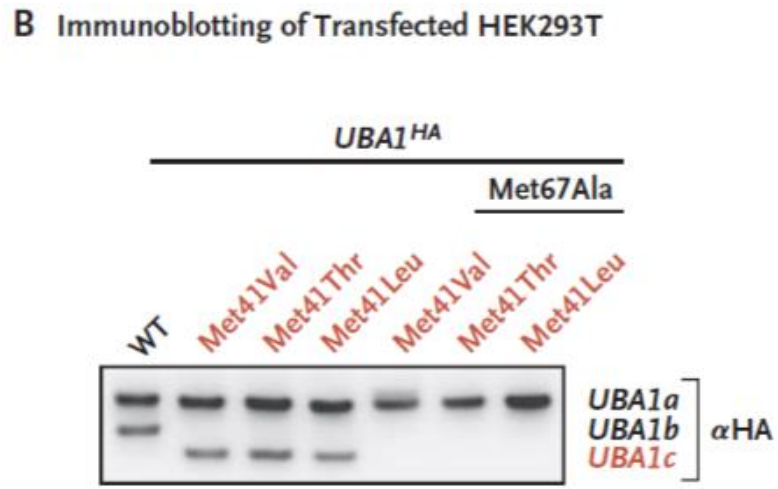




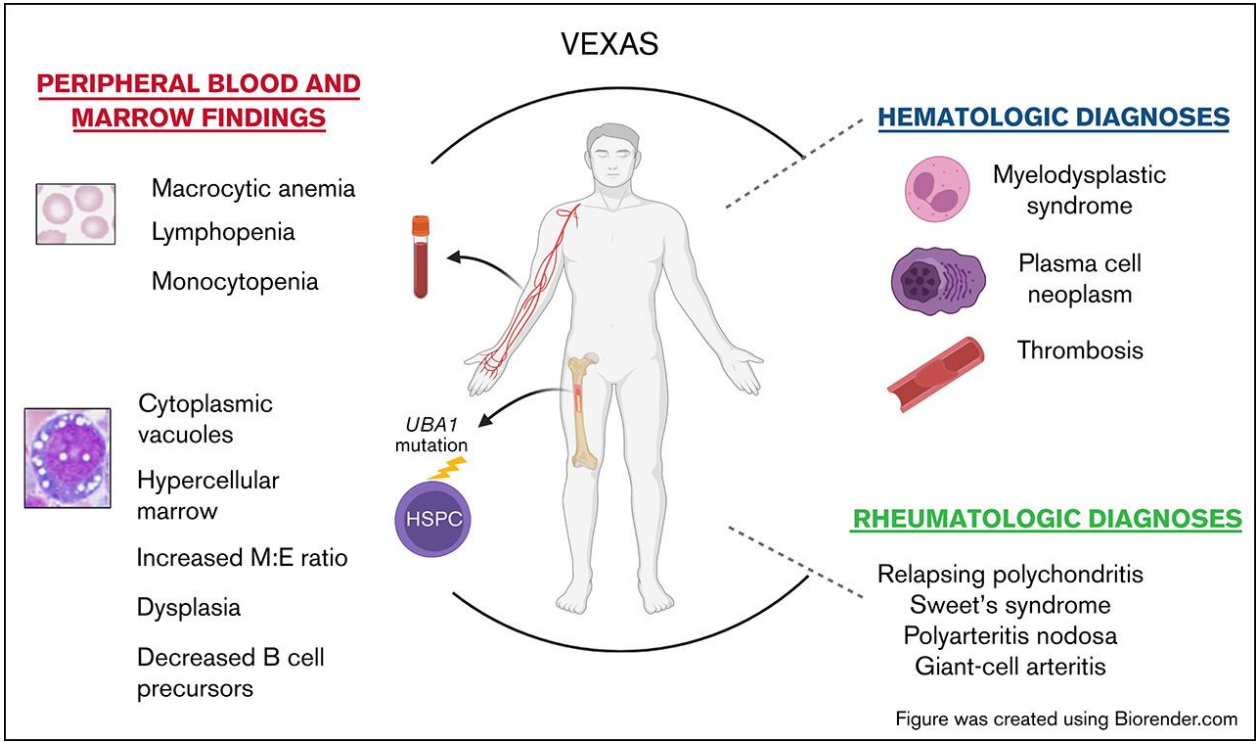
Genetik varyasyon ve fonksiyonel değişiklikler

- Başlama kodonu AUG (metiyonin kodlar)





VEXAS



Obiorah IE, et al. Blood Adv 2021

Elevated APR
Hematologic abnormalities
(macrocytic anemia, thrombocytopenia, lymphopenia, multiple myeloma, MDS)

more frequent in VEXAS-RP

A decision tree algorithm:
Male sex,
MCV >100 fl,
PLT <200,000/µl

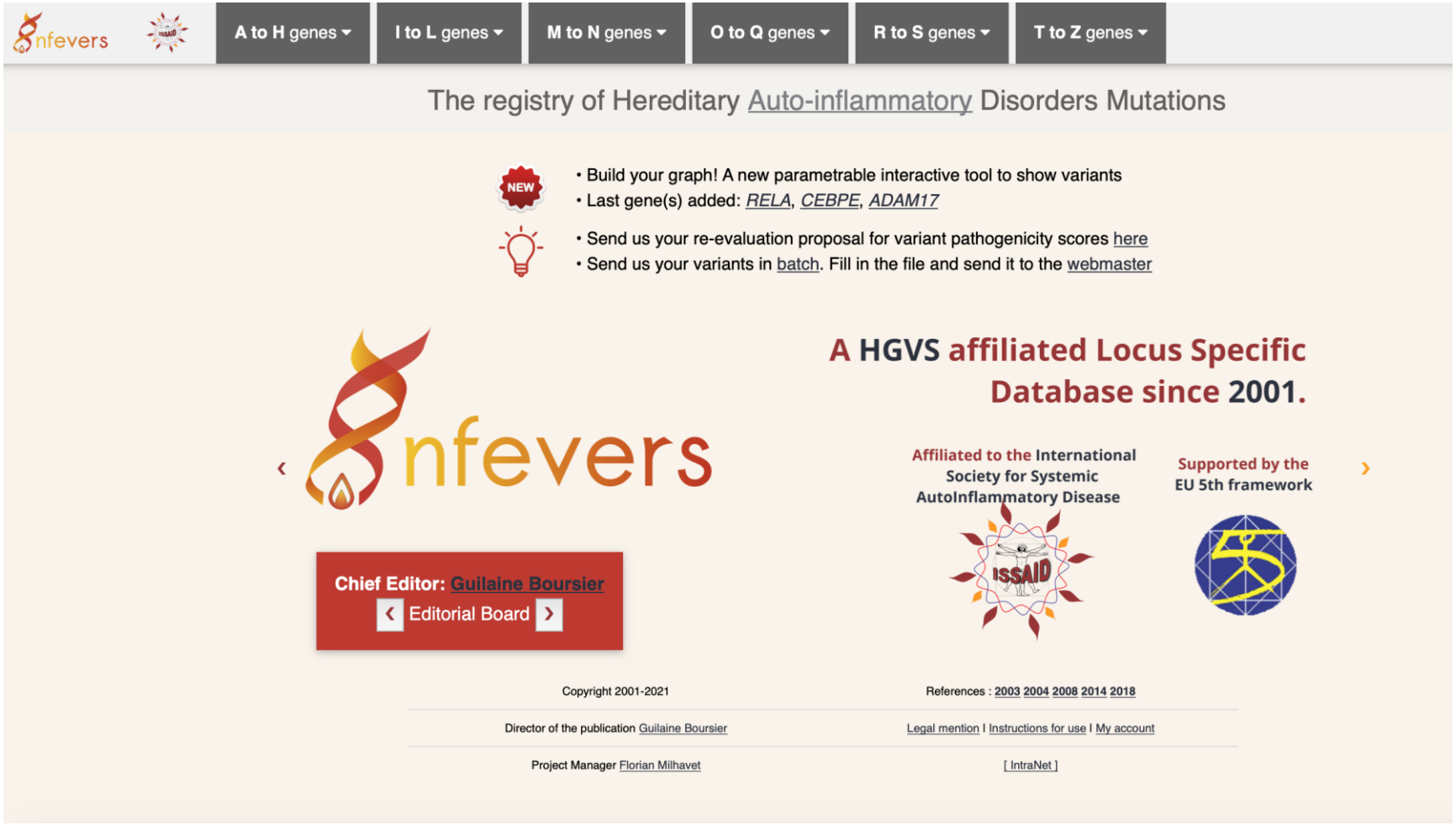
VEXAS-RP *vs* RP
100% sensitivity
96% specificity

Ferrada M. Arthritis Rheumatol 2021; 73:1886–95

Diagnosis

- Genetic diagnosis is the gold standard
  - Sanger sequencing for selected genes/exons
  - Next generation sequencing for several genes involved in hereditary autoinflammatory disorders
    - Deep sequencing
      - Somatic mosaicism
    - Cellular sources (peripheral blood, buccal mucosa, tissue, …)
  - Whole exome / whole genome sequencing
  - Functional importance of the variants
    - Benign, likely benign, likely pathogenic, pathogenic, variant of uncertain significance

Diagnosis



https://infevers.umai-montpellier.fr

Diagnosis

exon 10	c.2042C>T	p.(Thr681Ile)	T681I	Uncertain significance (VUS)	PROVISIONAL	See details	
exon 10	c.2049G>A	p.(Ser683=)	S683S	Likely benign	VALIDATED	See details	
exon 10	c.2053G>A	p.(Glu685Lys)	E685K	Uncertain significance (VUS)	VALIDATED	See details	
exon 10	c.2060G>A	p.(Gly687Asp)	G687D	Likely pathogenic	PROVISIONAL	See details	
exon 10	c.2063A>G	p.(Tyr688Cys)	Y688C	Likely pathogenic	VALIDATED	See details	
exon 10	c.2063A>T	p.(Tyr688Phe)	Y688F	Likely pathogenic	VALIDATED	See details	
exon 10	c.2064C>G	p.(Tyr688*)	Y688X	Likely pathogenic	VALIDATED	See details	
exon 10	c.2068G>C	p.(Val690Leu)	V690L	Likely benign	PROVISIONAL	See details	
exon 10	c.2069T>G	p.(Val690Gly)	V690G	Not classified	To be validated	See details	
exon 10	c.2072T>G	p.(Val691Gly)	V691G	Not classified	To be validated	See details	
exon 10	c.2076_2078del	p.(Ile692del)	I692DEL	Likely pathogenic	VALIDATED	See details	See details
exon 10	c.2078T>A	p.(Met693Lys)	M693K	Not classified	To be validated	See details	
exon 10	c.2079G>C	p.(Met693Ile)	M693I	Unsolved	UNSOLVED	See details	
exon 10	c.2080A>G	p.(Met694Val)	M694V	Pathogenic	VALIDATED	See details	See details
exon 10	c.2080A>T	p.(Met694Leu)	M694L	Likely pathogenic	VALIDATED	See details	
exon 10	c.2081_2083del	p.(Met694del)	M694DEL	Likely pathogenic	VALIDATED	See details	
exon 10	c.2081T>A	p.(Met694Lys)	M694K	Likely pathogenic	VALIDATED	See details	
exon 10	c.2082G>A	p.(Met694Ile)	M694I	Pathogenic	VALIDATED	See details	See details
exon 10	c.2084A>G	p.(Lys695Arg)	K695R	Likely pathogenic	VALIDATED	See details	
exon 10	c.2084A>T	p.(Lys695Met)	K695M	Unsolved	UNSOLVED	See details	
exon 10	c.2085G>C	p.(Lys695Asn)	K695N	Likely pathogenic	PROVISIONAL	See details	

https://infevers.umai-montpellier.fr

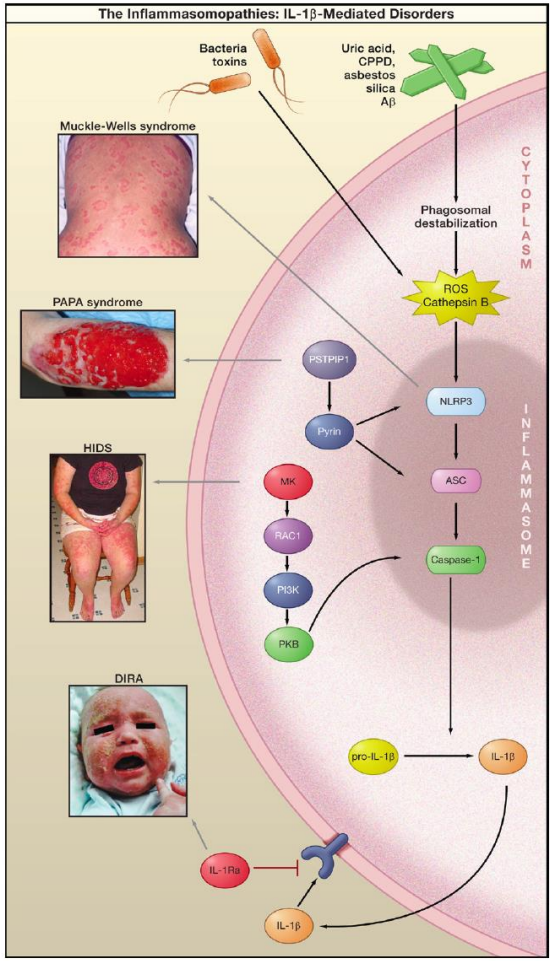
Treatment Approaches

- Tailored to the pathogenic pathways and disease severity
  - Symptomatic treatments: NSAIDs, glucocorticoids

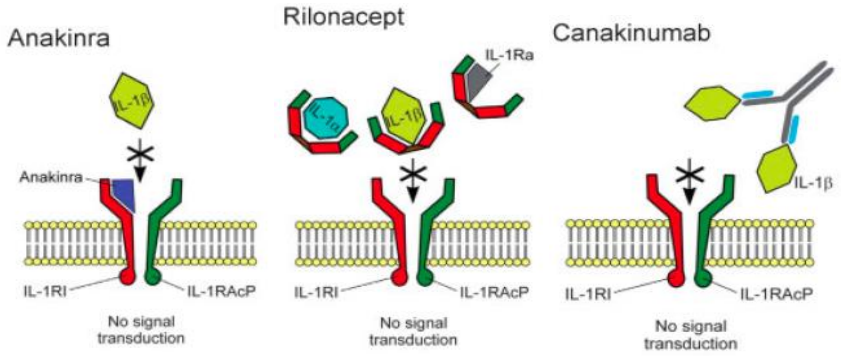
  - Targeted treatments for **inflammasomopathies**
    - Colchicine
      - *Documented efficacy in FMF*
      - *May show some efficacy in other conditions associated with low penetrant variants*

    - IL-1 inhibitors
      - Anakinra, canakinumab, rilonacept, …
    - Novel NLRP3 inhibitors?

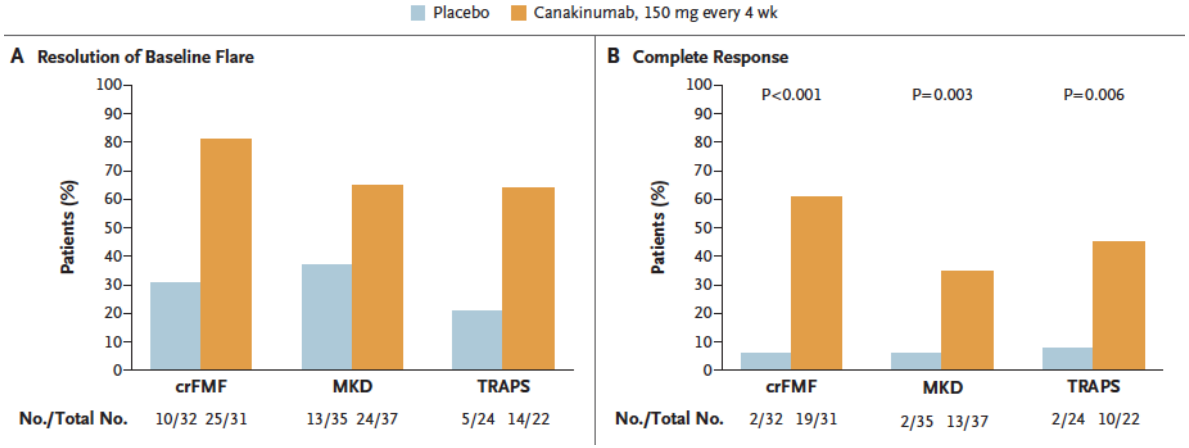
Treatment Approaches – IL-1 Blockade



Ann N Y Acad Sci 2009; 1182: 111-23.
Cell 2010; 140: 784-90



Lachmann HJ et al. Arthritis Rheum 2011; 63: 314-24



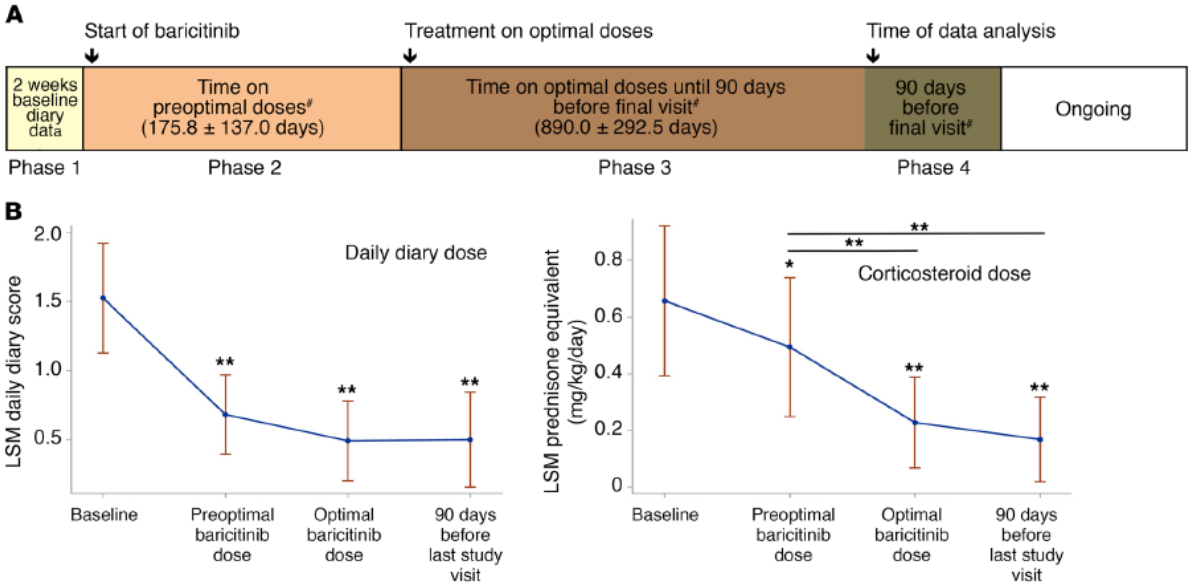
N Engl J Med 2018;378:1908-19

Treatment Approaches

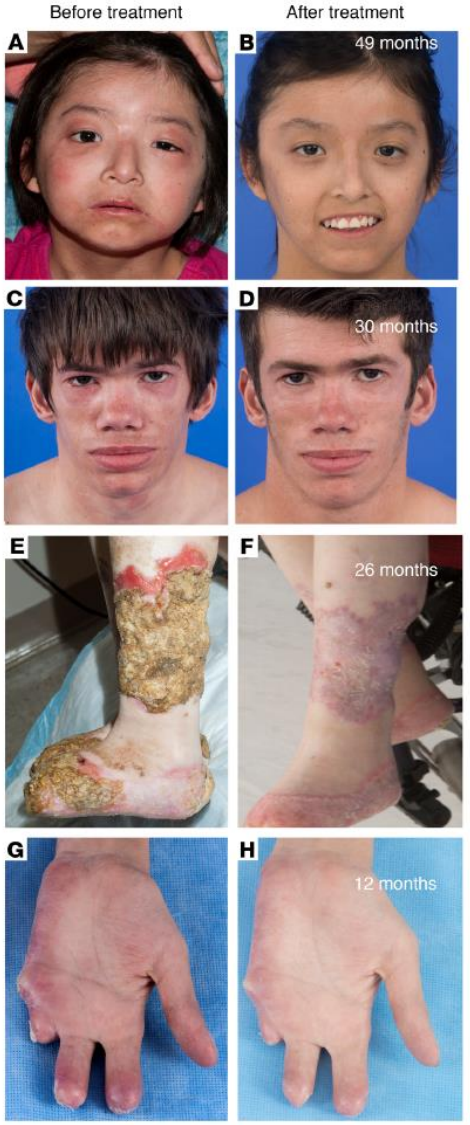
- Tailored to the pathogenic pathways and disease severity
  - Symptomatic treatments: NSAIDs, glucocorticoids
  - Targeted treatments for **interferonopathies**
    - Jak inhibitors
      - Baricitinib, tofacitinib, …

Treatment Approaches – Jak Inhibitors

- Inhibition of interferon signaling by Jakinibs in interferonopathies

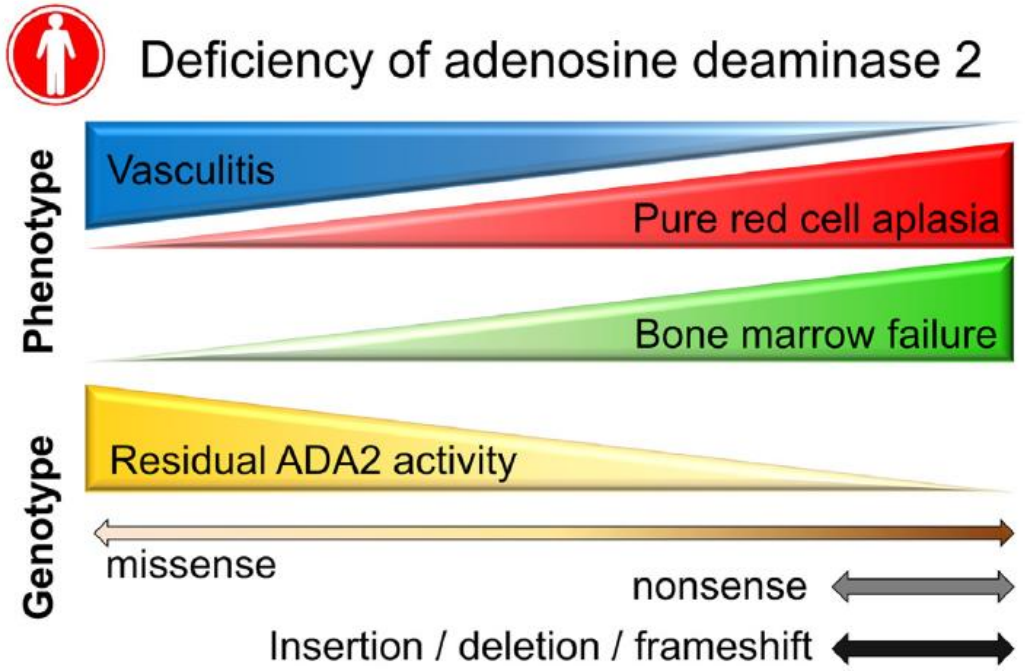


J Clin Invest 2018;128:3041–3052



Treatment Approaches

- Tailored to the pathogenic pathways and disease severity
  - Targeted treatments for **DADA2**
    - *Anti-TNF agents*
    - *Bone marrow transplantation*



J Allergy Clin Immunol 2020;145:1664-72

Autoinflammatory Disorders

- Episodes of seemingly unprovoked inflammation
  - *Vaccinations, infections, trauma, cold, exercise, stress, ...*
- Lack of obvious (primary) autoimmune pathology
  - High titer pathogenic autoantibodies, and
  - Antigen-specific autoreactive T cells in some patients (secondary)
    - *T cell activation*
    - *Polyclonal hypergammaglobulinemia*

Clinical disorders marked by

- abnormally increased inflammation
- mediated predominantly by the cells and molecules of the innate immune system
- with a significant host predisposition

Kastner et al. Cell 2010;140:784-90.