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The Expanding Universe of Autoinflammatory Diseases

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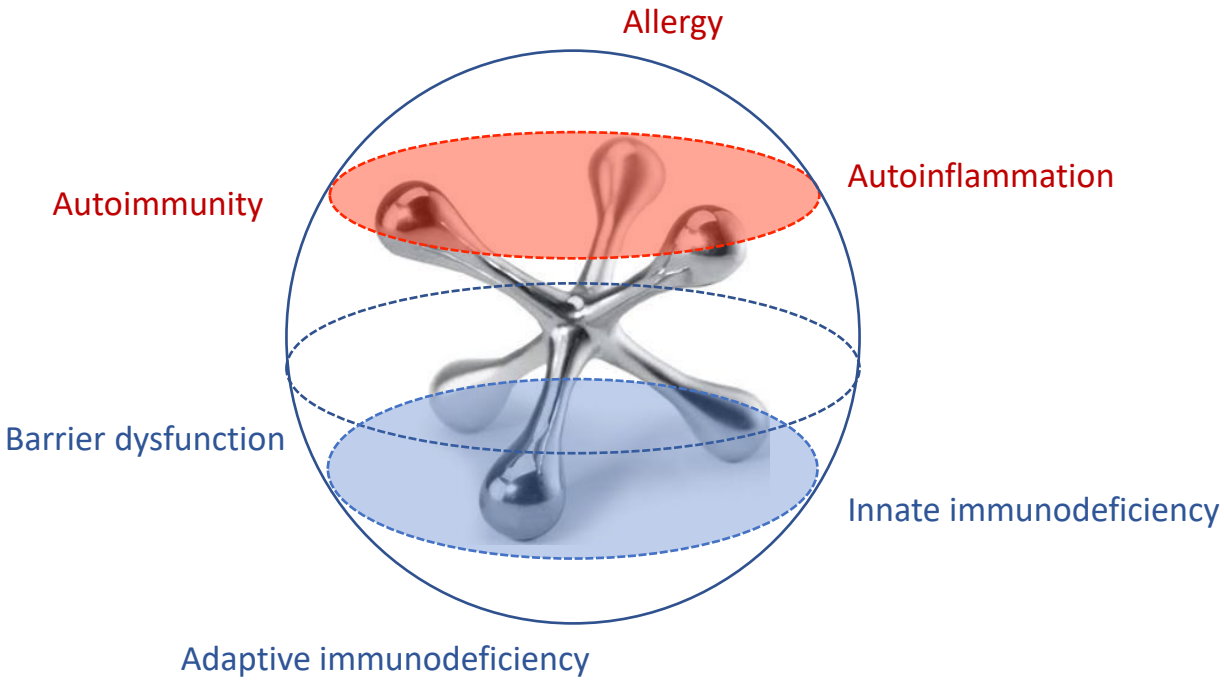
Learning Objectives

- *Upon completion of this learning activity, participants should be able to describe autonflammatory disorders as a unique clinical entity in the spectrum of inborn errors of immunity.*

- *Upon completion of this learning activity, participants should be able to recognize the shared and unique clinical presentations of autoinflammatory disorders.*

- *Upon completion of this learning activity, participants should be able to perform the initial clinical workup for suspected autoinflammatory disorders, and describe treatment options.*

The Allergist/Immunologist as a Jack-of-all-Trades



Broderick & Hoffman JACI 2020

Extremes of Innate Immunity

Immunodeficiency

- Defects in immune defenses which protect the host without the need of previous exposure.
- Neutrophils, NK cells, macrophages, complement
- Clinical severity often greatest in infancy

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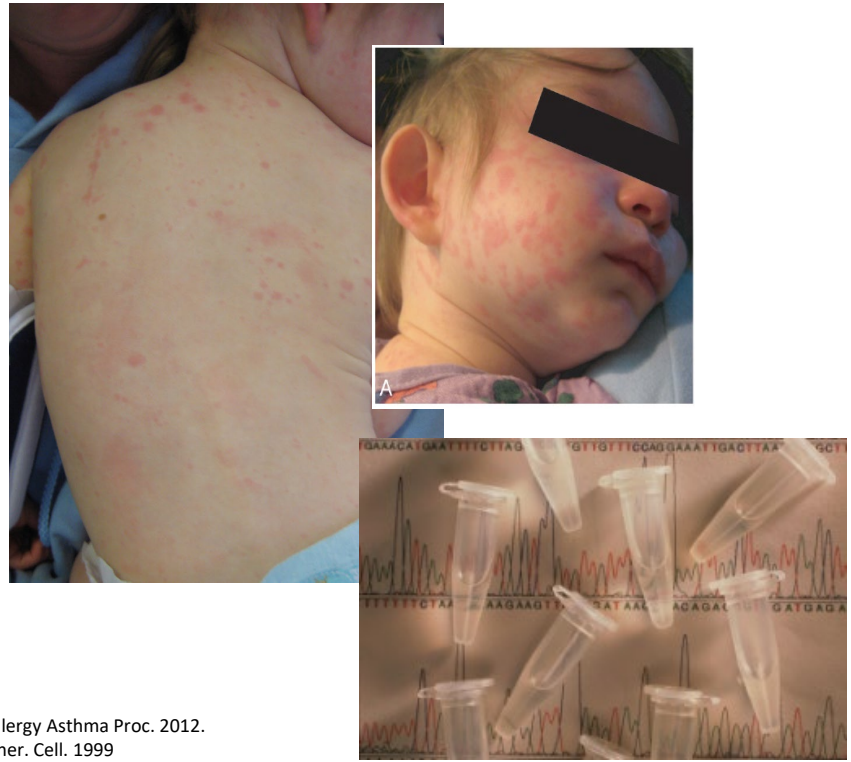
Autoinflammation

- Syndromes characterized by episodic or chronic inflammation
  - *Without* evidence of high-titer autoantibodies or antigen-specific T cells.
  - *Without* evidence of infection.
- Role of neutrophils/monocytes
  - IL-1, IL-18 TNF/NF-kb, and type I IFN

Autoinflammatory disease identification is driven by patients



Broderick L, et al. Allergy Asthma Proc. 2012.
McDermott, … Kastner. Cell. 1999
https://www.the-rheumatologist.org/

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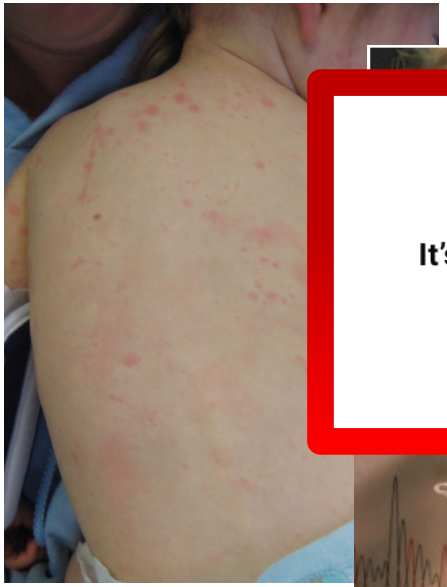
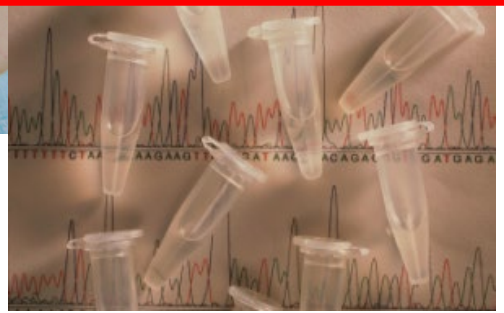


> It's the greatest example of bench to bedside you can think of.
>
> RONALD LAXER | HOSPITAL FOR SICK CHILDREN



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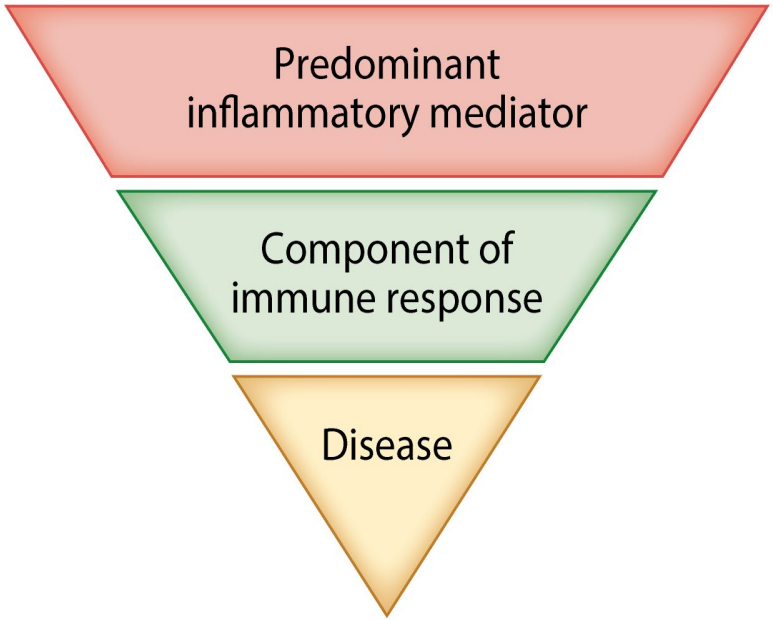
McDermott, … Kastner. Cell. 1999
https://www.the-rheumatologist.org/

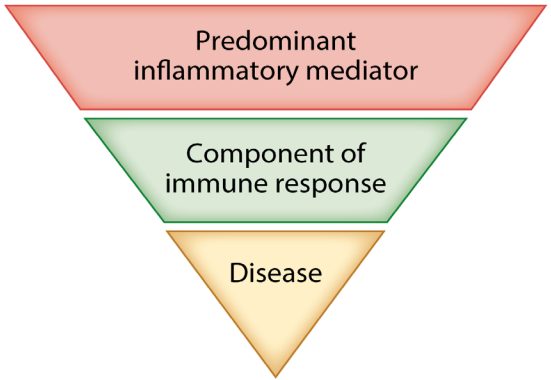
What is autoinflammation?

- Chronic or repeated episodes of inflammation with intervals that may be relatively symptom-free
- Systemic inflammation: fever, rash, organs (CNS, lungs, arthritis, conjunctivitis)
- Laboratory evidence of inflammation
  - Erythrocyte Sedimentation Rate (ESR)
  - C Reactive Protein (CRP)
  - Serum Amyloid A (SAA)

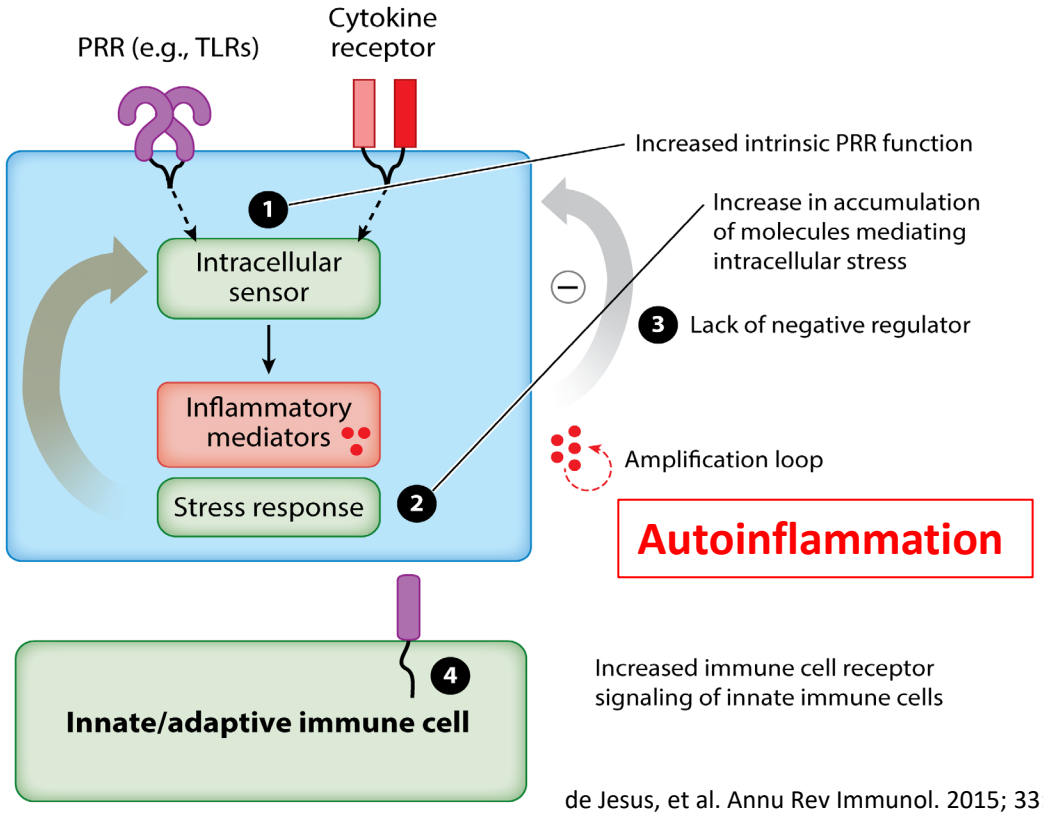


de Jesus, et al. Annu Rev Immunol. 2015; 33: 823–874.

Why is it called autoinflammation?



Genetically defined



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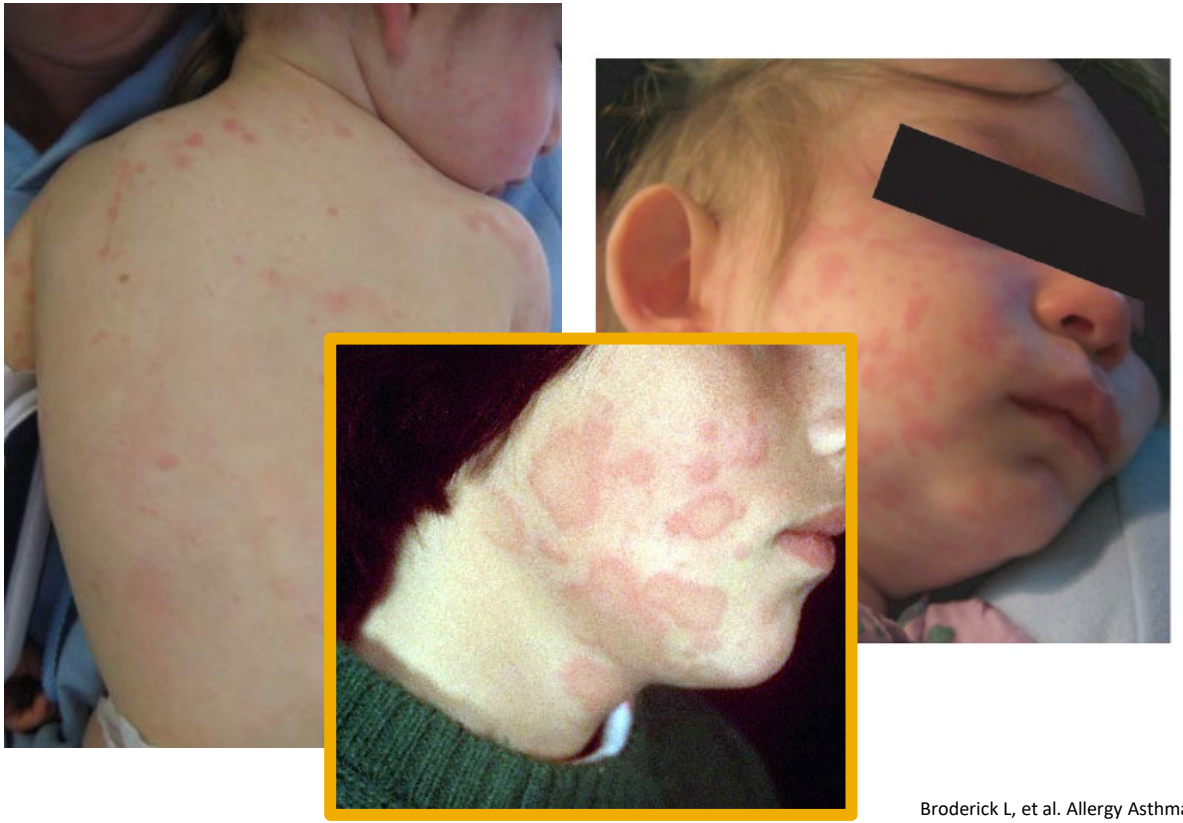
“My child has hives”

- Normal pregnancy, birth and first year of life
- Intermittent mild rash at age 9 months – antihistamines prn
- At 14 mo, acute episode with 8 days of fever, conjunctival injection, urticarial-like rash, and irritability
- Admitted with a presumptive diagnosis of Kawasaki Disease.
  - IVIG on 2 occasions, and subsequently infliximab
  - Multiple echocardiograms documented normal coronary artery internal dimensions.

Broderick et al, Allergy Asthma Proceedings, 2012

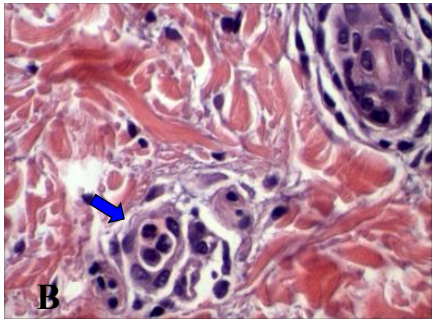
Urticarial-like Rash

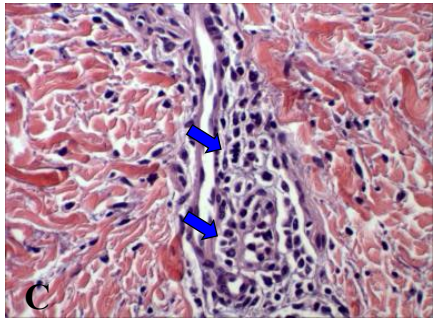


Broderick L, et al. Allergy Asthma Proc. 2012.

Laboratory Evaluation

- Laboratory evaluation was notable for elevated inflammatory markers (CRP, ESR, D-dimer, ferritin)
- Leukocytosis ($21.9x10^3$/ul) with neutrophilia, thrombocytosis (697K/ul)
- ANA negative, normal C3, C4
- Normal urinalysis
- Negative infectious workup





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Distinguishing criteria of urticaria and autoinflammatory syndromes

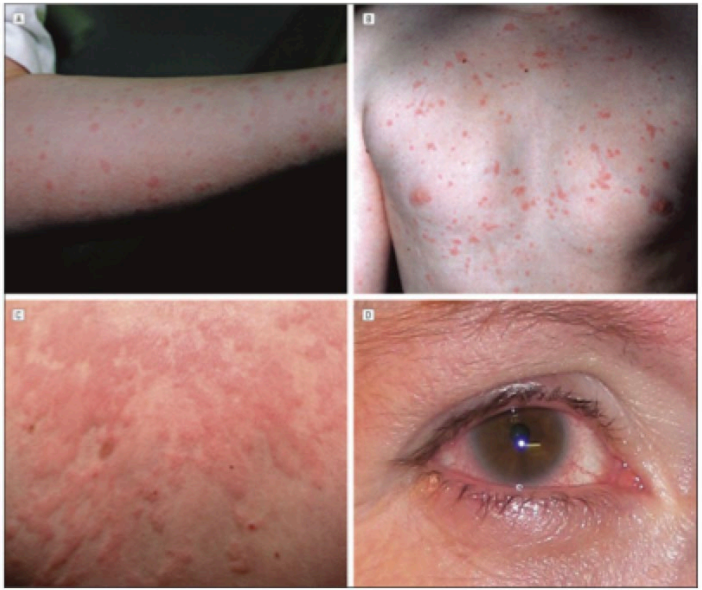
Characteristics of urticarial rash	Chronic urticaria	Autoinflammatory syndrome
Appearance	Papular wheals Wheal-and-flare reaction	Flatter wheals, erythematous patches but also more solid and stable lesions No wheal with surrounding flare
Localization	Asymmetrical distribution common	Rather symmetrical distribution
Duration of single lesion	Transient (minutes or few hours)	Hours, up to 24 h
Pruritus	Severe	May be absent, rather burning or painful
Angioedema	Often associated	Rare
Skin histopathology	Dermal oedema; partly sparse inflammatory infiltrate of perivascular eosinophils, neutrophils and lymphocytes	No significant dermal oedema; dense neutrophil-rich perivascular and interstitial infiltrates, but can also be rather nonspecific
Start of symptoms	All ages	Childhood (hereditary fever syndromes) Adulthood (acquired complex disorders)
Disease duration	Few years	Usually life-long
Response to antihistamines	Moderate – good Dose dependent	Missing
Systemic symptoms	None	Recurrent fever, fatigue, arthralgia and others
Inflammation markers	Within normal range	(Continuously) elevated
Family history	Negative	Often positive

Krause K, et al. Allergy. 2012.

Cryopyrin-Associated Periodic Syndromes exist along a continuum of severity

FCAS

12-24 hour attacks
Urticarial-like rash
Polyarthralgia
Conjunctivitis

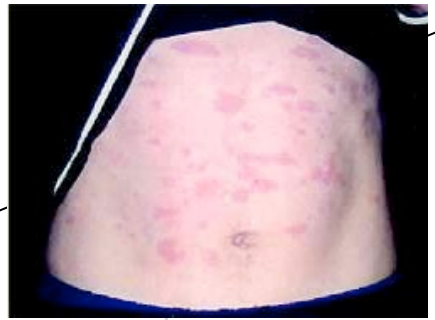


Severity

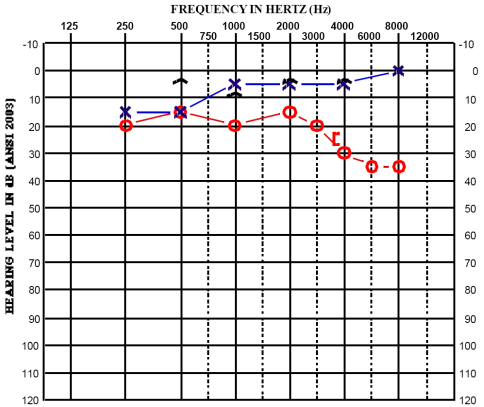
Arch Dermatol. 2006;142(12):1591-1597. doi:10.1001/archderm.142.12.1591

Cryopyrin-Associated Periodic Syndromes exist along a continuum of severity

MWS



2-3 day attacks
Urticarial-like rash
Polyarthralgia
Oligoarthritis
Conjunctivitis
Episcleritis
Sensorineural deafness
Headache

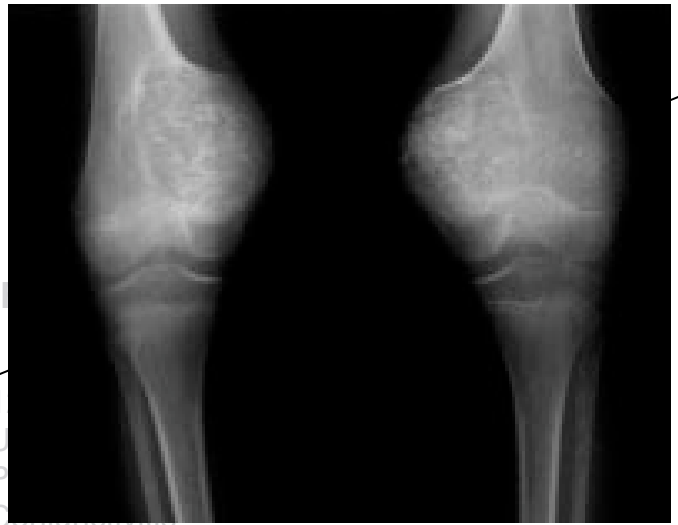


Severity

Hawkins et al. Arthritis Rheum. 2004 Feb;50(2):607-12.
Broderick, unpublished.

Cryopyrin-Associated Periodic Syndromes exist along a continuum of severity

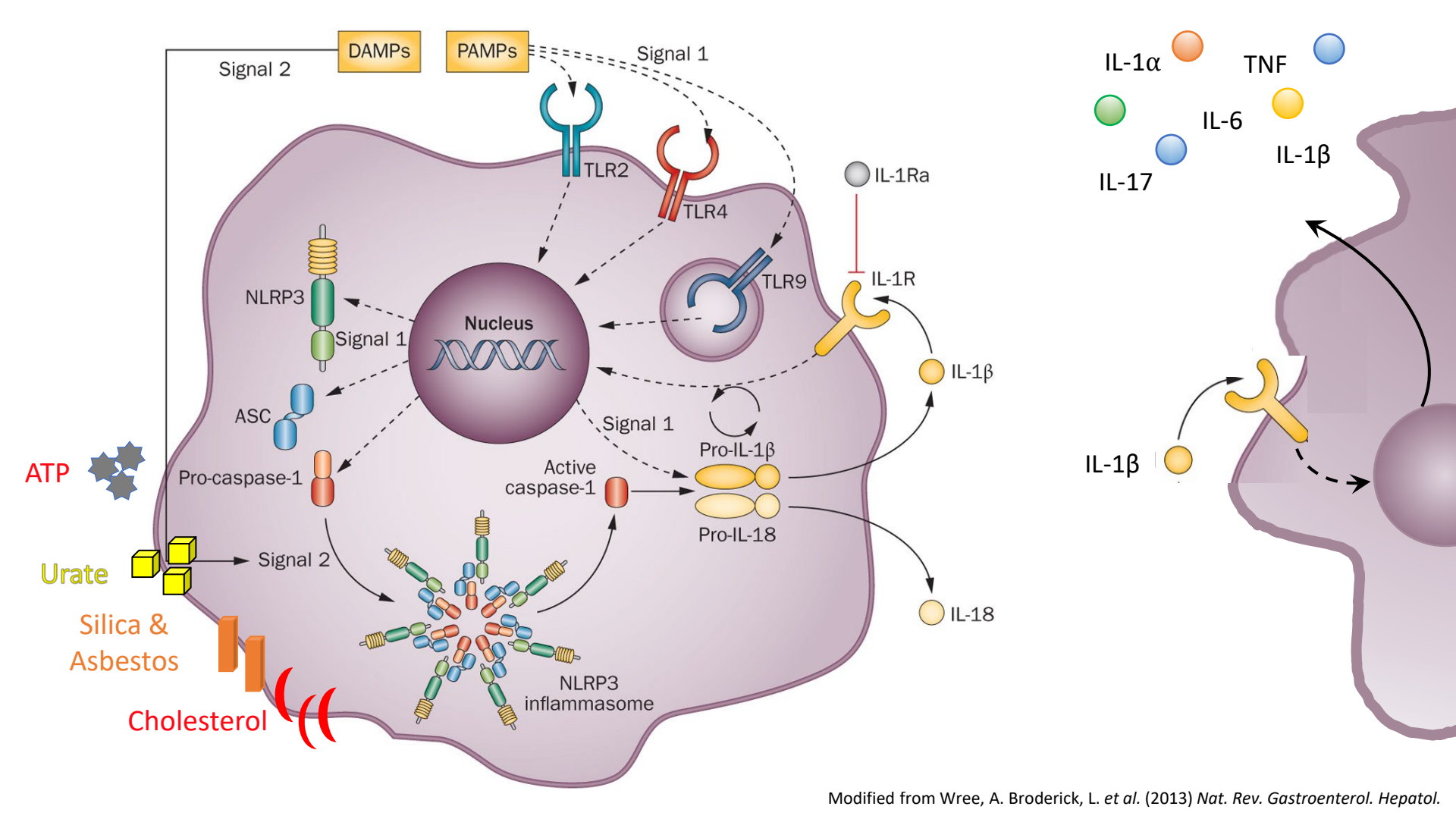
NOMID



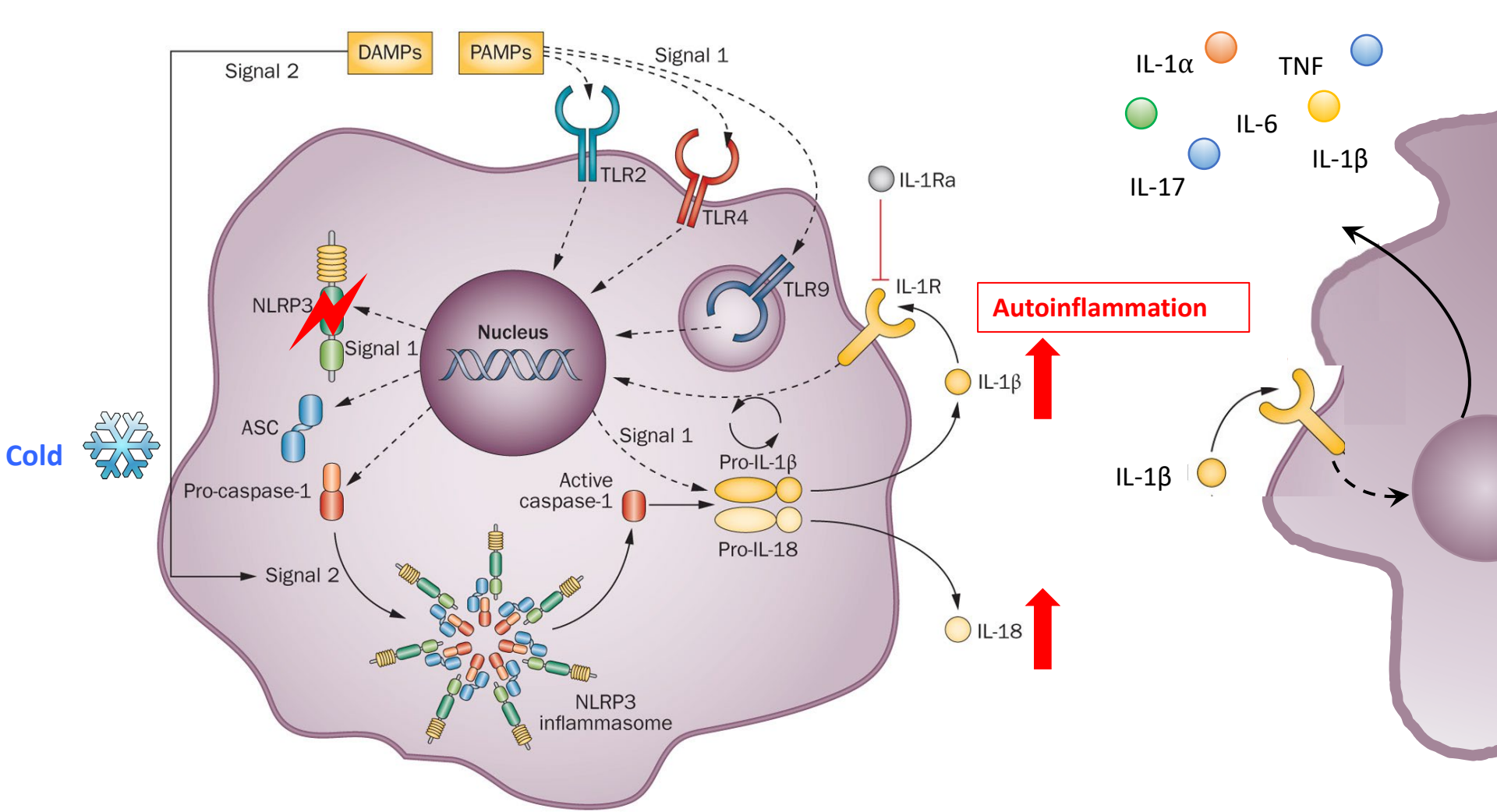
Continuous symptoms
Urticarial-like rash
Epiphyseal overgrowth
Contractures, arthritis
Conjunctivitis, uveitis
Vision loss
Sensorineural deafness
Chronic aseptic meningitis
Hepatosplenomegaly
Adenopathy

Severity

Image courtesy of Raphaela Goldbach-Mansky, M.D.



Modified from Wree, A. Broderick, L. *et al.* (2013) *Nat. Rev. Gastroenterol. Hepatol.*



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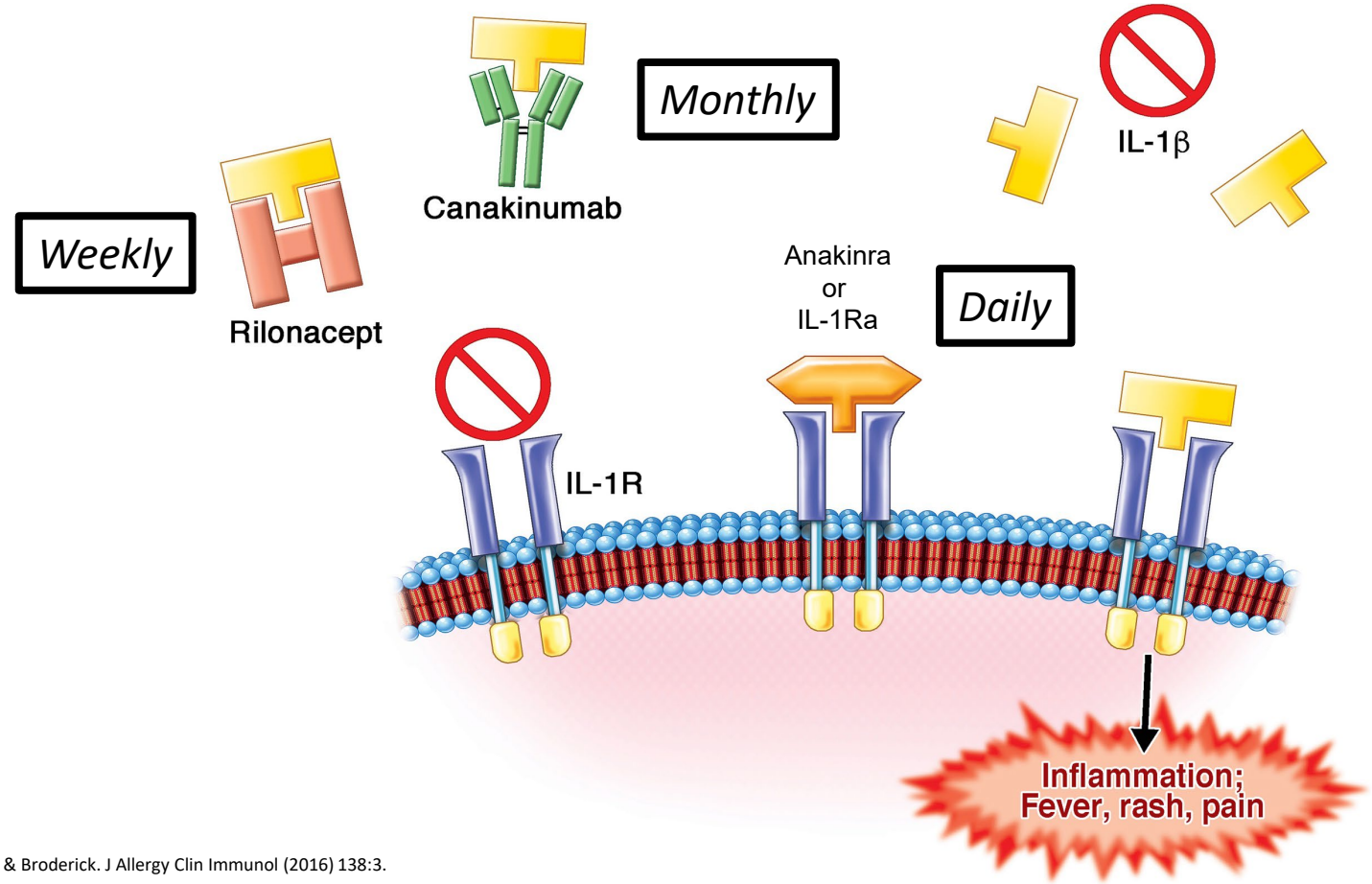
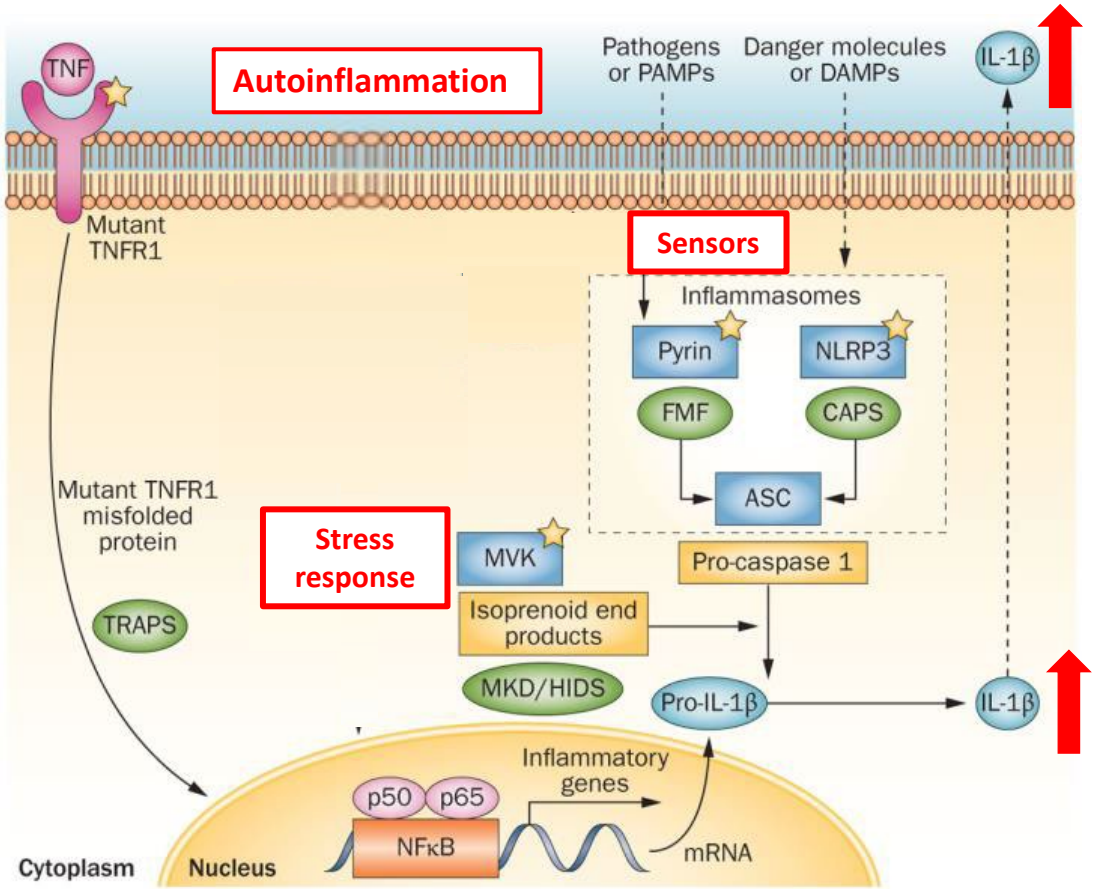
Therapies Targeting IL-1



Hoffman & Broderick. J Allergy Clin Immunol (2016) 138:3.

Monogenic Autoinflammatory Syndromes Driven by IL-1

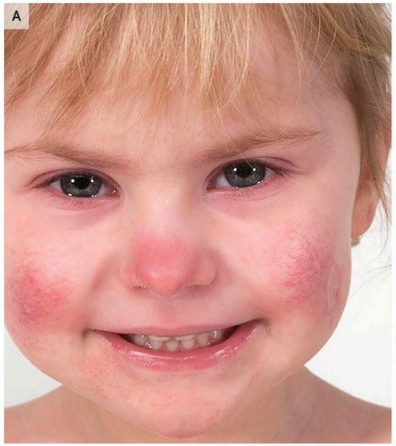
- Cryopyrin associated periodic syndrome (CAPS)
- Familial Mediterranean Fever (FMF)
- Mevalonate kinase deficiency / Hyper IgD syndrome (HIDS)
- Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

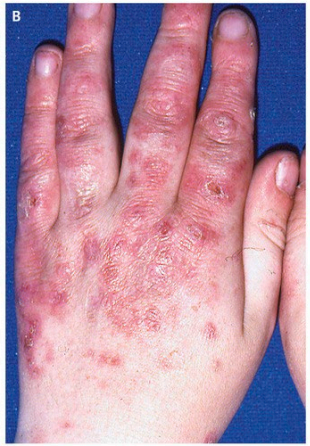


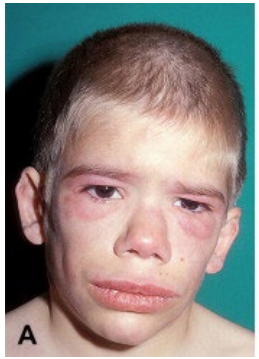
de Jesus, et al. Annu Rev Immunol. 2015; 33: 823–874.

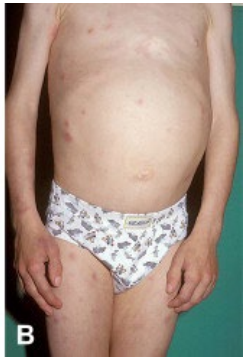
Ozen, S. & Bilginer, Y. (2013) *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2013.174

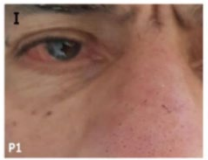
Additional phenotypes observed

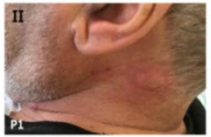


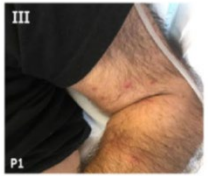


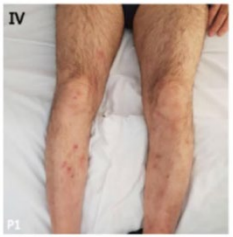


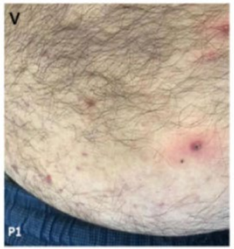


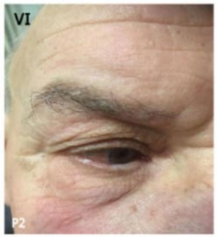


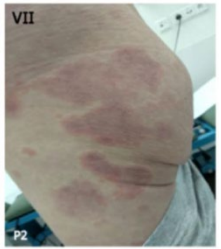


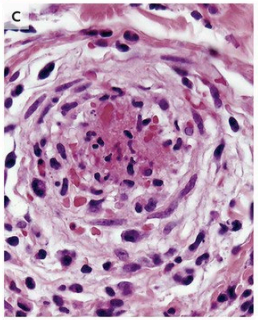


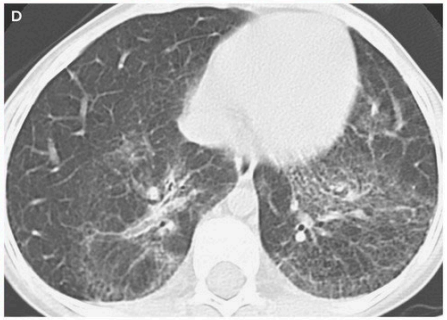


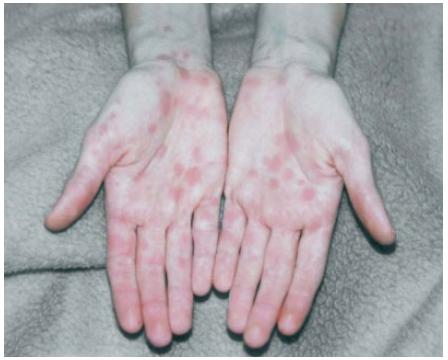


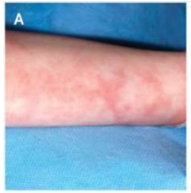


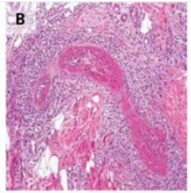


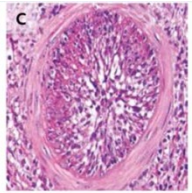


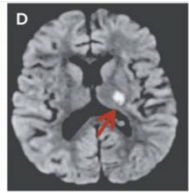


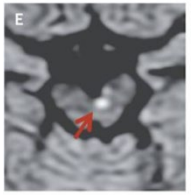


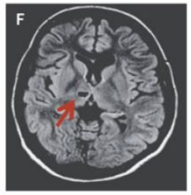


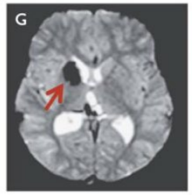


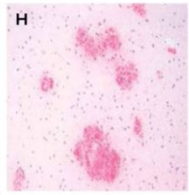






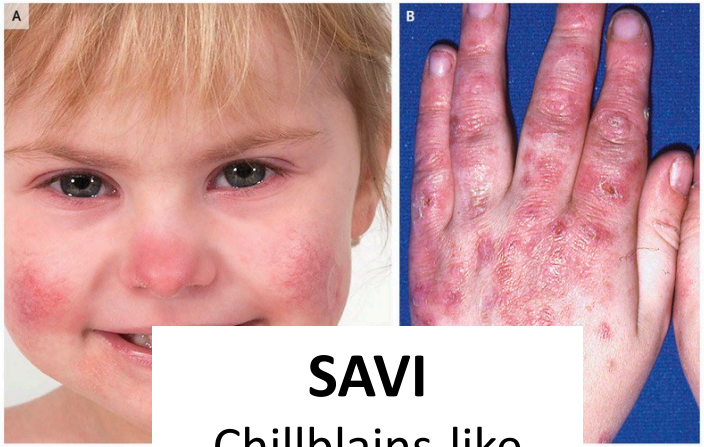




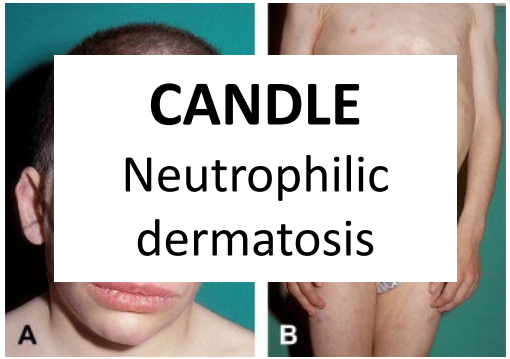


Liu et al NEJM 2014; Torrelo et al JAAD 2010; Staels et al Front Immuno 2021; Zhou et al NEJM 2014; Autoinflammatoryalliance.org SAIDsupport.org

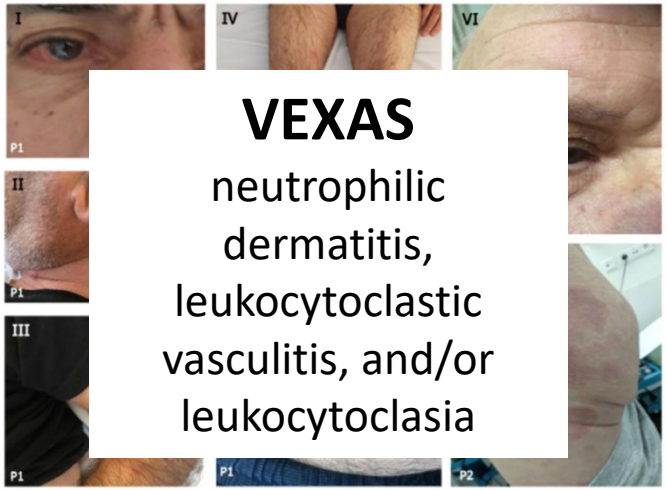
Additional phenotypes observed



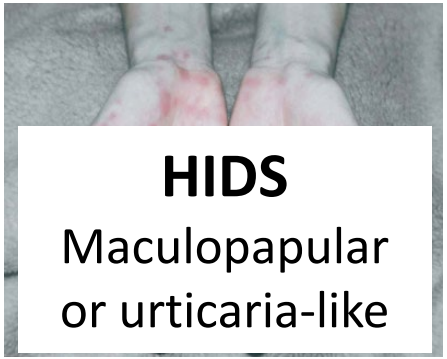
SAVI
Chillblains-like vasculopathy



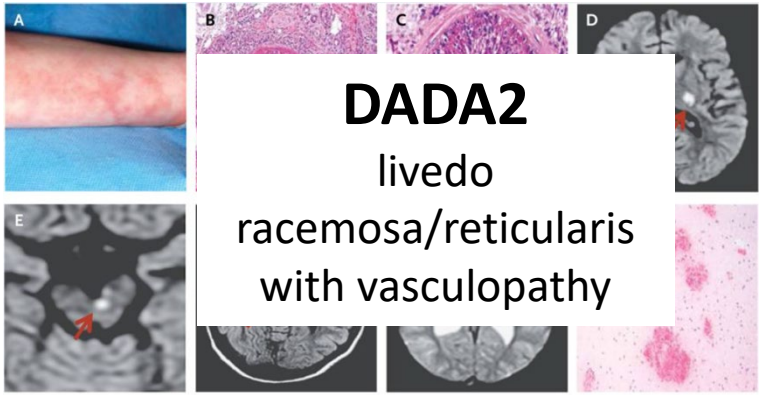
CANDLE
Neutrophilic dermatosis



VEXAS
neutrophilic dermatitis, leukocytoclastic vasculitis, and/or leukocytoclasia



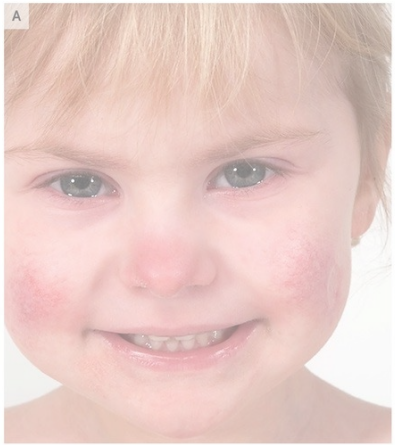
HIDS
Maculopapular or urticaria-like

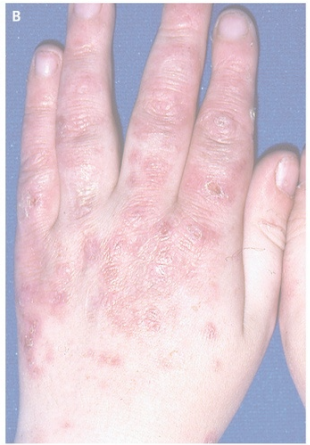


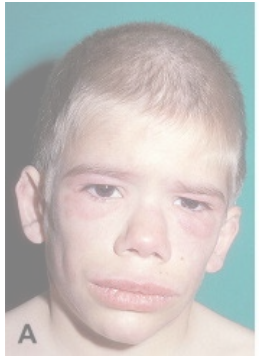
DADA2
livedo racemosa/reticularis with vasculopathy

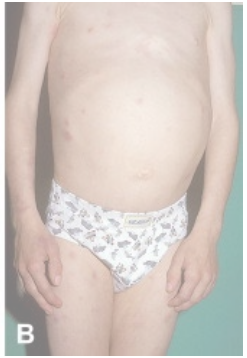
Liu et al NEJM 2014; Torrelo et al JAAD 2010; Staels et al Front Immuno 2021; Zhou et al NEJM 2014; Autoinflammatoryalliance.org SAIDsupport.org

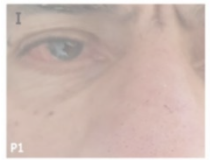
Additional phenotypes observed

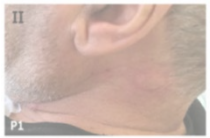


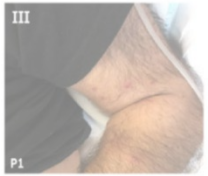


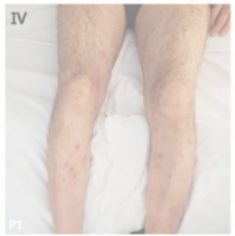


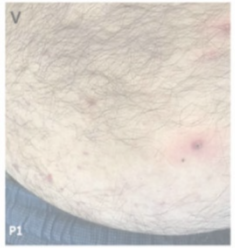


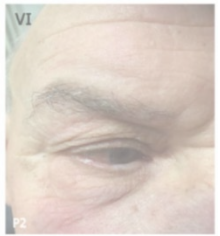


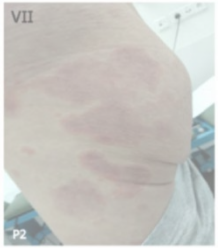


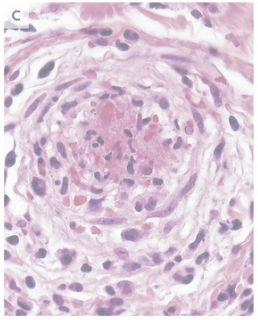


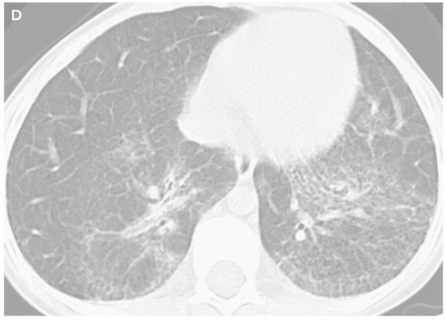


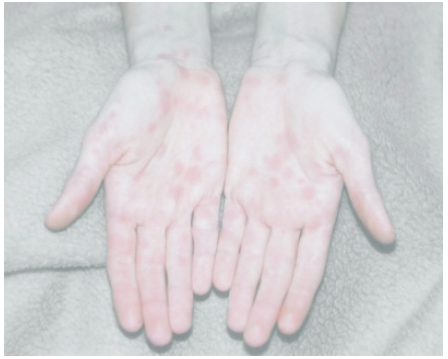


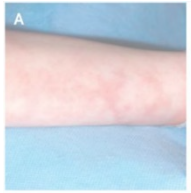


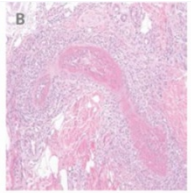


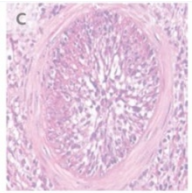


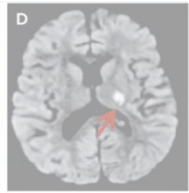


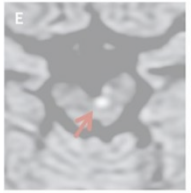


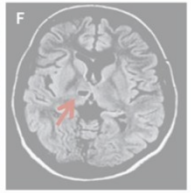


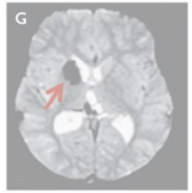






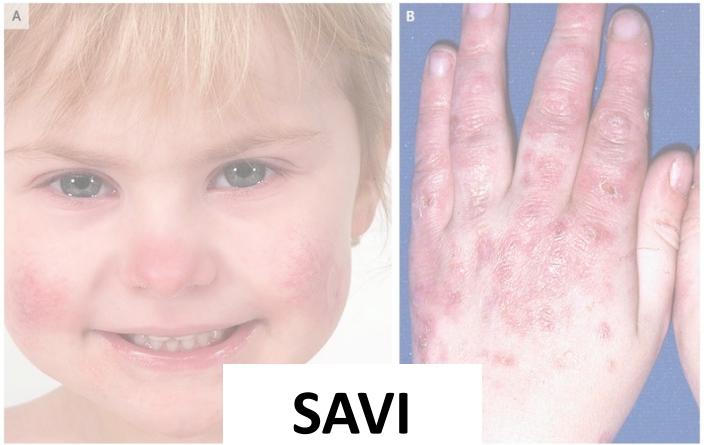




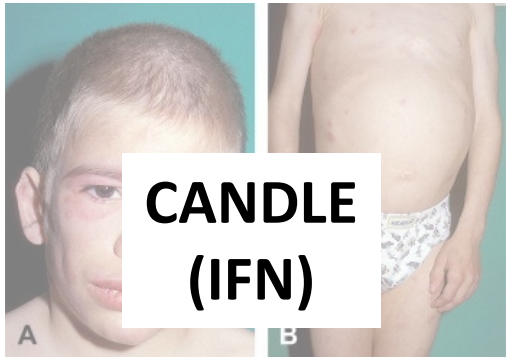


Liu et al NEJM 2014; Torrelo et al JAAD 2010; Staels et al Front Immuno 2021; Zhou et al NEJM 2014; Autoinflammatoryalliance.org SAIDsupport.org

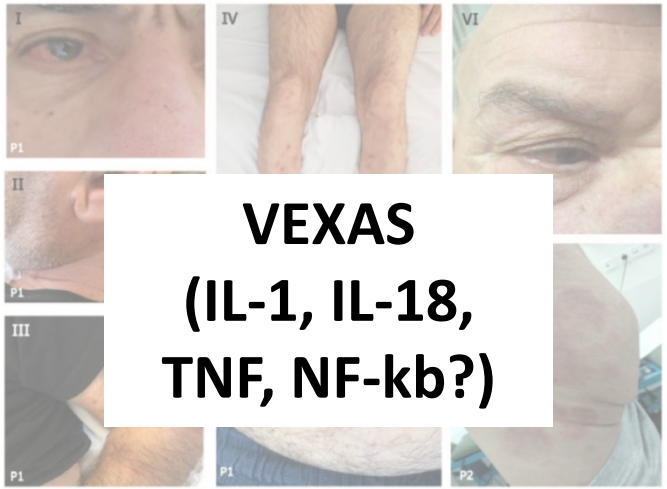
Additional phenotypes observed



SAVI
(IFN)

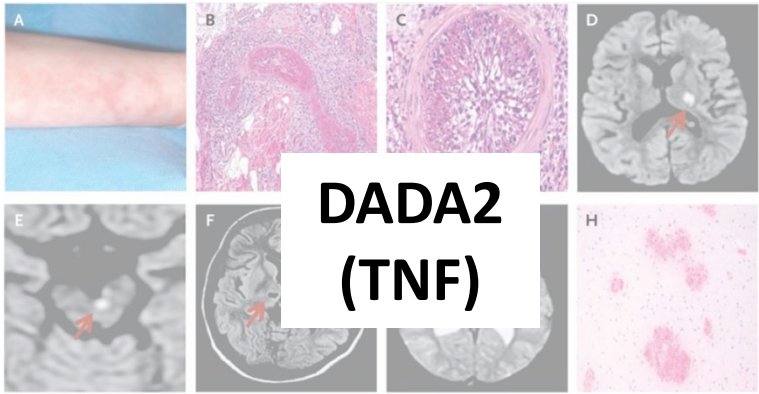


CANDLE
(IFN)



VEXAS
(IL-1, IL-18,
TNF, NF-kb?)

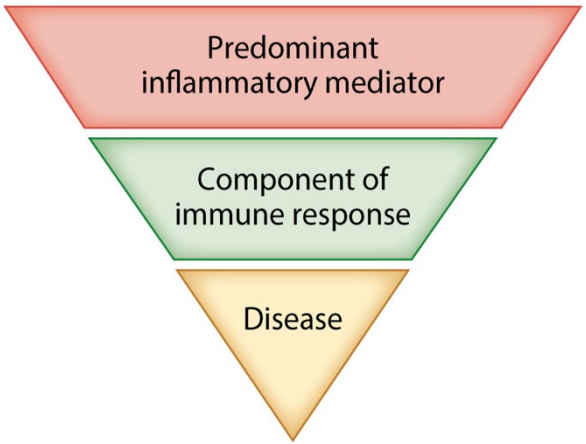
HIDS
(IL-1/IL-18)



DADA2
(TNF)

Liu et al NEJM 2014; Torrelo et al JAAD 2010; Staels et al Front Immuno 2021; Zhou et al NEJM 2014; Autoinflammatoryalliance.org SAIDsupport.org

Immune dysregulation in autoinflammatory diseases: beyond IL-1



- Increased intracellular sensors/PRRs
- Accumulation of intracellular stressors that trigger PRRs
- Loss of negative regulators of proinflammatory cytokines
- Increased signaling through receptors controlling innate immune function
- Unclassified

de Jesus, et al. Annu Rev Immunol. 2015; 33: 823–874.

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Inflammasomopathies and other IL-1 family conditions	Pyrin activation	FMF	*MEFV*	AR or AD	fever, pain, (abdominal, chest, joint), rash	IL-1, colch.
		PAAND	*MEFV*	AD	fever, myalgia, myositis, rash, abscesses	IL-1, colch.
		MKD	*MVK*	AR	fever, pain (abdominal, extremity), vomiting, rash	IL-1
		PAPA	*PSTPIP1*	AD	pyoderma gangrenosum, arthritis	IL-1, TNF
		Hz/Hc[12]	*PSTPIP1*	AD	rash, FTT, hepatosplenomegaly, neutropenia	IL-1, TNF
		PFIT[13]	*WDR1*	AR	fever, infection, oral inflammation, perianal ulceration	IL-18
	Cryopyrin activation	FCAS	*NLRP3*	AD	cold urticaria, extremity pain, conjunctivitis, fever	IL-1
		MWS	*NLRP3*	AD	urticarial rash, extremity pain, hearing loss, conjunctivitis, fever	IL-1
		NOMID	*NLRP3*	AD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1
		Majeed's[14]	*LPIN2*	AR	osteomyelitis, fevers, rash, dyserythropoietic anemia	IL-1
	NLRC4 activation	AIFEC	*NLRC4*	AD	enterocolitis, rash, arthritis, fever	IL-1, IL-18
		FCAS/ NOMID	*NLRC4*	AD	cold urticaria, extremity pain, fever, CNS disease	IL-1
	NLRP12 activation	FCAS	*NLRP12*	AD	cold urticaria, extremity pain, fever	TNF, IL-1
	NLRP1 activation	NAIAD[15]	*NLRP1*	AD	Ocular, laryngeal, skin dyskeratosis, fever, arthritis	IL-1, TNF
	Receptor antagonist deficiency	DIRA	*IL1RN*	AR	pustular rash, osteomyelitis, periostitis, fever,	IL-1
		DITRA	*IL36RN*	AR	pustular psoriasis, fever, malaise	TNF, IL-17/12/23?
Type I Interferonopathies	Nucleic acid processing and degradation	Aicardi-Goutières syndrome	*TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1*	AR (AD: *IFIH1*)	fever, neurologic decline, encephalopathy, cerebral calcification, chilblains, autoantibodies	JAK, RTI?
		monogenic SLE	*DNASE1/2/1L3, complements*	AR (AD: *DNASE1*)	autoantibodies, cytopenias, glomerulonephritis, skin rash, oral ulcers, arthritis	JAK?
	Nucleic acid sensing	SMS	*IFIH1, DDX58a*	AD	calcification of aorta / cardiac valves, osteopenia, acro-osteolysis, dental anomalies	JAK?
		SAVI	*TMEM137*	AD	Chilblain's rash, small vessel vasculitis, arthritis, ILD	JAK
	Proteasome	CANDLE / PRAAS, PRAID[16]	*PSMB4, PSMA3, PSMB8, POMP, PSMG2,PSMB9, PSMB10*	Digenic, AR (AD: POMP)	fever, joint contractures, annular plaques, eyelid swelling, hepatosplenomegaly, lipodystrophy, FTT, developmental delay, anemia	JAK
	IFN signaling	AGS-like	*USP18, ISG15, STAT2*	AR	skin ulcerations, seizures, hydrocephalus, cerebral calcifications, respiratory failure	JAK
	other	SPENCD[17]	*ACP5*	AR	skeletal dysplasia, short stature, cerebral calcification, cytopenias, autoantibodies	?
NF-κB and/or aberrant TNF activity	dysregulation of NFκB signaling	HA20	*TNFAIP3*	AD	oral, gastrointestinal and genital ulcerations, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
		RELA haploinsuf.[18]	*RELA*	AD	oral and gastrointestinal ulcerations, cytopenias, lymphoproliferative disease	TNF
		ORAS	*OTULIN*	AR	fever, panniculitis, diarrhea, arthritis, FTT	TNF
		LUBAC deficiency[19,20]	*HOIL1, HOIP*	AR	fever, recurrent infection, FTT, hepatosplenomegaly, amylopectin-like deposits in muscles	TNF?
	Dysregulation of TNF	Blau	*NOD2*	AD	granulomatous dermatitis, uveitis, polyarticular arthritis	TNF
		TRAPS	*TNFRSF1A*	AD	episodic fever, abdominal pain, headache, conjunctivitis, painful centrifugal rash	IL-1, TNF
		DADA2	*ADA2*	AR	systemic vasculitis, fever, rash, stroke, cytopenias, hypogammaglobulinemia	TNF, HSCT
		CRIA[21,22]	*RIPK1*	AD	fever, lymphadenopathy, hepatosplenomegaly	IL-6?

More than 40 monogenic disorders

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
other mechanisms	Golgi-ER transport	COPA	*COPA*	AD	arthritis, ILD, diffuse alveolar hemorrhage, autoantibodies	IL-17? JAK?
	Intracellular calcium signaling	PLAID	*PLCG2*	AD	cold urticaria, atopy, granulomatous dermatitis, hypogammaglobulinemia, infection, autoantibodies	?
		APLAID	*PLCG2*	AD	blistering skin lesions, ILD, bronchiolitis, eye inflammation, enterocolitis, immunodeficiency	?
	tRNA biogenesis	SIFD[23]	*TRNT1*	AR	fever, developmental delay, seizures, microcytic anemia hypogammaglobulinemia	TNF
	Lipid metabolism? ER stress?	LACC1 deficiency[24,25]	*LACC1/FAMIN*	AR	fever, systemic JIA, oligoarticular/polyarticular JIA	?
	Cytokine dysregulation	VEO-IBD[26,27]	*IL-10, IL10RA, IL10RB*	AR	Early-onset colitis, FTT	HSCT, IL-1?
	Actin assembly	ARPC1B deficiency[28, 29]	*ARPC1B*	AR	platelet abnormalities, bleeding, recurrent infection, small vessel vasculitis, eczema, arthritis	?
	Actin polymerization	CDC42 deficiency[30,31]	*CDC42*	AR	Neurodevelopmental defects, facial dysmorphism cytopenias, recurrent infection, fever, rash	IL-1

Now learning about overlap diseases

Nigrovic, Lee, Hoffman. *Journal of Allergy and Clinical Immunology* 2020

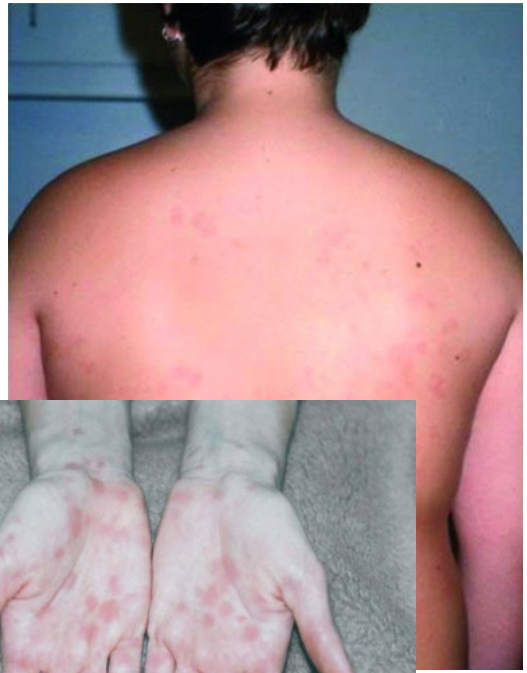
“I’ve never heard of most of these syndromes…how many patients can you actually find?”

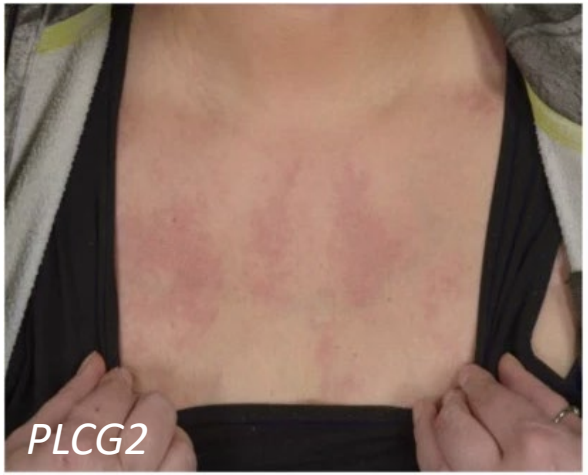
You won’t find them if you don’t <u>think</u> about them!

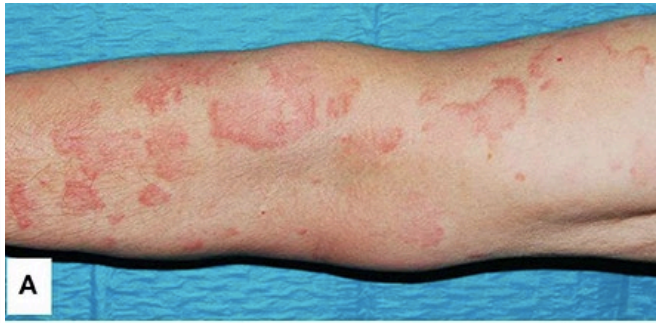
Disease Mimicry:
Features Common to Allergy/Immunology

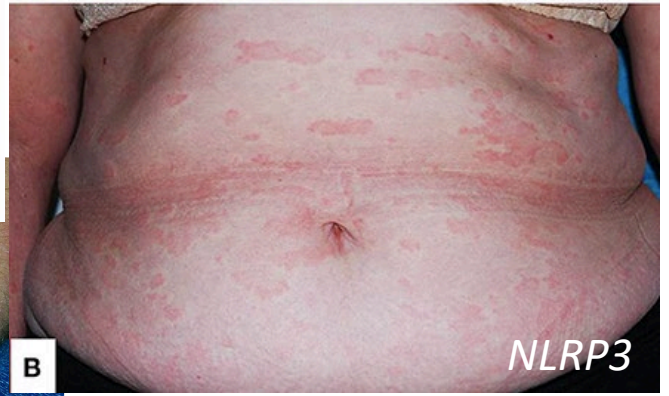
- Rashes
- Cold-induced symptoms
- Conjunctivitis
- Lymphadenopathy
- Recurrent infections
- Recurrent fever
- Aphthous stomatitis
- Abnormal blood cell counts
  - Cytopenias, anemia

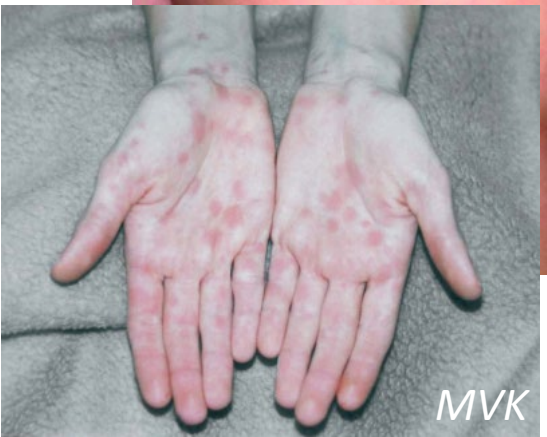
“I have hives and want to know what I’m allergic to.”

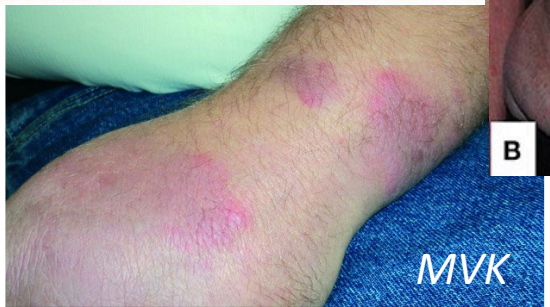












Figueras-Nart, et al. Front Immunol. 2019.
Novice et al. J Clin Immunol 2020.
Krause K, et al. Allergy. 2012.
Sieward R, Am J Kidney Dis , 2006.
Kuijk LM et al. 2007.

“My child has….”

- Hives: Cryopyrin associated periodic syndrome (CAPS), Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), deficiency of the IL-1Ra (DIRA), pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA)

- Cold urticaria: Familial cold autoinflammatory syndrome (FCAS), PLCG2-associated antibody deficiency and immune dysregulation (PLAID)

- Food allergies/celiac disease: familial Mediterranean fever (FMF), TRAPS

- Recurrent infections: PFAPA, Hyper IgD syndrome (HIDS), Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), PAPA

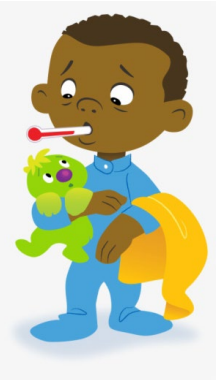
“My child is sick all the time.”

- 3yo male with 4 days of fever
- Sore throat, swollen “glands,” tired
- No upper respiratory signs, body aches, or rash
- Acetaminophen & ibuprofen provide minimal relief
- Otherwise healthy with normal growth and development

“My child is sick all the time.”

3 year old male with 1 year history of recurrent episodes of high fever and pharyngitis.

- 10 episodes of fever in last year (2-5 days long) occurring every 4-6 weeks.
- Symptoms of sore throat, swollen glands, and malaise
- No upper respiratory signs, joint pain, ocular findings, or rash during episodes
- Healthy between episodes with normal growth and development
- Small aphthous ulcers noted on exam during episode
- Leukocytosis during attack
- Ibuprofen and acetaminophen provide some relief, and antibiotics are not helpful



Periodic fevers, Aphthous stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome

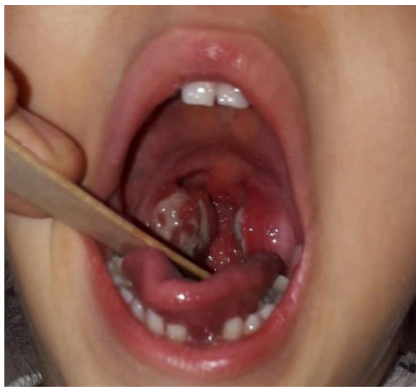
Gary S. Marshall, MD

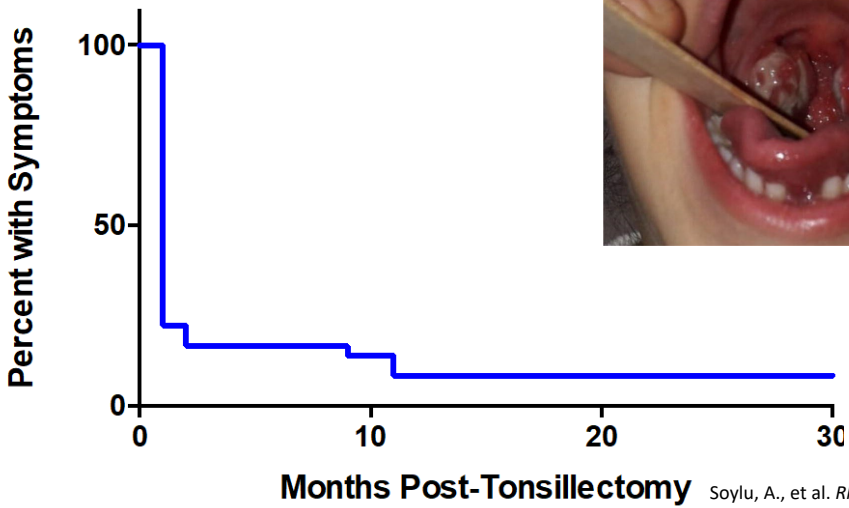
- Age of Presentation < 5 years
- Episodes last 3-6 days and occur like **CLOCKWORK** every 3-6 weeks
- Fever and at least one of the following:
  - Aphthous stomatitis
  - Cervical adenitis
  - Pharyngitis
  - **Absence of upper respiratory infection**
- Asymptomatic interval between episodes
- Normal growth and development
- No known mortality; impact on quality of life

Therapies for PFAPA

- Medical Therapy
  - Supportive care
  - Antipyretics
  - Antibiotics have no demonstrable utility
  - Cimetidine,[1] Montelukast,[2] Colchicine
  - Prednisone[1]
  - Vitamin D[5]

- Surgical Therapy
  - Adenotonsillectomy as therapy for PFAPA.[3,4]





Soylu, A., et al. *Rheumatol Int* (2021)
Luu..Broderick et al JoCI 2020

[1]Feder M. *Acta Paediatr.* 2010 ;99(2):178
[2]Lierl MB. Abstract. *JACI* 2008. S228
[3]Licameli G, et al. *Arch Otolaryngol Head Neck Surg*. 2008. 134(2):136
[4]Renko M et . al. *J Pediatr*. 2007. 151(3):289
[5]Stagi S. et al. *Int J Pediatr Otorhinolaryngol.* 2014 Jun;78(6):964

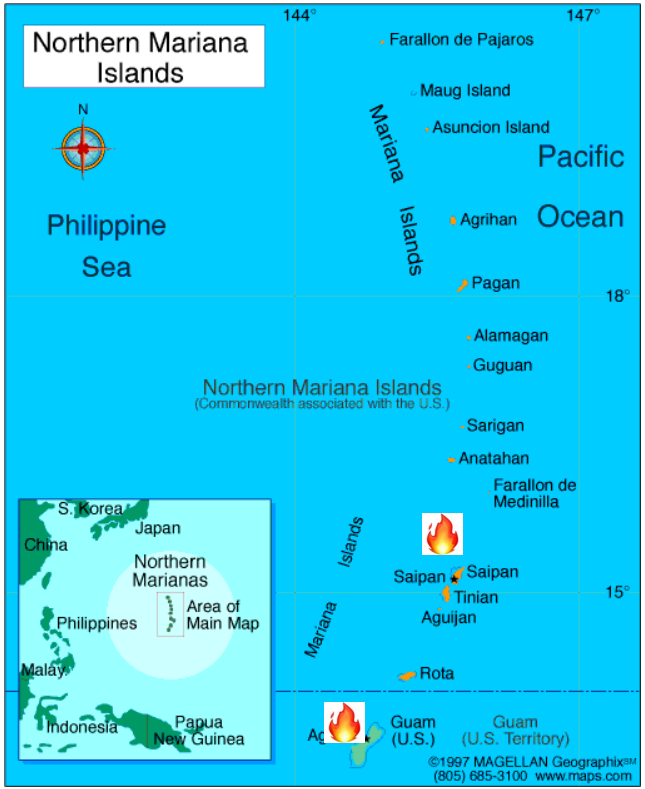
Are PFAPA and other recurrent fever disorders becoming more common, or just more frequently recognized?

Rady Children's Hospital – San Diego Allergy/Immunology Recurrent Fever Disorders Clinic

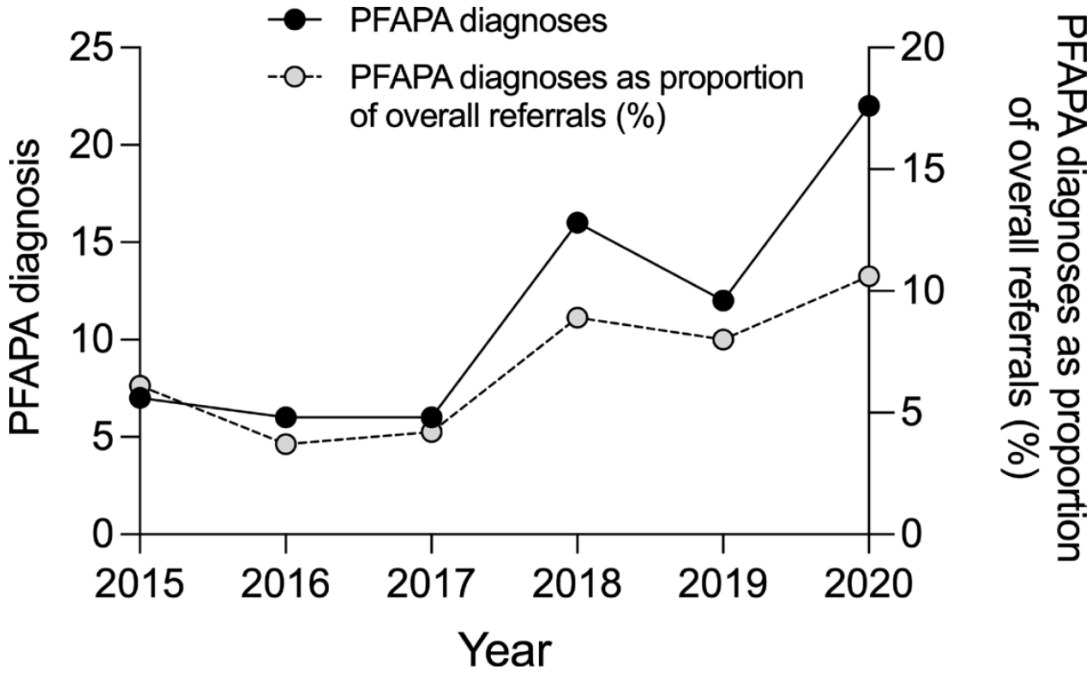
Lori Broderick, M.D., Ph.D.
(Director)

Hal Hoffman, M.D.

PFAPA incidence: ~2.3 / 10,000



Rise in children presenting with PFAPA syndrome during the COVID-19 pandemic



Ng KF, Morgan J, Cutts T, et al. Arch Dis Child 2021.

Rise in children presenting with PFAPA syndrome during the COVID-19 pandemic

Table 1 Incidence rate of children diagnosed with PFAPA syndrome and their characteristics before and during the COVID-19 pandemic

	Pre-COVID-19 pandemic **Jan 2015 to Dec 2019 (n=51)**	COVID-19 pandemic **Jan 2020 to Mar 2021 (n=26)**
PFAPA incidence rate (per 1 000 000 person-years)*	9.85	24.67
Gender (male:female)	28:23 (55%:45%)	15:11 (58%:42%)
Age (years), median (range)	4.8 (1.3–12.8)	5.4 (1.3–15.5)
Colchicine treatment	25 (51%)	17 (65%)
Tonsillectomy	24 (49%)	Insufficient time elapsed to assess
Clinical resolution	41 (89%)	Insufficient time elapsed to assess

*Incidence rate calculated using population estimates for children aged 0–16 years from published data (Office for National Statistics).[5]

Ng KF, Morgan J, Cutts T, et al. Arch Dis Child 2021.

Evolution of recurrent fever clinic

- Initial target population: Autoinflammatory patients

Diagnoses with a medical home in the autoinflammatory clinic	
CAPS / NLRP3-spectrum disorders	NLRP12-associated autoinflammatory disease
Familial Mediterranean fever	Pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH) syndrome
Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)	Other genetically defined autoinflammatory disorders: • PLAID/APLAID (*PLCG2*) • *STAT3* GOF • Haploinsufficiency A20 (*TNFAIP3*)
Hyper-IgD syndrome/MKD	Recurrent pericarditis
	Behcet's syndrome
PFAPA syndrome	Undifferentiated autoinflammatory disease

Recurrent Fever

- Temperatures >38°C or 100.4°F
- Fever log with numbers &/or documented by clinician
- Episodes recurring for ≥4 months

Diagnostic criteria for PFAPA syndrome

1. Regularly recurring fevers onset <5 yrs of age
2. Symptoms in the absence of URI
3. At least one of the following clinical signs:
    - Aphthous stomatitis
    - Cervical lymphadenitis
    - Pharyngitis
4. Exclusion of cyclic neutropenia (& monogenic d/o)
5. Completely asymptomatic intervals
6. Normal growth and development

- Some inflammatory labs / CBC
- 2-5 days of prednisolone
- +/- antibiotics

PFAPA Syndrome

“My child has PFAPA.”

Alternate diagnoses made in recurrent fever clinic

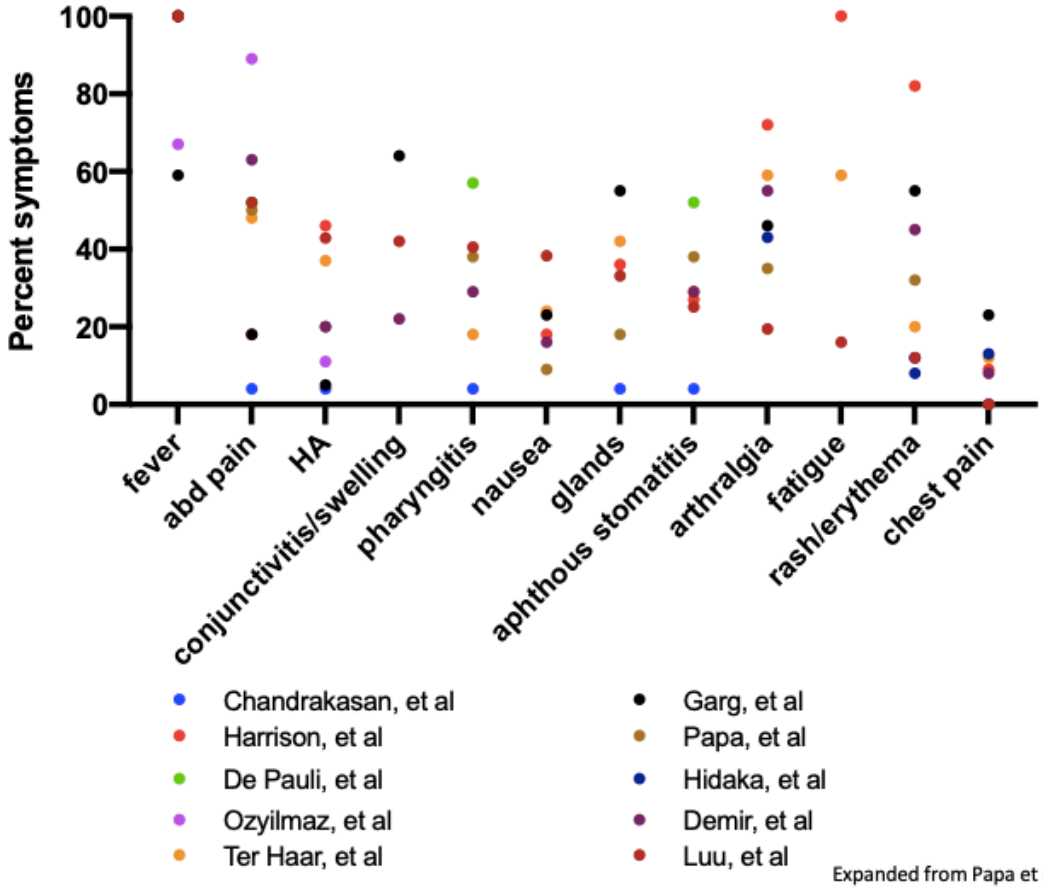
- Dental/pharyngeal abscess; severe dental decay
- Recurrent/chronic rhinosinusitis
- Recurrent aphthous stomatitis
- Hypogammaglobulinemia/transient hypogammaglobulinemia of infancy
- Specific antibody deficiency
- Transient C4 deficiency of childhood
- Progressive VUR with uveitis
- Takayasu’s arteritis
- Inflammatory bowel disease (Crohn’s)
- Leukemia (ALL, AML)

The allergist/immunologist can address these diagnoses

Broderick & Hoffman *JACI* 2020

Recurrent fever is…common?

- 2/3 of studies focus on pediatric patients
  - Onset up to 76 years reported
- 4-24 episodes per year
  - 2-7 days duration
- 11-33% have a positive family history



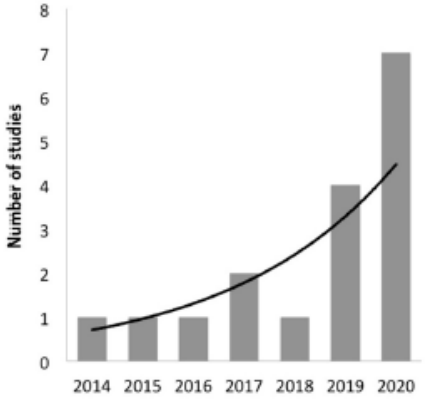
Expanded from Papa et al 2021

SURF, uSAID, incomplete PFAPA…

- Syndrome of undifferentiated recurrent fevers (SURF)
- undifferentiated or undefined SAID (uSAID)

- 70-80% of patients with systemic autoinflammatory diseases do not obtain a molecular diagnosis.
  - PFAPA commonly diagnosed

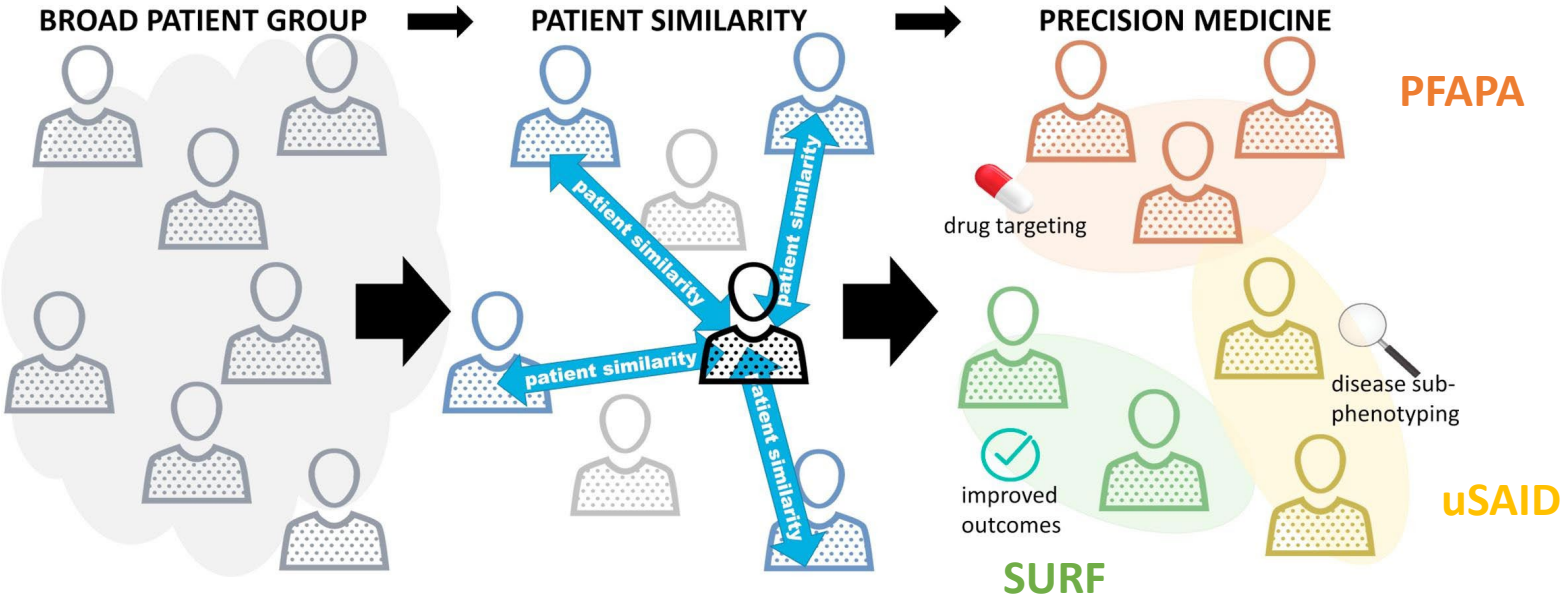
- Defining features
- Molecular pathways
- Best options for therapy



Papa et al J Clin Med 2021

More than a name: Phenotype and why it matters

Phenotype = the set of observable characteristics



Parimbelli, et al (2018) Journal of Biomedical Informatics

Prospective study: referrals for “recurrent fever”

n = 75	Median, range
Self-reported Gender	Male 61% Female 39%
Age (current)	5 years (0.75 – 21 years)
Age (onset)	1.5 years (0 - 16 years)
Episode	3 – 4.5 days (1 – 60 days)
Maximum temperature	102.3°F (99 – 107°F)
Episode duration	36.9 days (7 – 120 days) *45% reported monthly or variable*

Broderick & Hoffman *JACI* 2020

Recurrent Fever

- Temperatures >38°C or 100.4°F
- Fever log with numbers &/or documented by clinician
- Episodes recurring for ≥4 months

Recurrent Fever Disorders

- Duration of fever episodes
- Duration of well intervals
- Associated symptoms
- Triggers (cold, immunizations)
- Response therapy
- Similarity of episodes

Immunodeficiency

- Infections in multiple anatomic locations
- Number and severity of infections
- Pathogens identified or suspected
- Need for antimicrobials to clear infections
- Failure to thrive, chronic infectious diarrhea

Atopy

- Nasal, pharyngeal, skin symptoms
- Seasonality
- Aeroallergen triggers

Positive family history may be a feature of all

Labs when Afebrile

- CBC with manual differential
- Inflammatory markers
- Immunoglobulins
- Antibody titers

Labs when Febrile

- CBC with differential
- Inflammatory markers

Additional considerations

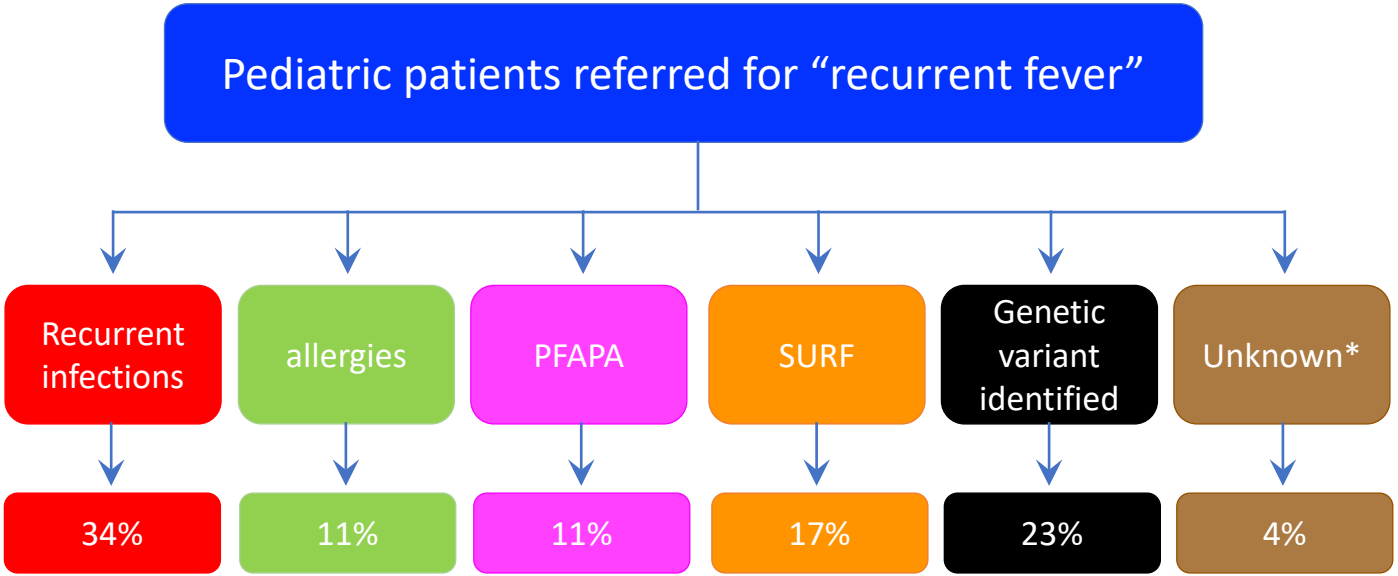
- Percutaneous skin testing
- Ice cube challenge
- Sinus CT
- Abdominal CT

Re-immunization challenge and titers
Treatment of atopy

Genetic testing to further stratify, define diagnosis, prognosis and best therapeutic target

Broderick & Hoffman *JACI* 2020

Diagnostic Spectrum of Patients Referred to a Pediatric Fever Clinic



Broderick & Hoffman *JACI* 2020

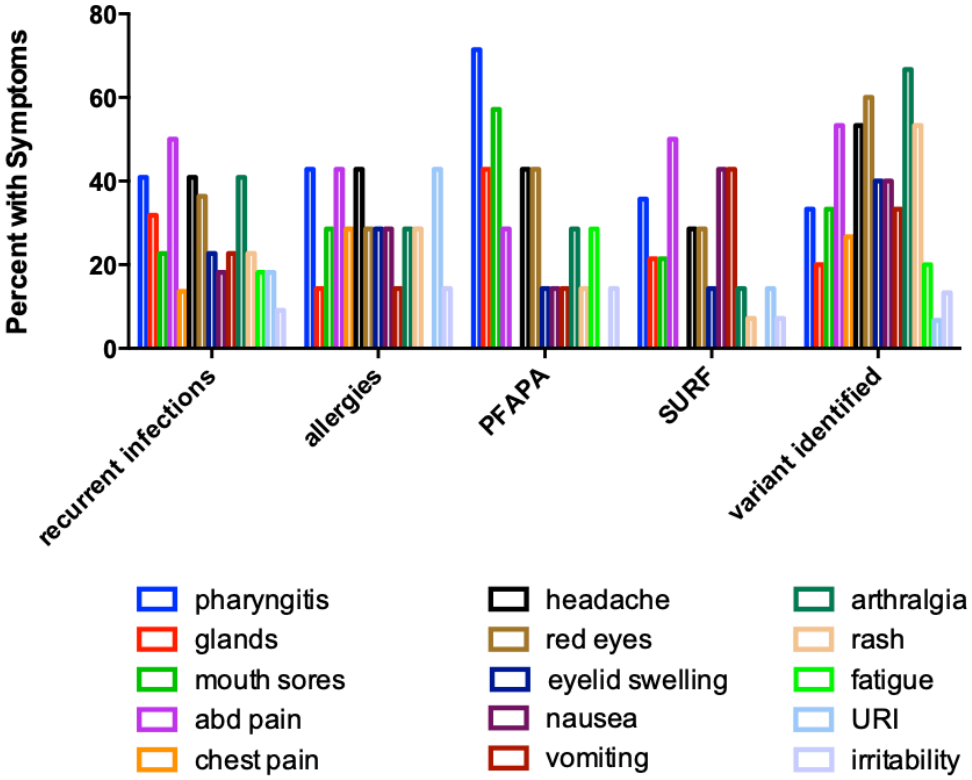
** Unknown = family didn’t complete questionnaire/obtain labs*

Fever episodes are highly similar among groups

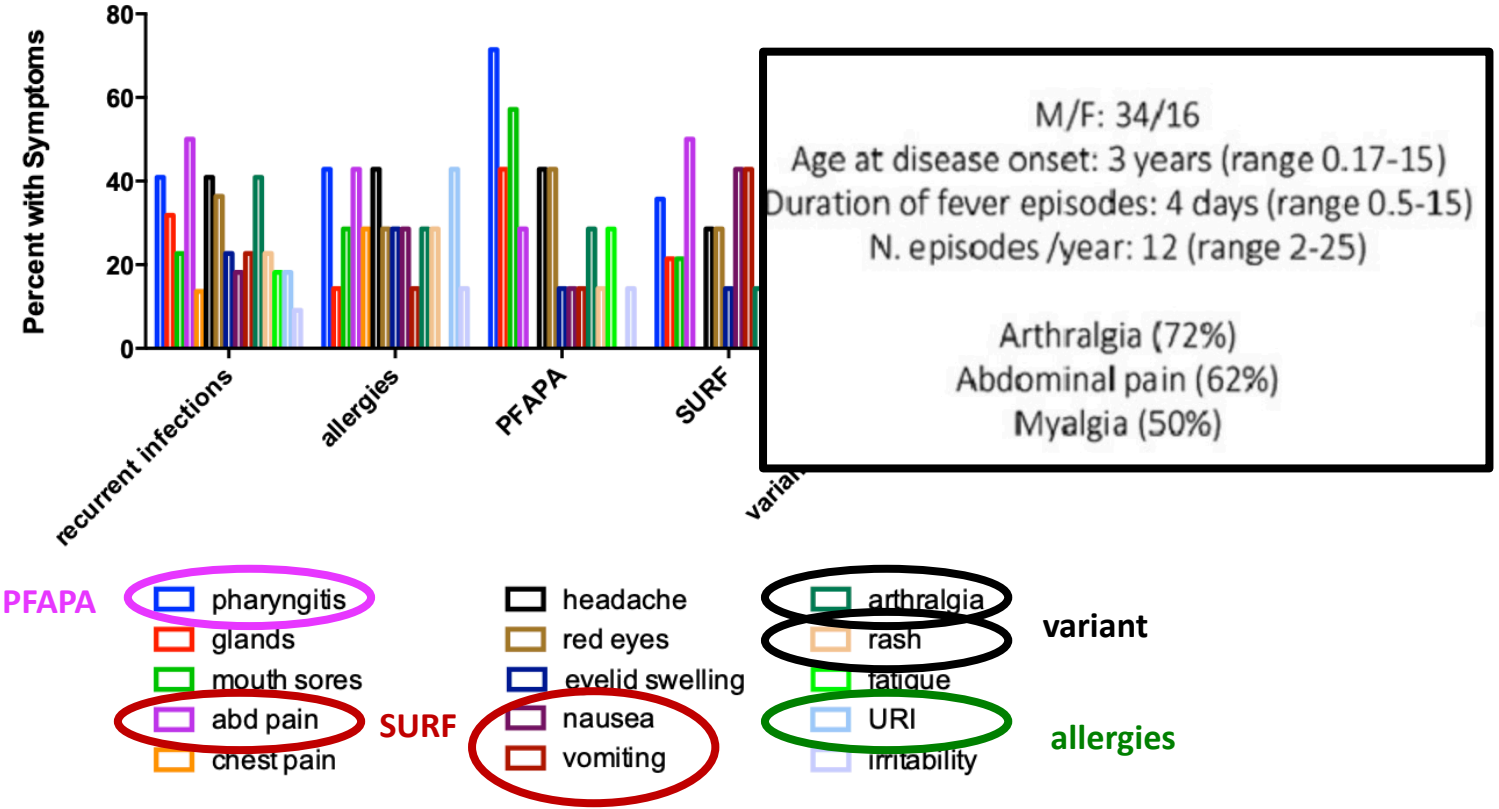
	Recurrent Infections	Allergic rhinitis	PFAPA	SURF	Variant identified	*p* value*
Patients, n (%)	22 (34%)	7 (11%)	7 (11%)	14 (22%)	15 (23%)	
Age of onset (mean, range)	2.2 years (0.5-7 years)	3.7 years (0.25-9 years)	1.78 years (1-2.5 years)	1.2 years (birth – 6 years)	3.4 years (birth to 16 years)	n.s.
Max temperature (°C, average, range)	39.1 (37.7-41.1)	38.4 (37.2-40)	40 (38.8-41.1)	40 (38.8-41.6)	39.7 (37.3-40.7)	n.s.
Duration (average, range)	4.5 (1-13 days)	9 (3-60 days)	3.9 (3-6 days)	4.4 (3-7 days)	4.5 (1-10 days)	n.s.
interval (average, range)	31.9 (10-120 days)	30.1 (14-60 days)	27.2 (21-35 days)	29 (21-120 days)	23.2 (7-60 days)	n.s.

Broderick & Hoffman *JACI* 2020

Associated symptoms distinguish phenotypes

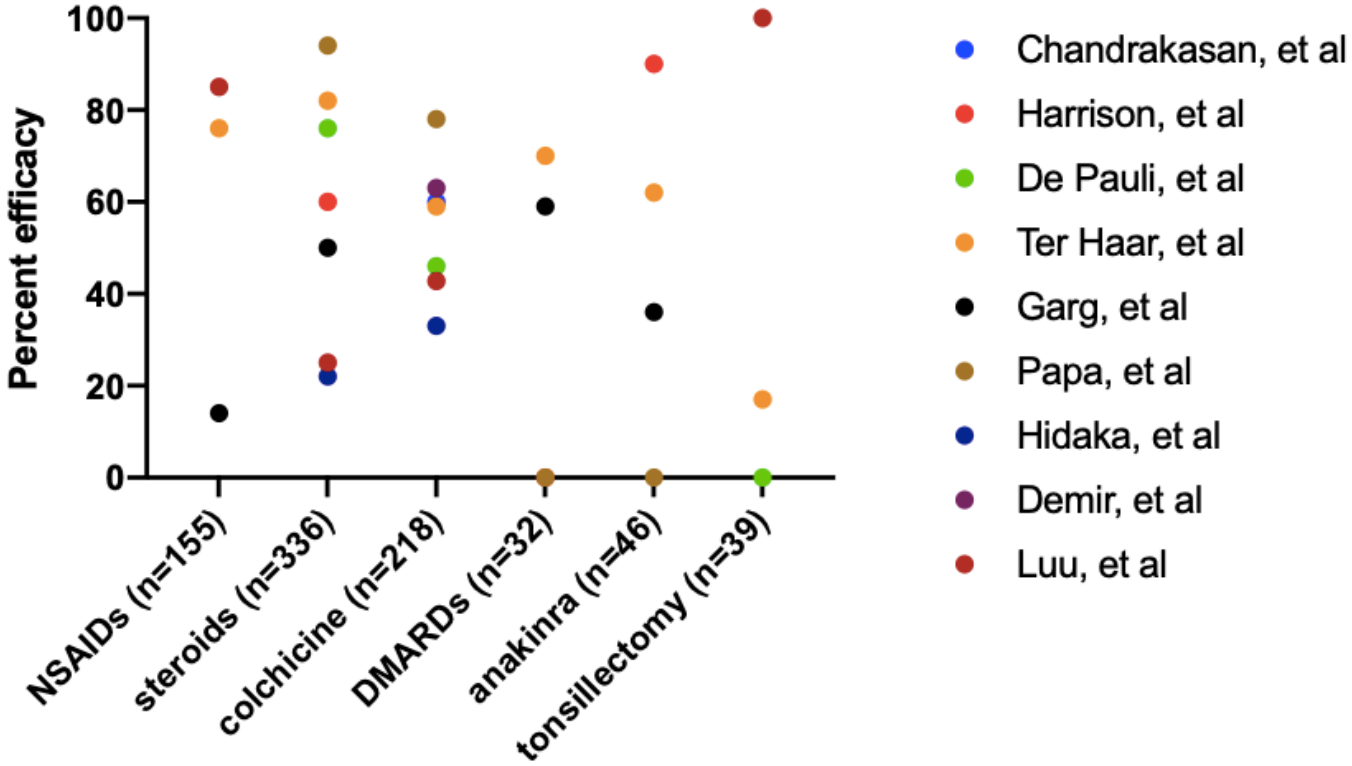


Associated symptoms distinguish phenotypes



Sutera et al. Semin Arthritis Rheum. 2022

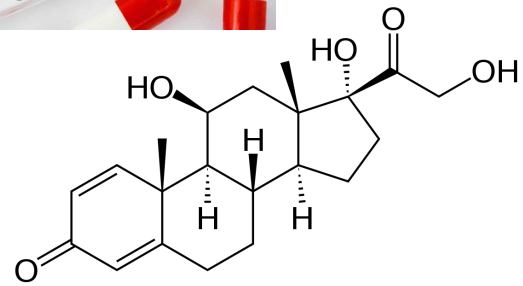
Therapeutic responses are variable across uSAID/SURF cohorts

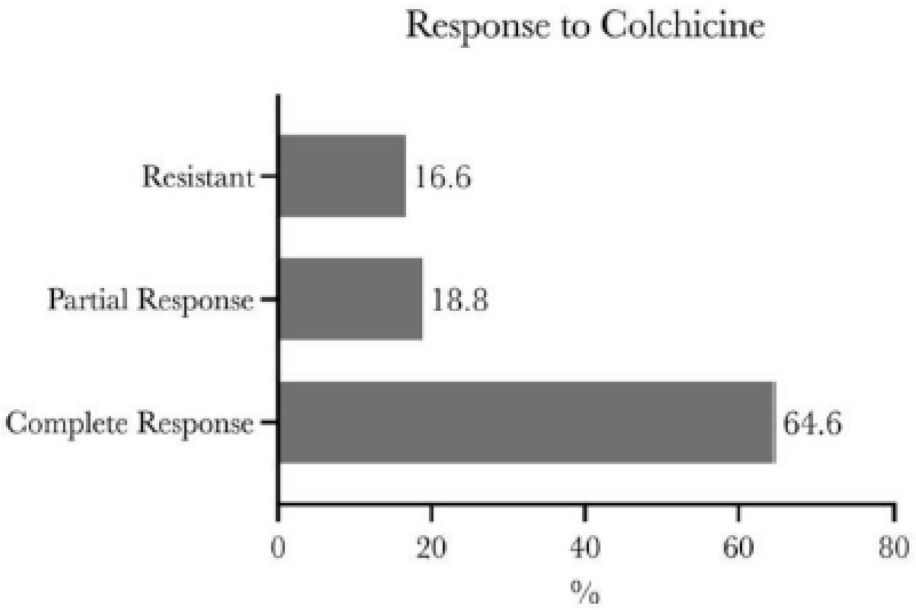


Modified from Papa et al J Clin Med 2021

Treatment of fevers is based on clinical presentation…

- Anti-pyretics
- PRN steroids
- Colchicine
- IL-1 blockade





Generalized lymphadenopathy and the presence of exudative tonsillitis are associated with colchicine resistance

Sutera et al. Semin Arthritis Rheum. 2022

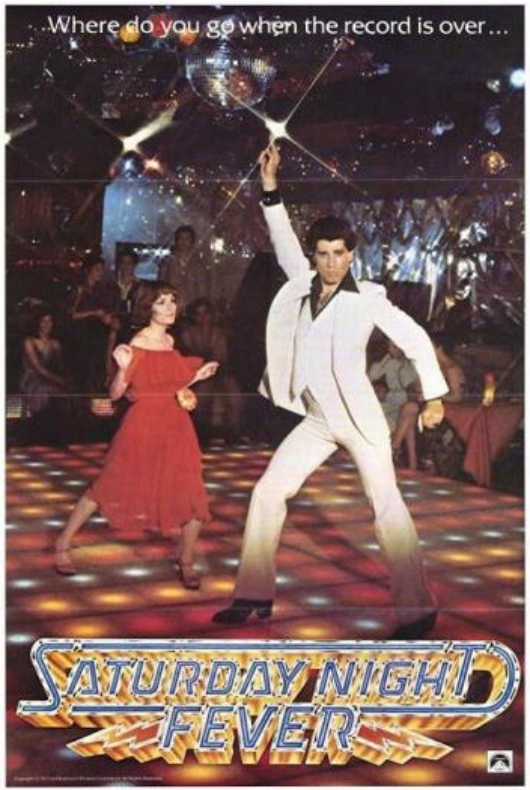
Summary II: Undifferentiated, non-infectious fevers

- SURF patients are a large and heterogeneous population
- Phenotype still being defined
  - *Should a VUS in a known gene be labeled SURF?*
- Contribution of multiple genes
  - “burden of variants”
- Response to medications and tonsillectomy is variable
- Decisions should be made jointly between physicians, families and patients.

Fevers are a common presenting symptom! When should autoinflammatory disorders be considered?

Practical Advice

Are All Fevers Bad?



- *Give me the power to produce fever, and I will cure all disease*.

—Parmenides, c. 500 BCE[1]

- Increased mobility of leukocytes
- Enhanced leukocyte phagocytosis
- Decreased effects of endotoxin
- Increased proliferation of T cells
- Enhanced activity of interferon

[1]Shaheen, Seif O. JACI 2015; 135:449.

Fever Patterns: What can they tell us?

	Self-limited infection in a healthy patient
Periodicity of episodes	Irregular
Characteristics of episodes	Waning and waxing course of a single illness (eg, EBV); multiple simple illnesses (ie, different symptoms, exanthems, diagnoses)
Clustering of episodes	Concurrent illness in contacts (home, daycare, school); few-to-no episodes in summer
Course of episodes	Each as expected for infectious agent
History of identifiable childhood illnesses	Expected course (eg, chickenpox, HSV stomatitis, gastroenteritis)
Interval between episodes	Completely well (or frequently atopic symptoms)
Catch-up growth and energy	Excellent

Abbreviations: AOM, acute otitis media; EBV, Epstein-Barr virus; HSV, herpes simplex virus.

* Conditions such as acquired (HIV-associated) or congenital immunodeficiency, cystic fibrosis, or ciliary dyskinesia.

Long SS. Pediatr Clin N Am. 2005; 52: 811.

Fever Patterns: What can they tell us?

	Self-limited infection in a healthy patient	Immunodeficient or compromised patient
Periodicity of episodes	Irregular	Relapse/recurrence of bacterial infection quickly after discontinuation of antibiotics
Characteristics of episodes	Waning and waxing course of a single illness (eg, EBV); multiple simple illnesses (ie, different symptoms, exanthems, diagnoses)	Slow response to treatment of bacterial infections (eg, sinopulmonary); some episodes require hospitalization/parenteral antibiotic therapy
Clustering of episodes	Concurrent illness in contacts (home, daycare, school); few-to-no episodes in summer	Ill during all seasons, when others are and are not
Course of episodes	Each as expected for infectious agent	Even simple infections (eg, AOM, skin and soft tissue infections) are protracted; skin infections heal with scarring
History of identifiable childhood illnesses	Expected course (eg, chickenpox, HSV stomatitis, gastroenteritis)	Severe and protracted course; hospitalization
Interval between episodes	Completely well (or frequently atopic symptoms)	Never well generally; lingering specific symptoms
Catch-up growth and energy	Excellent	Poor

Abbreviations: AOM, acute otitis media; EBV, Epstein-Barr virus; HSV, herpes simplex virus.

* Conditions such as acquired (HIV-associated) or congenital immunodeficiency, cystic fibrosis, or ciliary dyskinesia.

Long SS. Pediatr Clin N Am. 2005; 52: 811.

Fever Patterns: What can they tell us?

	Self-limited infection in a healthy patient	Immunodeficient or compromised patient	Autoinflammatory disorder (IL-1)
Periodicity of episodes	Irregular	Relapse/recurrence of bacterial infection quickly after discontinuation of antibiotics	Clockwork periodicity or irregularly frequent or occasional
Characteristics of episodes	Waning and waxing course of a single illness (eg, EBV); multiple simple illnesses (ie, different symptoms, exanthems, diagnoses)	Slow response to treatment of bacterial infections (eg, sinopulmonary); some episodes require hospitalization/parenteral antibiotic therapy	Abrupt onset and cessation; fever dominant; no respiratory tract symptoms
Clustering of episodes	Concurrent illness in contacts (home, daycare, school); few-to-no episodes in summer	Ill during all seasons, when others are and are not	Episodes during all seasons; contacts are not ill before or after
Course of episodes	Each as expected for infectious agent	Even simple infections (eg, AOM, skin and soft tissue infections) are protracted; skin infections heal with scarring	Identical, symptoms predictable course
History of identifiable childhood illnesses	Expected course (eg, chickenpox, HSV stomatitis, gastroenteritis)	Severe and protracted course; hospitalization	Expected course (often notably less ill, less frequently than peers)
Interval between episodes	Completely well (or frequently atopic symptoms)	Never well generally; lingering specific symptoms	Completely well
Catch-up growth and energy	Excellent	Poor	Excellent

Abbreviations: AOM, acute otitis media; EBV, Epstein-Barr virus; HSV, herpes simplex virus.

* Conditions such as acquired (HIV-associated) or congenital immunodeficiency, cystic fibrosis, or ciliary dyskinesia.

Long SS. Pediatr Clin N Am. 2005; 52: 811.

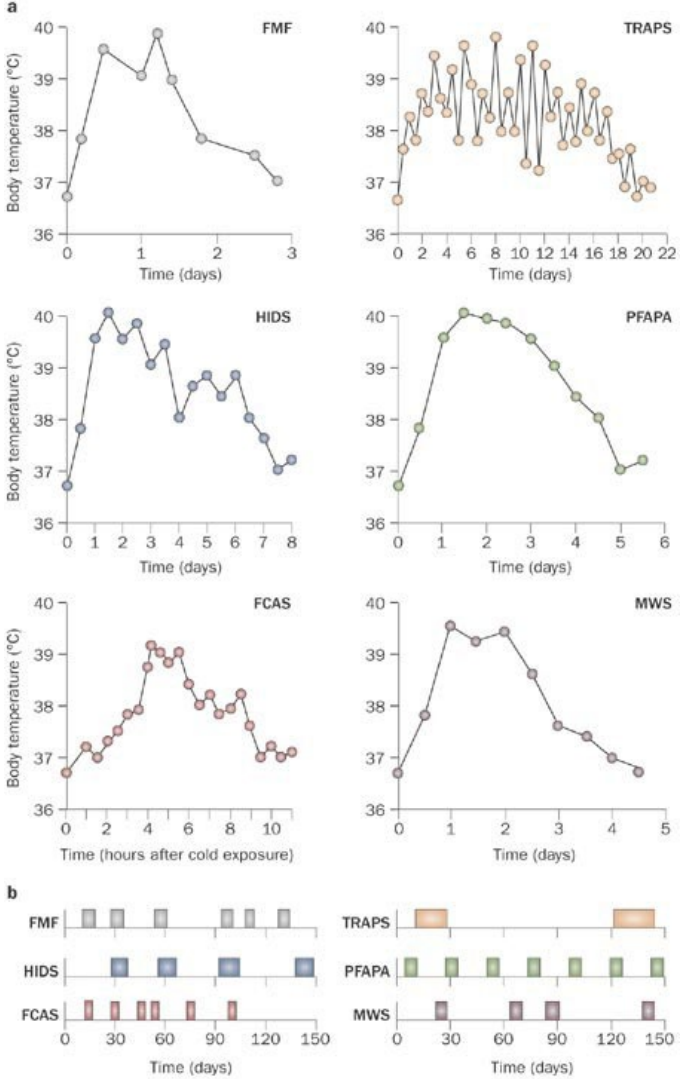
LOTS of questions…to differentiate all aspects of immunity

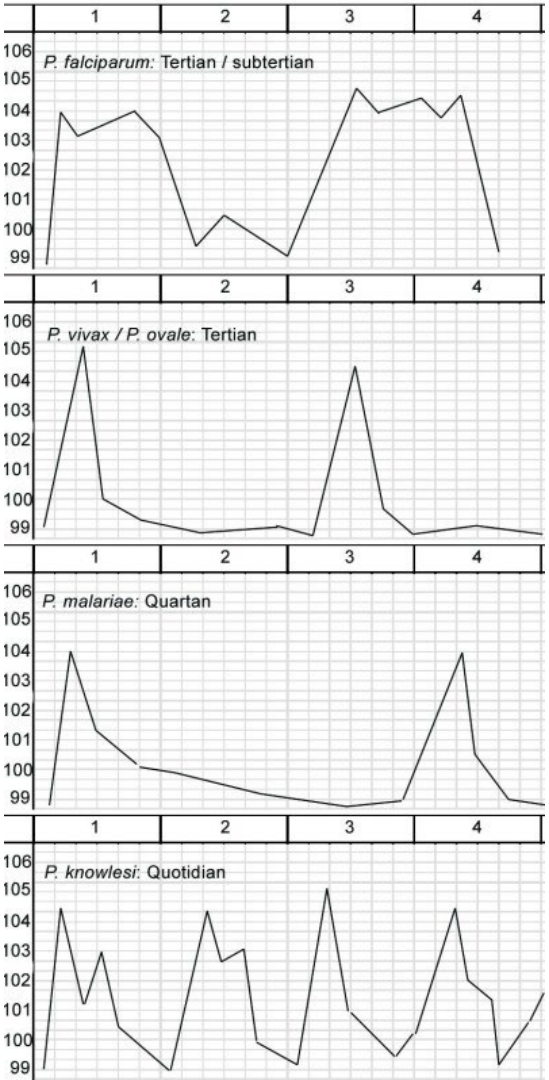
- At what age did the first typical fever episode occur?
- Is there a family history of similar fevers?

- Identifying Fever Patterns
  - How long do the typical fever episodes last?
  - How often do the fever episodes occur?
  - Is there a set periodicity or variable interval between attacks
  - What other symptoms are associated with fever?

- What therapies have been effective? Which have been ineffective or worsened symptoms?

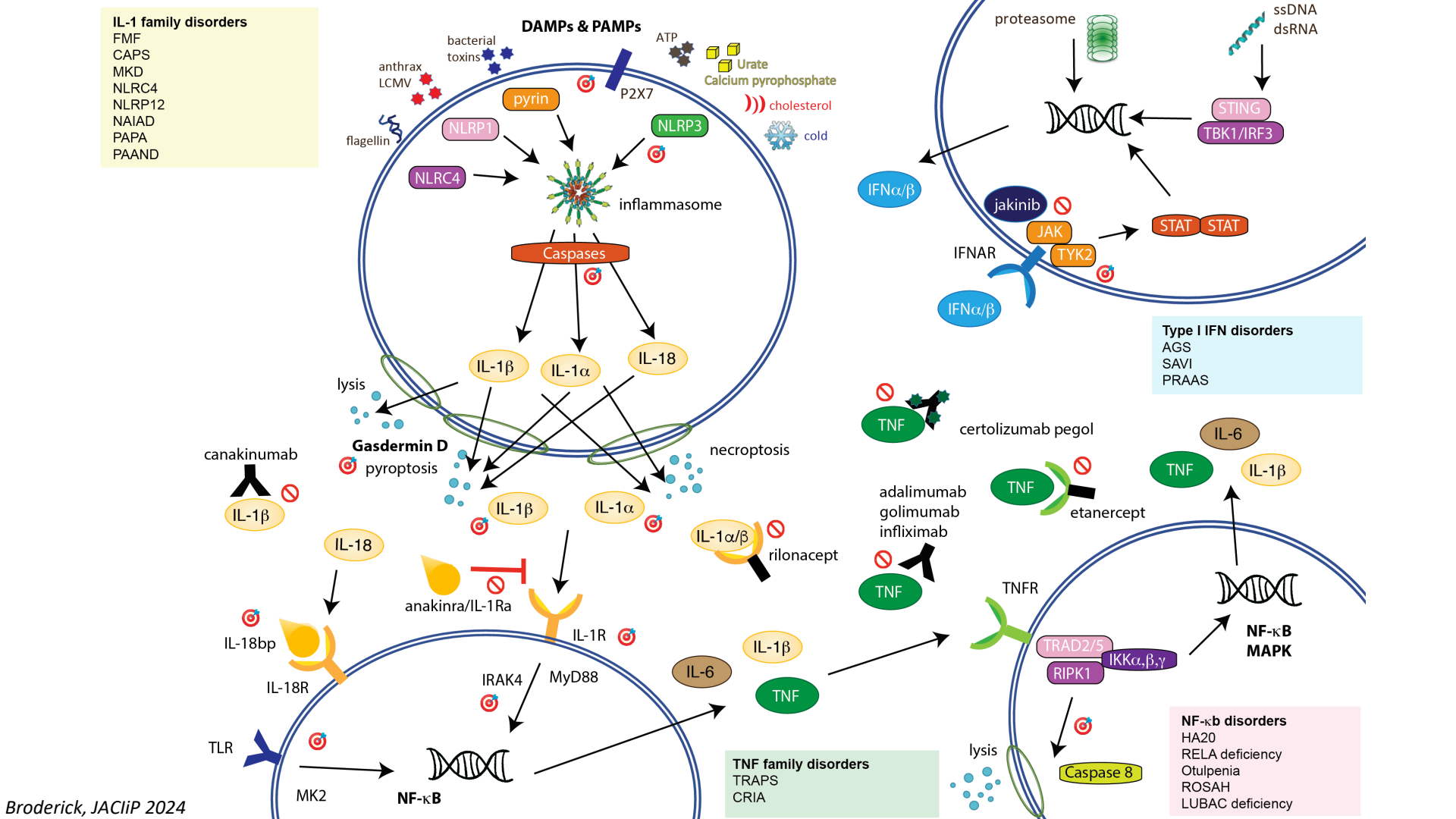
Broderick, L. Curr Allergy Asthma Rep (2016) 16: 2. doi:10.1007/s11882-015-0578-1





Hoffman & Simon.
Nat Rev Rheumatol (2009)
https://www.malariasite.com/

What about the patients that don’t have fever?



Broderick, JACIiP 2024

Recurrent / chronic inflammatory episodes

- Similar features: rash or pustules, CNS, musculoskeletal or serosal symptoms
- Specific triggers are characteristic for certain autoinflammatory diseases
  - Cold (FCAS, SAVI), immunizations (HIDS/MVK)
- In many autoinflammatory disorders, episodes can be precipitated by:
  - emotional stress
  - exercise
  - minor infections
  - fatigue
  - menstrual cycle
  - pregnancy improves, delivery provokes attack

Evaluation of Inflammation:
Most patients have had some labs already

- Febrile episodes are accompanied by elevated levels of acute phase proteins and leukocytosis.
  - Subclinical inflammatory responses can be detected in the symptom-free intervals in *most*.
  - PFAPA will have complete normalization between episodes.
  - Interferonopathies may have increased ESR but normal or low CRP

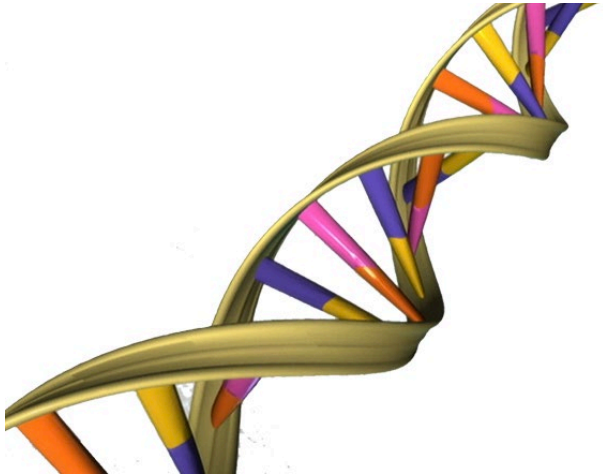
- Other signs of chronic inflammation: restricted growth, chronic anemia

- Basic labs can help define pathways:
  - CRP: IL-1 and IL-6
  - ESR: TNF
  - Ferritin: IL-18

Genetic Testing

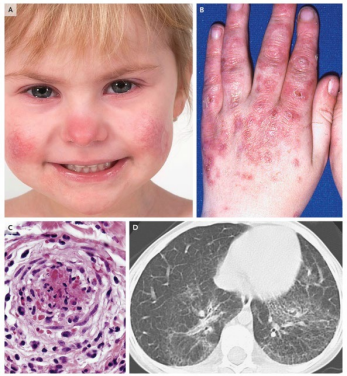
- Confirm diagnosis
- Define prognosis

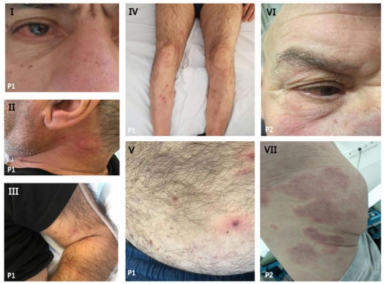
- Single gene testing
- Panels of 7 - >400 genes
- Whole exome or whole genome



It can be complicated…

Mono- and Polygenic Causes of Autoinflammation





Autosomal dominant

APLAID, AMPS, Blau, CAMPS, CAPS, Cherubism, DSAP, FCAS2, HA20, NAIAD, NLRC4-MAS, PAAND, PAPA, PRAID, SAVI, TRAPS, TRAPS11, vibratory urticaria

Autosomal recessive

CANDLE, DADA2, DIRA, DITRA, FMF, Hydatidiform mole, Histiocytosis-lympadenopathy plus syndrome, HOIL-1 deficiency, HOIP deficiency, IL-10D, Majeed, MKD, ORAS, PFIT, PRASS, SIFD, sJIA (monogenic forms), VEOIBD

Mosaicism

Blau, CAPS, NLRC4-MAS, SAVI, TRAPS

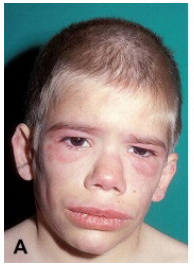
AID

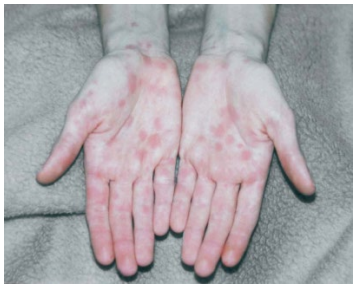
Digenic

PRASS

Multigenic / multifactorial

Behçet disease, sporadic CNO, Crohn disease, gout, MAS, PFAPA, Schnitzler syndrome, adult-onset Still disease, sJIA, …





Liu et al NEJM 2014; Torrelo et al JAAD 2010; Staels et al Front Immuno 2021; Zhou et al NEJM 2014; Autoinflammatoryalliance.org SAIDsupport.org; Jéru, I. *Curr Allergy Asthma Rep* **19,** 41 (2019).

Genetic Testing

Variants of Unknown Significance

- Single nucleotide changes are very common
- Prediction tools may not be accurate
- *In vitro* function not available
- Can have no impact or be low penetrance

Mutation negative patients

- Mutation in another exon
- Mutation in another gene - *NLRP12, NLRC4*
- Somatic mosaicism
  - 4.2 – 35 %

70-80% of patients will fail to achieve a molecular diagnosis

“There’s no such thing as bad luck,
only genes that have yet to be discovered.”

Jean-Laurent Casanova, MD, PhD

Professor, University of Paris/ Hôpital Necker-Enfants Malades - AP-HP

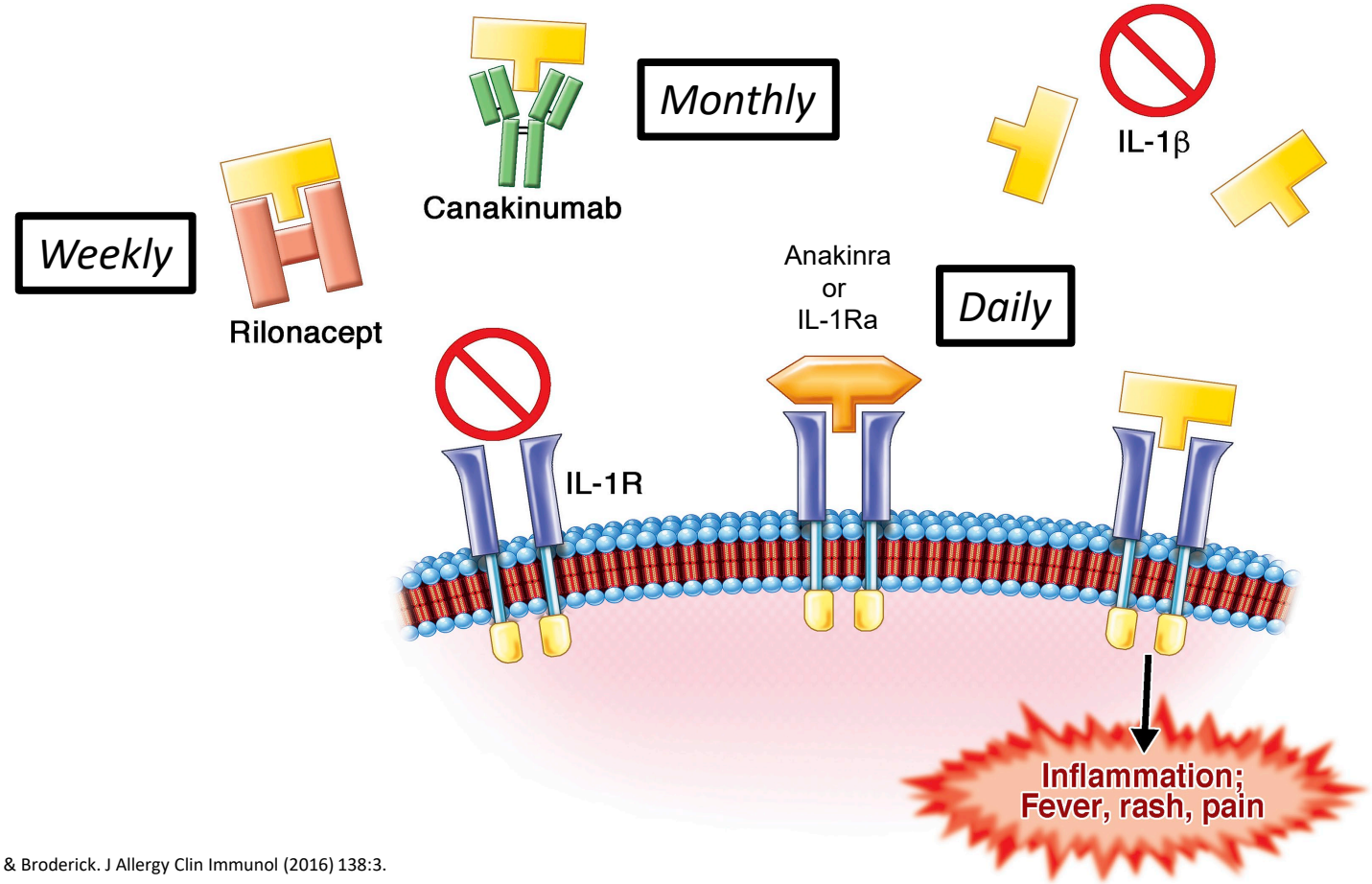
Professor at Rockefeller University/Howard Hughes Medical Institute, New York

Goals of Therapy

- Diagnosis
- Prevention or decreasing frequency of episodes
- Reduction in severity of symptoms
- Quality of life (work, school)
- Prevention of long term consequences
  - Amyloidosis
  - Hearing loss or other CNS manifestations
  - Lung disease
  - Hepatic disease

Romano M, et al Annals of the Rheumatic Diseases 2022

Therapies Targeting IL-1

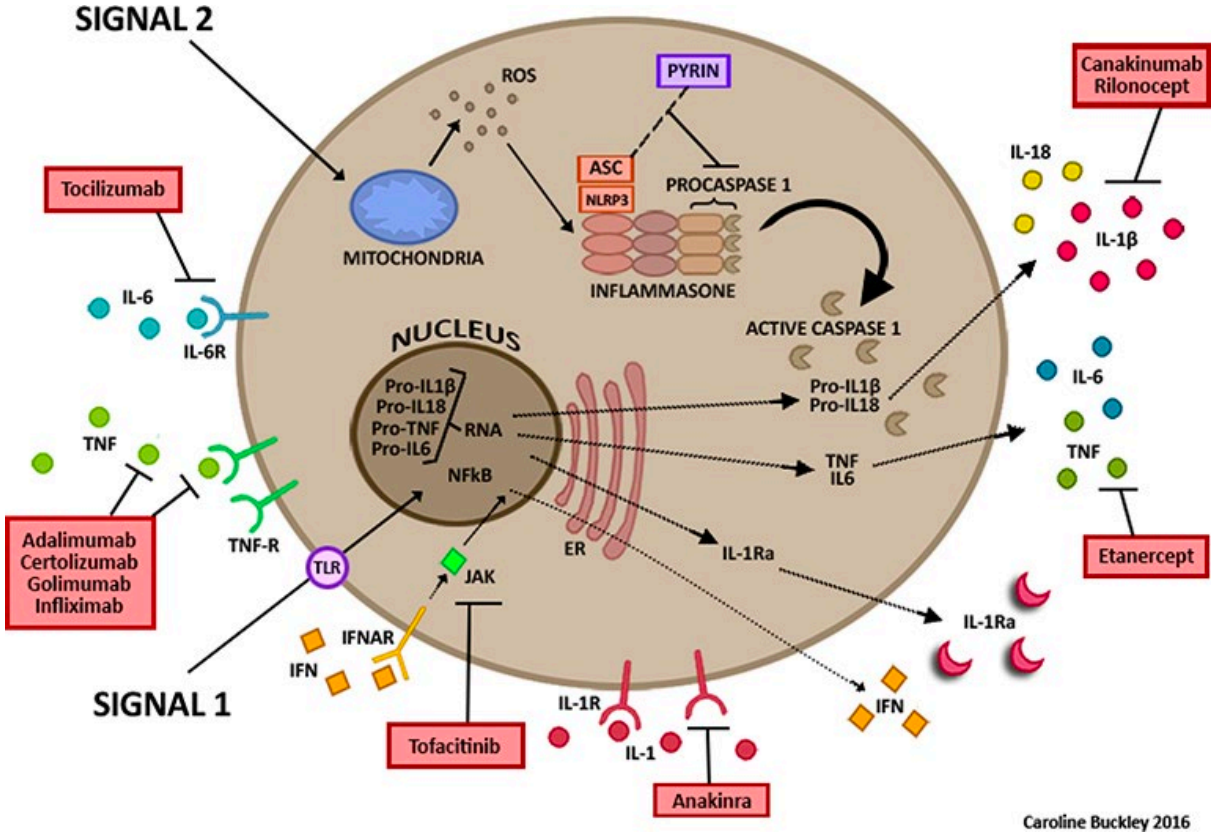


Hoffman & Broderick. J Allergy Clin Immunol (2016) 138:3.

IL-1 Targeted Therapy Issues

- Infections
  - Gram positive pathogens
  - Increased upper respiratory infections
- All injectable
- Costs
- Incomplete responses or reduced response over time

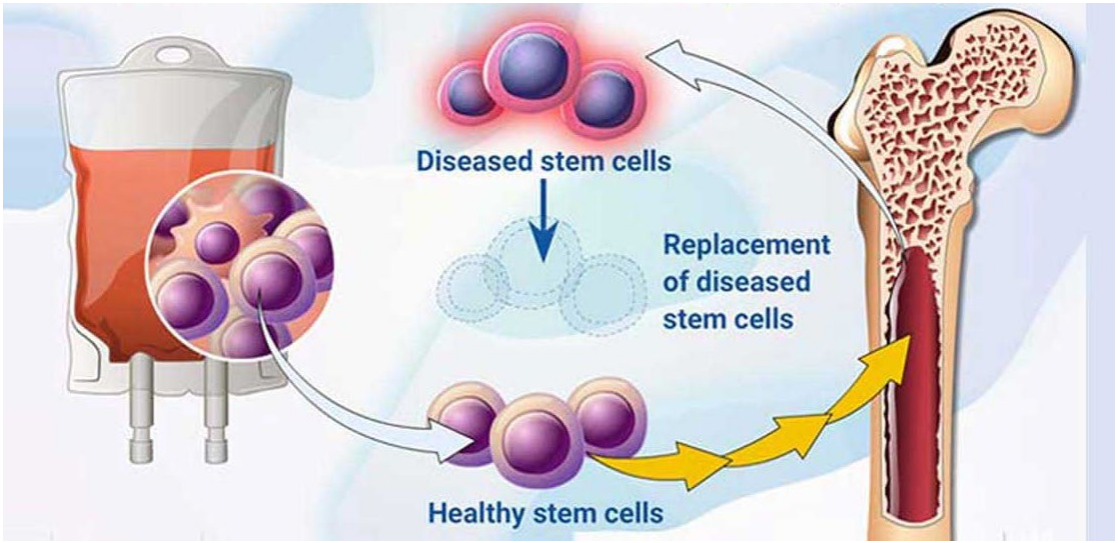
Targeted sites for therapeutic agents used in autoinflammatory diseases: *think molecularly*



Clues to use

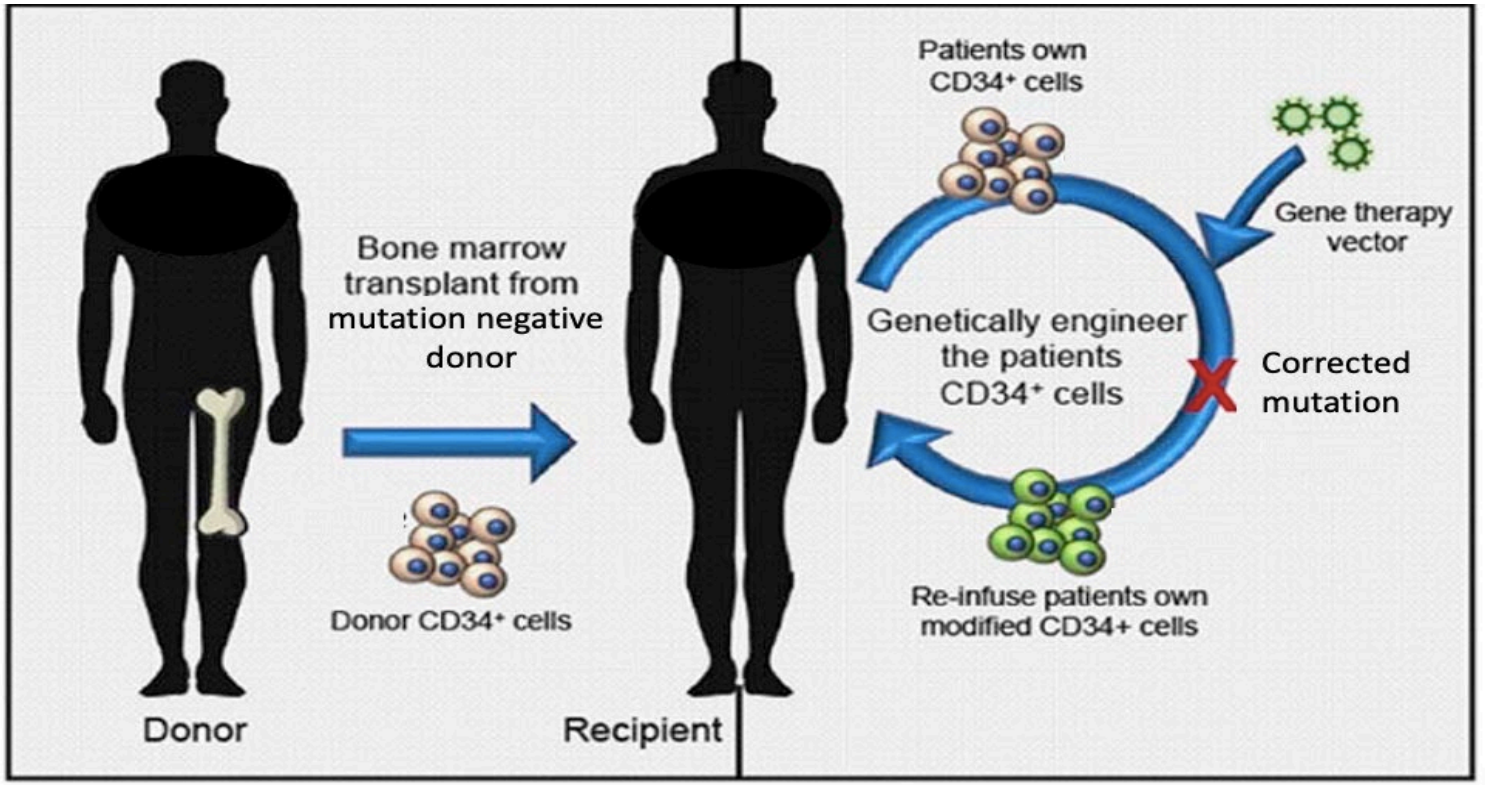
- CRP, ESR, ferritin
- *Serum cytokines*
  - *(IL-18, CXCL9)*
- *IFN signature*
- *STAT phosphorylation*

What about bone marrow transplants or gene therapy?



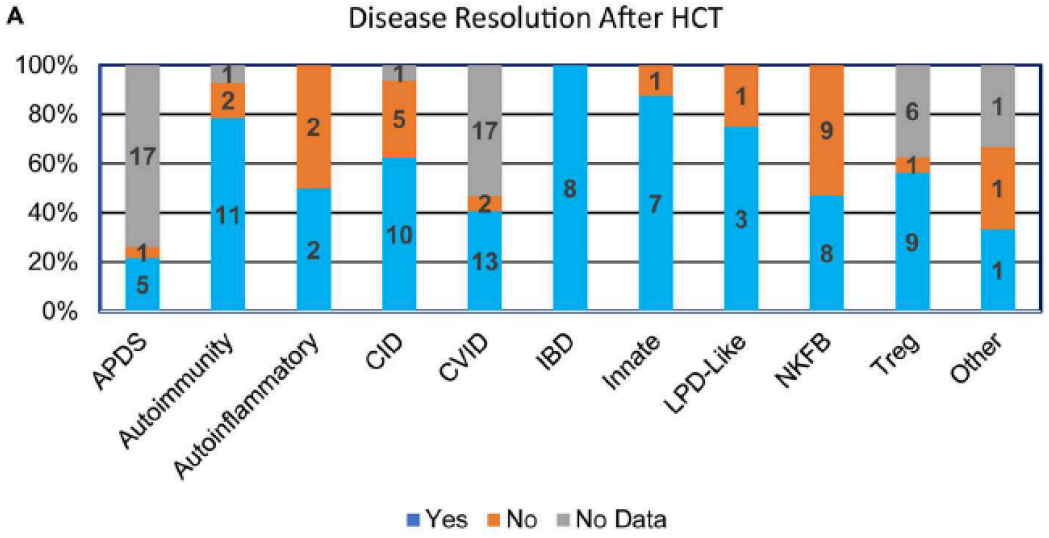
Treatment is great but what about a CURE?

- Bone marrow (stem cell) transplant vs. Gene therapy (editing)



Adapted from Hayworth et al. Cytotherapy, 2017

HSCT in patients with Primary Immune Regulatory Disorders



Group	Genes/Pathways	# of HCT Patients (% of Total)
APDS	PIK3CD	20 (8.8%)
	PIK3R1	3 (1.3%)
Autoimmunity	C1Q	3 (1.3%)
Autoinflammatory	ADA2	2 (0.9%)
	MVK	1 (0.4%)
	PSTPIP1	1 (0.4%)
CID	CD40L	3 (1.3%)
	DOCK8	2 (0.9%)
	MALT1	1 (0.4%)
	RAG1	1 (0.4%)
	ZAP70	3 (1.3%)
	Unknown gene	6 (2.7%)
CVID	TNFRSF13B (TACI)	1 (0.4%)
	Unknown gene	31 (13.7%)
IBD	IL10R	7 (3.1%)
	Unknown gene	1 (0.4%)
Innate	CD18	1 (0.4%)
	IFNGR	1 (0.4%)
	LAD	2 (0.9%)
	STAT1-GOF	3 (1.3%)
	TLR3 and STAT1-LOF	1 (0.4%)
LPD-Like	ITK	1 (0.4%)
	SAP	1 (0.4%)
	XIAP	1 (0.4%)
	Unknown gene	1 (0.4%)
NFKB	IKBKB-LOF	4 (1.8%)
	IKBKG	10 (4.4%)
	NFKBIA	2 (0.9%)
	Other	1 (0.4%)
Tregopathies	CTLA4	13 (5.8%)
	FOXP3	62 (27.4%)
	IL2RA (CD25)	1 (0.4%)
	LRBA	4 (1.8%)
	STAT3-GOF	12 (5.3%)
	Unknown gene	5 (2.2%)
Other*	TCF4	1 (0.4%)
	TTC7A	2 (0.9%)

Chan, AY. *et al.* (2020). *Frontiers in Immunology*


TAKE HOME

Summary & Ongoing challenges

- Suspect autoinflammation
  - Unexplained systemic inflammation
- Pattern Recognition
  - Symptom patterns
  - Family history
- Testing
  - Inflammation during and between episodes
  - Genetics

Summary & Ongoing challenges

- Targeted therapies are available
- Phenotypes still being defined
- Evaluation of inflammation
  - Interfebrile periods are equally important to febrile episodes
- Contribution of multiple variants
  - “burden of variants”
- Response to medications is variable – think biologically
- Decisions should be made jointly between physicians & patients.

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Resources

- The Autoinflammatory Alliance
  - http://autoinflammatory.org/
- orphanet
  - http://www.orpha.net
- The International Society of Systemic Autoinflammatory Diseases
  - https://www.issaid.org/

Autoinflammatory Search: The Systemic Autoinflammatory Diseases (SAID) Database

http://www.autoinflammatory-search.org/search/index