

Autoinflammatory Disease in 2025 (tales from the clinical realm)

Amanda K. Ombrello, M.D.
National Human Genome Research Institute
19 September 2025

Who Am I?

- Internal Medicine and Pediatrics
- Adult and Pediatric Rheumatology
- National Institutes of Health x 15.5 years
- Autoinflammatory Disease
 - Identified, characterized and treatment of 7 new diseases



SAINT LOUIS UNIVERSITY
—
SCHOOL OF MEDICINE



New Clinic Patient #1

- 35 year old female presenting to establish care. Born in Armenia but moved to the US when she was 17. Reportedly healthy but records show repeated ER visits over the course of the past decade for abdominal pain. Multiple CTs negative for acute abdomen etiology but did have an appendectomy (normal path) for presumed appendicitis. She reports episodes last 24-48 hours and are “excruciating” where she prefers to lie curled in a ball. ER notes report concern that she is drug seeking but patient reports she does not take any pain medications regularly...only during episodes. Also, occasional episodes of chest pain accompany the abdominal pain. Negative family history. Baseline laboratory studies unremarkable (Chemistry, CBCdiff, APRs, hepatic panel) aside from UA showing 1+ protein.

New Clinic Patient #2

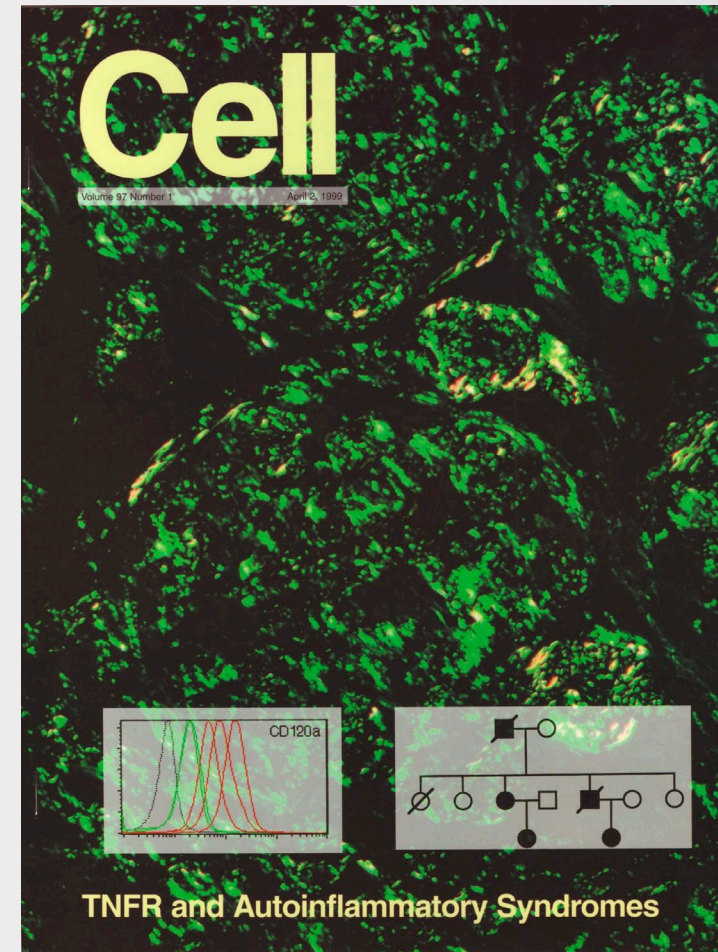
- “Doc, my child won’t stop getting sick. He is 4 years old and has had 23 illnesses with fevers. They are really high. He has been treated for ear infections and strep throat a lot of times but the fevers keep coming back. His doctor sent him to see an infectious disease doctor but they said everything looks fine. How can that be? He is sick ALL THE TIME! He gets sent home from daycare and my husband and I have to swap staying home from work. He gets dehydrated and we have to take him to the ER for IV fluids. We can’t keep doing this. Can you help us?”

“Autoinflammatory Disease”

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

- “conditions characterized by seemingly unprovoked episodes of inflammation, without high-titer autoantibodies or antigen-specific T-cells”



McDermott MF, et al. *Cell*. 1999;97(1):133-144.

Autoinflammatory vs Autoimmune Diseases

Autoinflammatory Diseases

- Disorders of the innate immune system
- Seemingly unprovoked episodes of intense inflammation
- Lack high-titer autoantibodies or antigen-specific T-cells

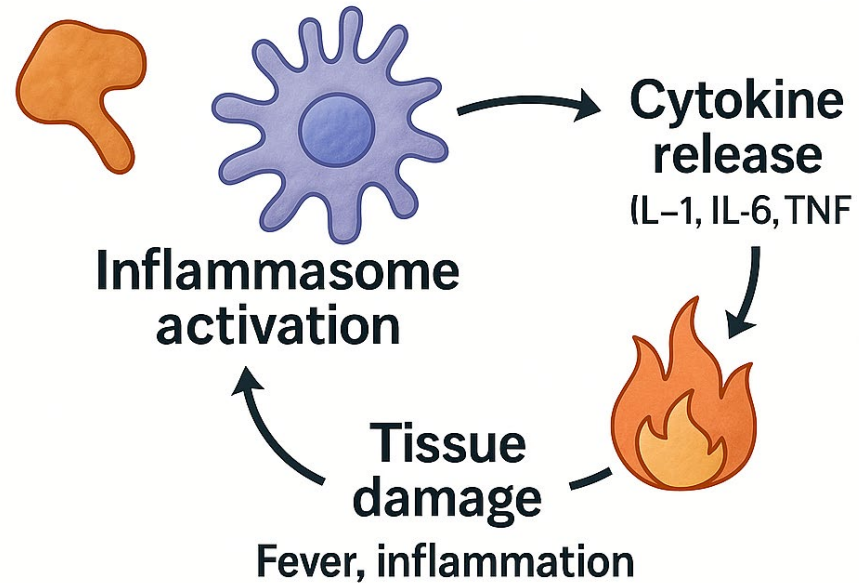
Examples: Familial Mediterranean Fever (FMF), Cryopyrin-Associated Periodic Syndromes (CAPS)

Autoimmune Diseases

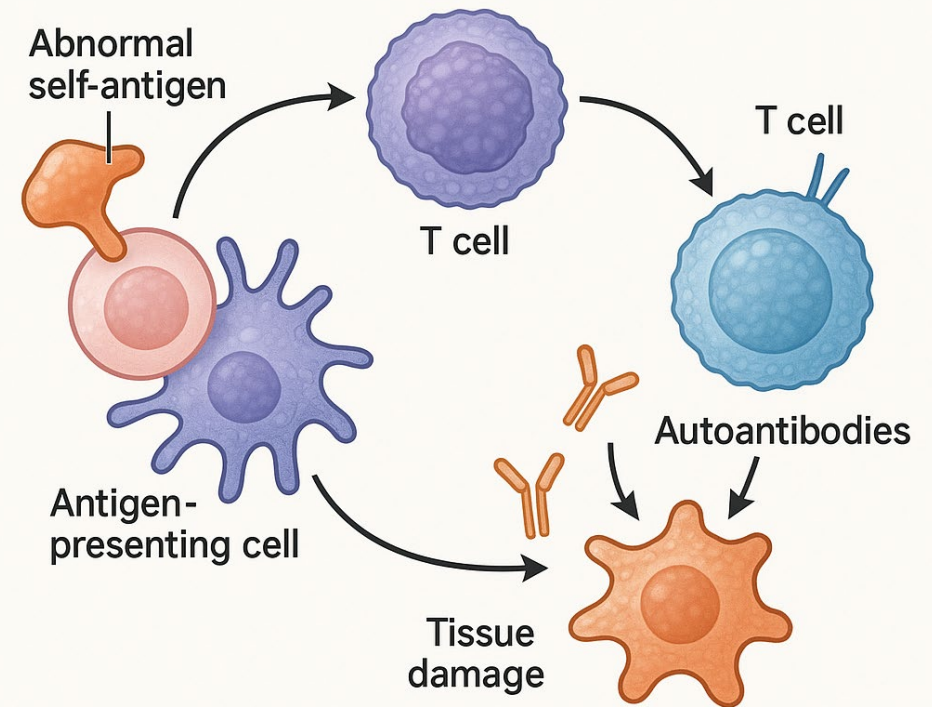
- Disorders of the adaptive immune system
- Driven by high-titer autoantibodies and antigen-specific T-cells

Examples: Systemic Lupus Erythematosus (SLE), Type 1 Diabetes, Rheumatoid Arthritis

Activation of the Innate Immune System in Autoinflammatory Disease



Activation of the Adaptive Immune System in Autoimmune Disease



What Does Autoinflammatory Disease Look Like?

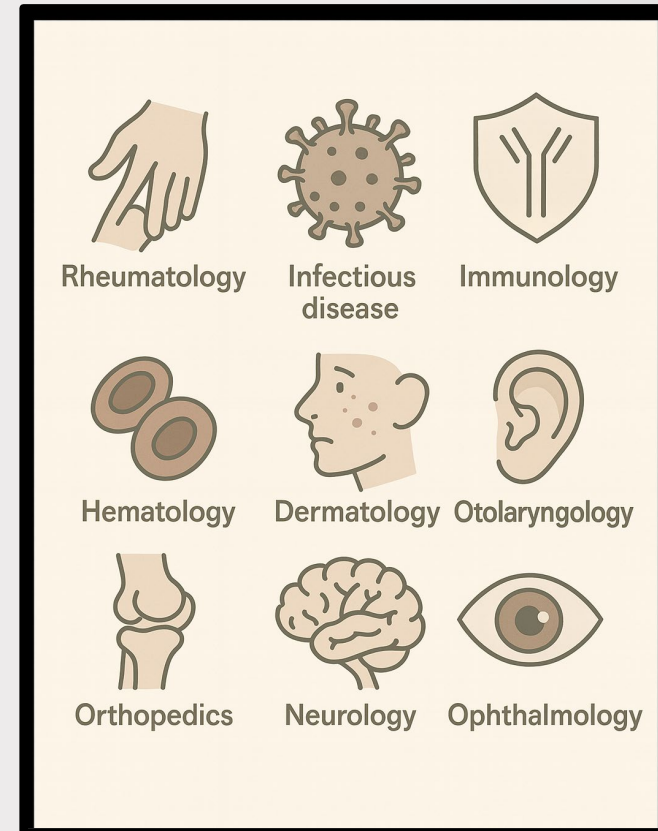


What Does Autoinflammatory Disease Look Like?



Where will one encounter autoinflammatory disease?

- Primary care
- Emergency room/urgent care
- Subspecialty clinics
 - Rheumatology
 - Infectious disease
 - Immunology
 - Hematology
 - Dermatology
 - Otolaryngology
 - Orthopedics
 - Neurology
 - Ophthalmology
 - And just about anywhere else!



Fever pattern

- **FEVER DIARY**
- Age of onset
- Frequency
- Duration
- Regularity
- Height of fever and route
- Prodromal signs/symptoms
- Triggers
- Interim period



Common Presenting Features

- Rash
 - Distribution/appearance/timing
- Lymphadenopathy
 - Localized/Generalized
- Pleuritis/Peritonitis
- Constipation/Diarrhea
- Oral Ulcers
- Arthralgias/Myalgias



Other Important History

- Organomegaly
- Ophthalmologic
 - Conjunctivitis, episcleritis, periorbital edema
- Genitourinary
 - Testicular/scrotal pain
 - Genital ulcers
- Immune/infectious history
- Hearing loss
- CNS manifestations
- Response to vaccinations
- Ethnic background



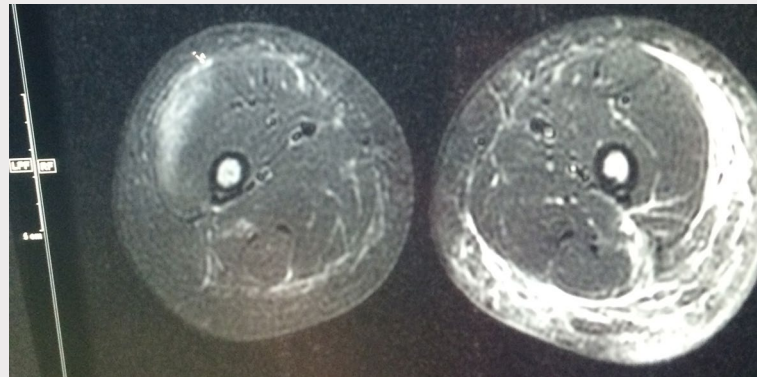
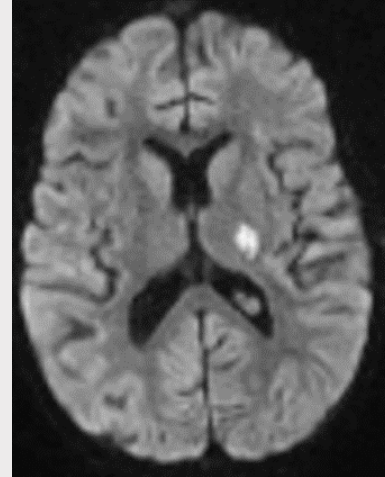
Examination Findings

- **BENIGN!**
- Vital Signs
- Periorbital edema/conjunctivitis/ptosis
- Oral ulcers/pharyngitis
- Lymphadenopathy (localized versus generalized)
- Rebound tenderness/guarding
- Arthritis
- Skin findings



Laboratory/Imaging

- Importance of baseline and flare labs
- CBC diff and CMP
- ESR and CRP
- Immunoglobulins
- CK, LDH, aldolase
- Autoantibodies
- Imaging as clinically indicated
- Urinalysis



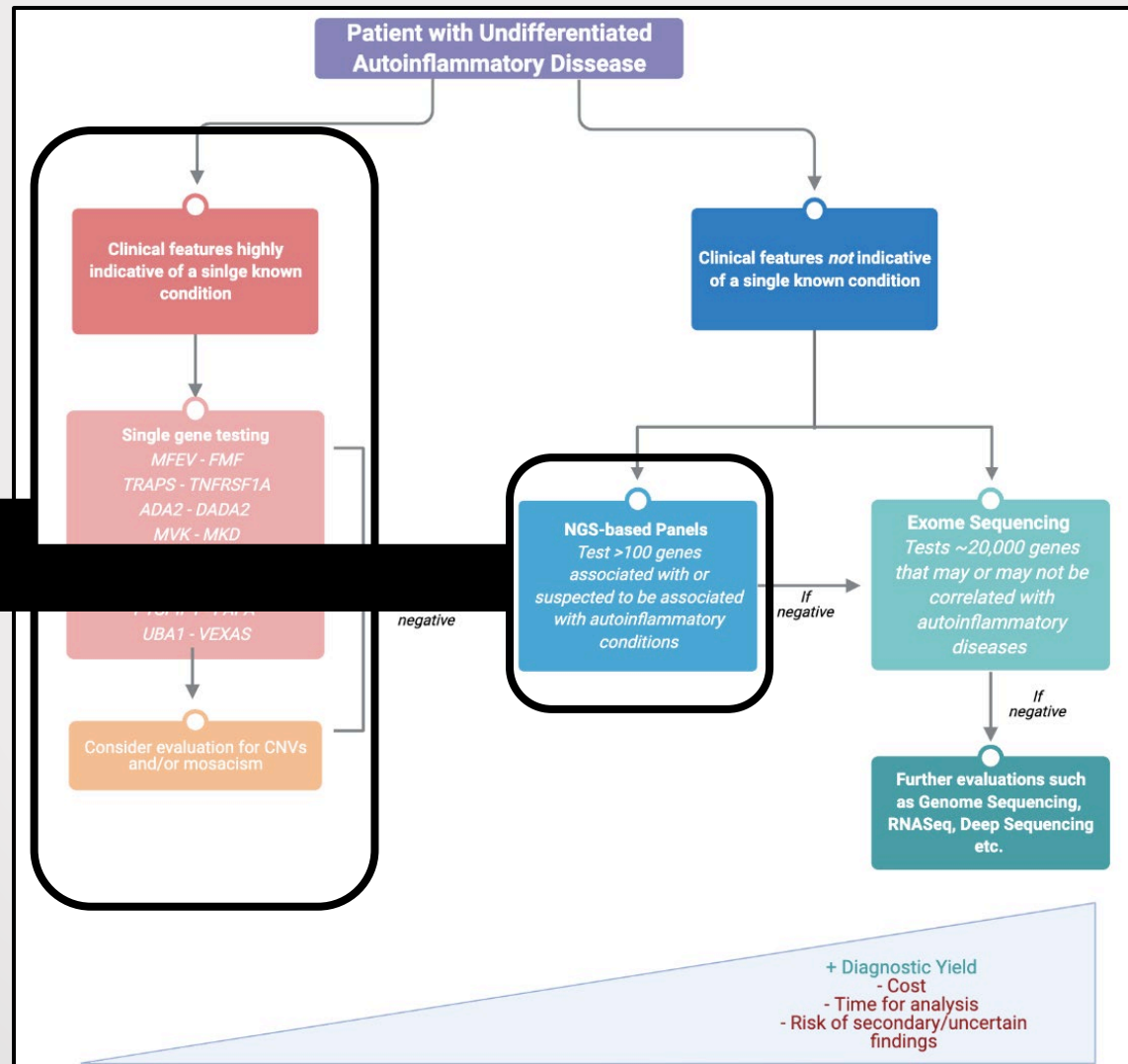
What to do next?????

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Genetic Testing



INVITAE



Back to the patients

...

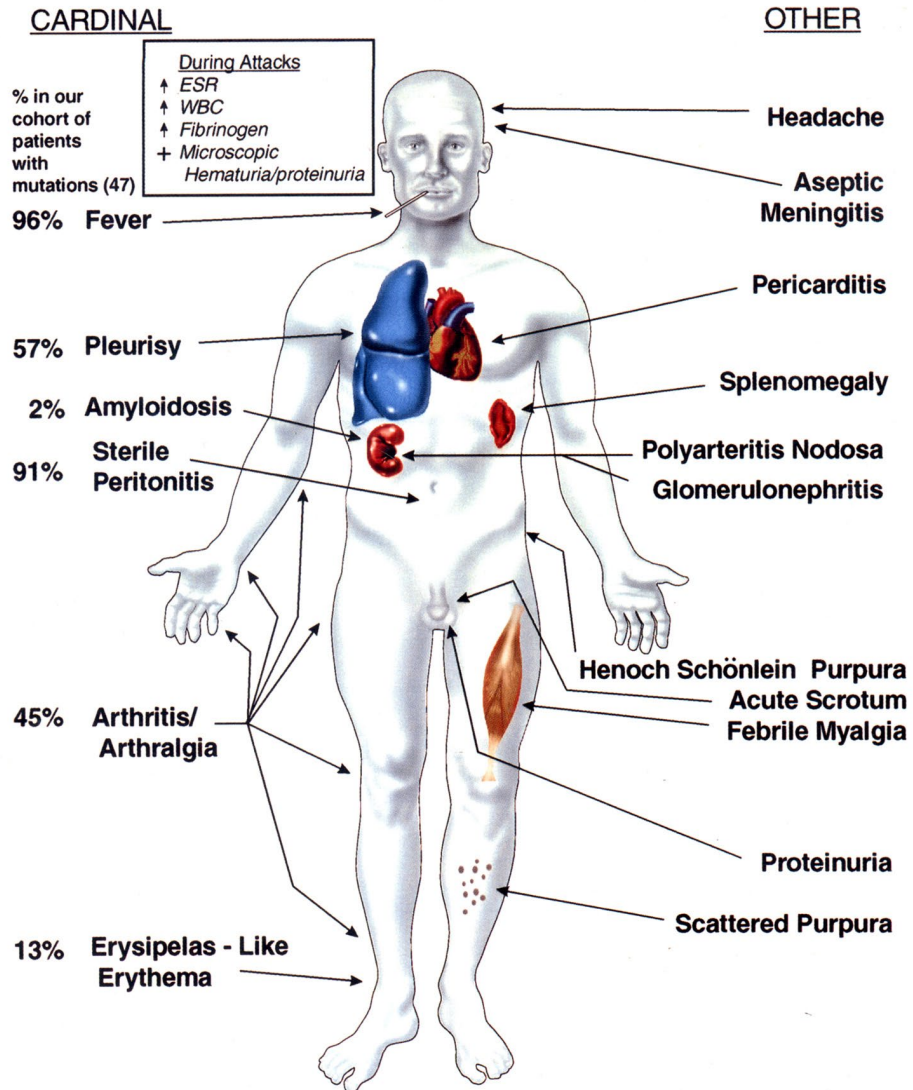
An origin story

New Clinic Patient #1

- 35 year old female presenting to establish care. Born in Armenia but moved to the US when she was 17. Reportedly healthy but records show repeated ER visits over the course of the past decade for abdominal pain. Multiple CTs negative for acute abdomen etiology but did have an appendectomy (normal path) for presumed appendicitis. She reports episodes last 24-48 hours and are “excruciating” where she prefers to lie curled in a ball. ER notes report concern that she is drug seeking but patient reports she does not take any pain medications regularly...only during episodes. Also, occasional episodes of chest pain accompany the abdominal pain. Negative family history. Baseline laboratory studies unremarkable (Chemistry, CBCdiff, APRs, hepatic panel) aside from UA showing 1+ protein.

FAMILIAL MEDITERRANEAN FEVER

Signs and Symptoms

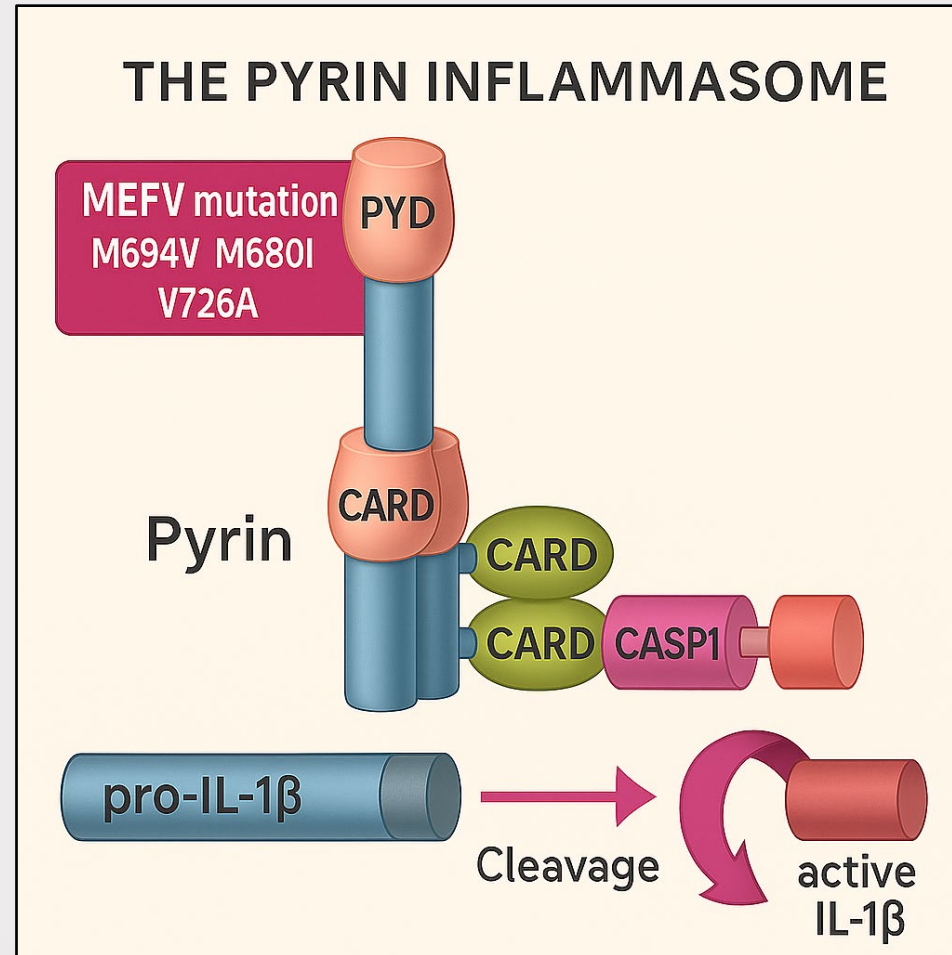


Familial Mediterranean Fever

Autosomal recessive
Mutations in *MEFV*

Samuels et al., *Medicine (Baltimore)* 77:268, 1998

The Pyrin Inflammasome



Cutaneous Manifestations of FMF (Erysipeloid Erythema)



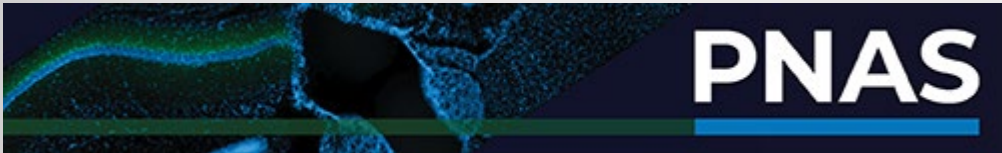
Clinical Features and Response to Colchicine Therapy in Patients with Familial Mediterranean Fever

Feature	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	42	26	47	43	27
Sex	M	F	F	M	M
Ancestry	Hebrew	Hebrew	Syrian	Hebrew	Hebrew
Illness Duration (years)	27	20	41	20	4
Serum Uric Acid (mg/dL)	6.1	4.0	3.1	8.2	6.4
Attack Frequency Before Tx	3–4 / wk	4 / wk	4 / wk	6–10 days	6 / wk
Colchicine Duration (months)	54	27	20	16	10
No. of Attacks After Tx	1	2	0	0	1*

**Note: Attack occurred shortly after discontinuation of colchicine.*

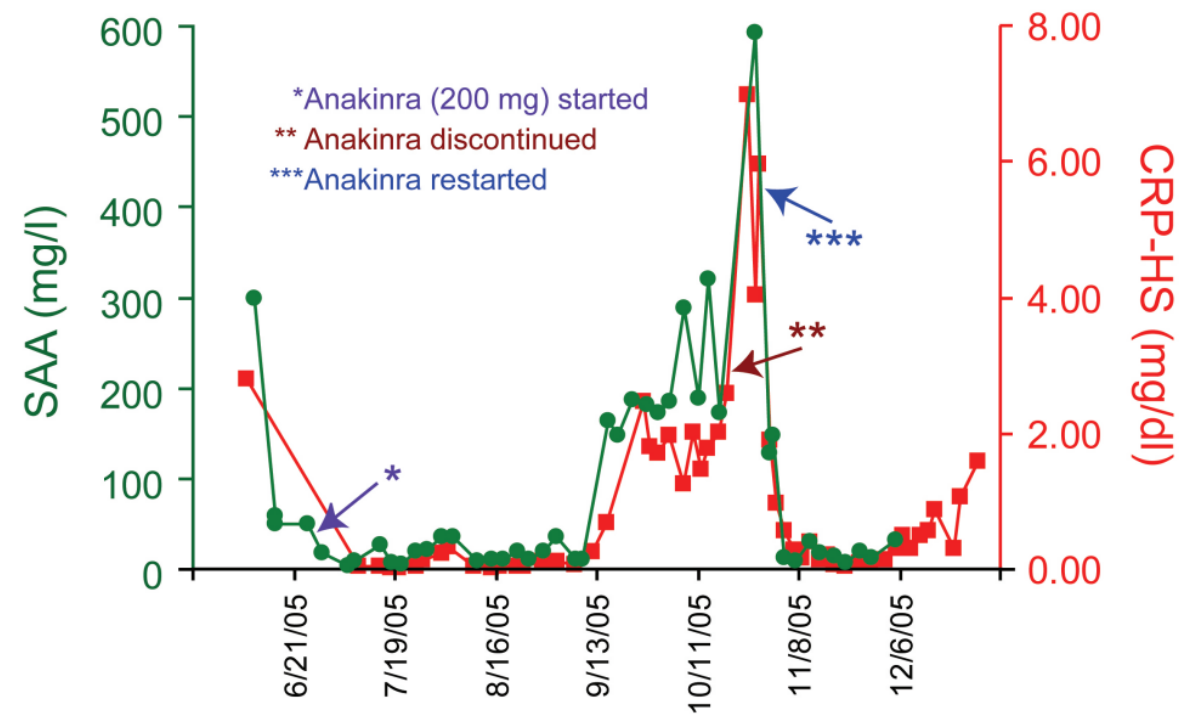
Reference: Goldfinger SE. "Colchicine for Familial Mediterranean Fever." N Engl J Med. 1972;287(25):1302. (Dec 21, 1972).

FMF Treatment



The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1 β production

Chae JJ, et al. *Proc Natl Acad Sci U S A*. 2006 Jun 27;103(26):9982-7.



FMF Treatment

- 2016—canakinumab FDA approved for the treatment of FMF, TRAPS, and MKD



Why is there such a high carrier frequency of *MEFV* mutations in certain Middle Eastern populations?

	V726A	M694V	M680I	Total
Turkish	0.039	0.062	0.026	0.127
Armenian	0.046	0.047	0.018	0.111
Arab	0.076	0.006	0.025	0.107
Non-Ashkenazi Jewish	0.068	0.039	0	0.107

Park et al., *Nat Immunol* 21:857, 2020

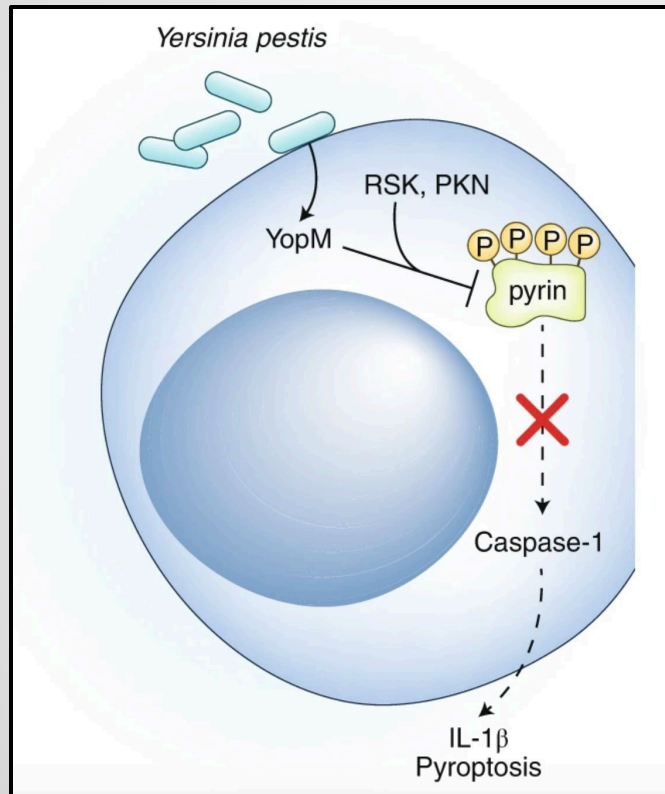
The carrier frequency of cystic fibrosis, the most common lethal recessive disorder in North America, is ~4%.

THE BLACK PLAGUE

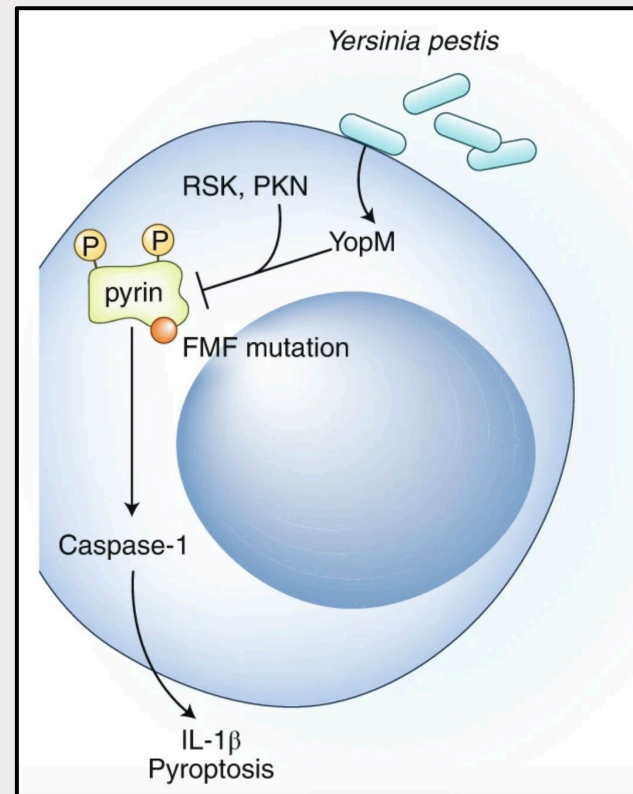


The Faustian Bargain of FMF

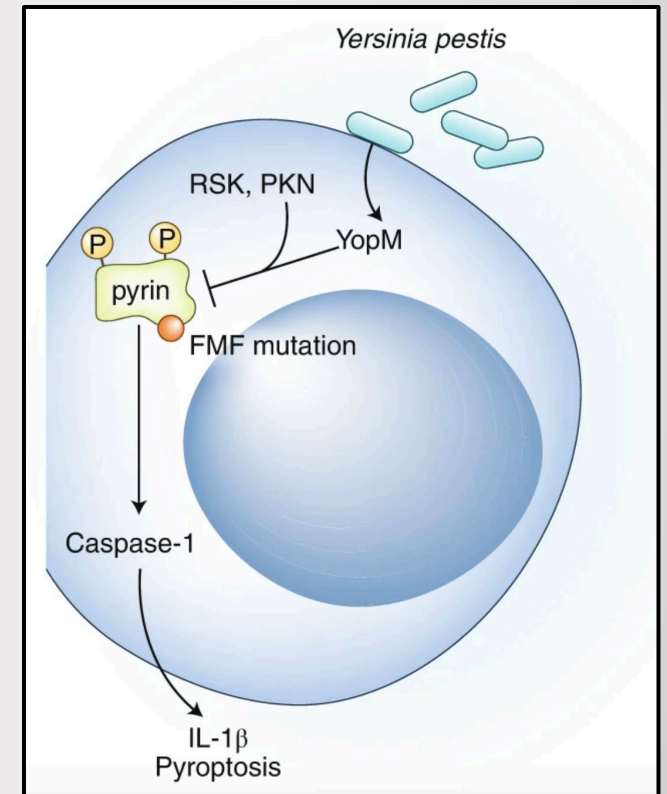
Healthy subject



**Patient with FMF
(< 1% population)**



**FMF Carrier
(~ 10% population)**



Patient #2

...

Linking the rare to the common

New Clinic Patient #2

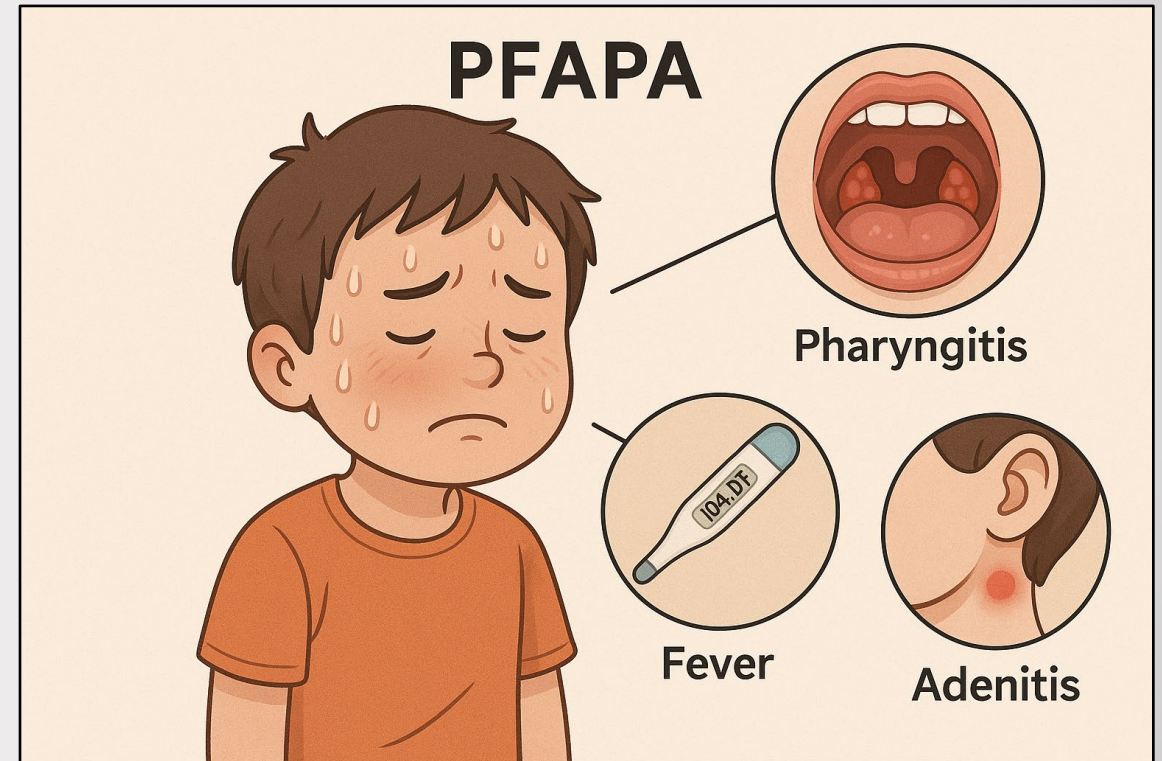
- “Doc, my child won’t stop getting sick. He is 4 years old and has had 23 illnesses with fevers. They are really high. He has been treated for ear infections and strep throat a lot of times but the fevers keep coming back. His doctor sent him to see an infectious disease doctor but they said everything looks fine. How can that be? He is sick ALL THE TIME! He gets sent home from daycare and my husband and I have to swap staying home from work. He gets dehydrated and we have to take him to the ER for IV fluids. We can’t keep doing this. Can you help us?”

A bit more history

- Cyclical nature
- Sore throat
- Oral ulcers
- Cervical lymphadenopathy
- No family history
- Completely well in between flares
- Onset at age 2.5 years

The Syndrome of Periodic Fevers with Aphthous Stomatitis, Pharyngitis, and Cervical Adenopathy

- Most common periodic fever syndrome in children
- Most clock-like in regularity of any of the pediatric periodic fever syndromes
- Dramatic initial response to corticosteroids, but attacks often then become more frequent
- Runs in families, but not in a Mendelian pattern
- Patients usually “outgrow” it by young adulthood
- Tonsillectomy/adenoidectomy may be effective treatment
- Often responds to intermittent anakinra; approximately 30% of patients respond to oral cimetidine



Genetic risk variants for PFAPA, the most common periodic fever syndrome of children

SNP	Nearest gene	Risk allele	ORmeta	Pmeta (Bonferroni corrected)
rs17753641	IL12A	G	2.13	6×10^{-9}
rs7574070	STAT4	A	1.51	0.0001
rs1518110	IL10	A	1.45	0.003
rs7616215	CCR1-CCR3	T	1.38	0.02

Manthiram et al. PNAS 117:14405, 2020

GWAS of Canker Sores

Implicates Th-1 Pathway and Shared Genetic
Architecture with Immune-Mediated Disease

Fah Sathirapongsasuti

23andMe, Inc.

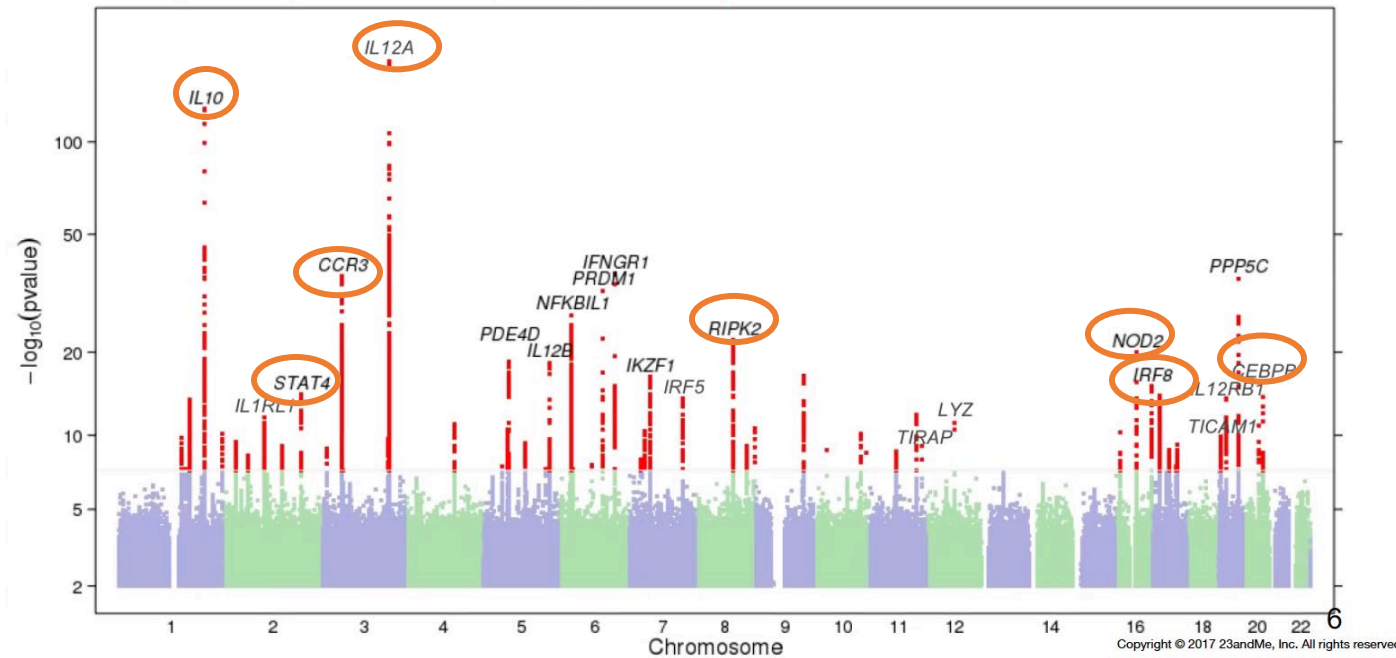
ASHG '17

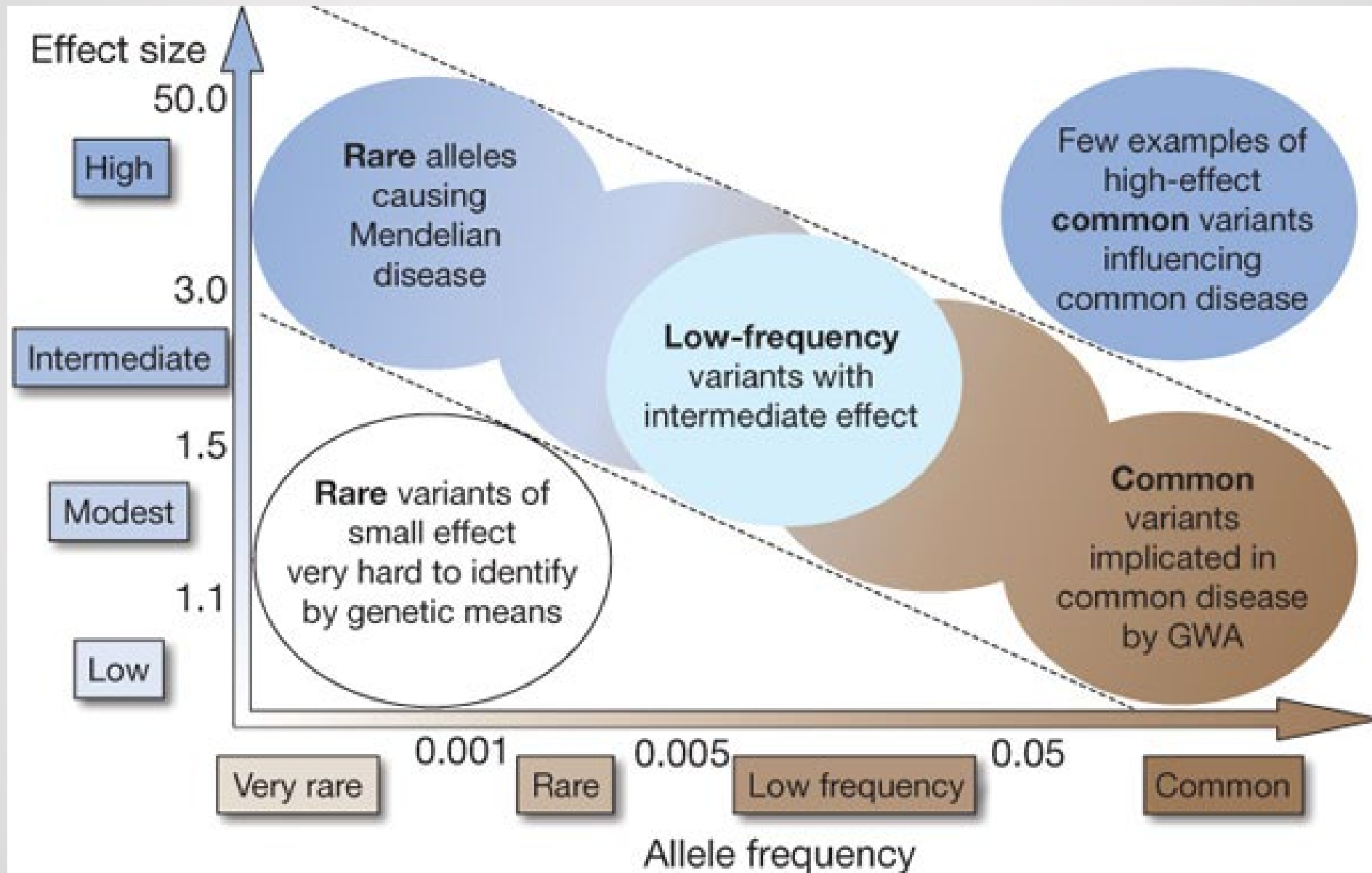
Canker Sore GWAS

Canker Sores GWAS

178,409 cases (59.8% female); 66,603 controls

47 loci significantly associated at $p < 5E-8$; 75 loci at $p < 1E-6$





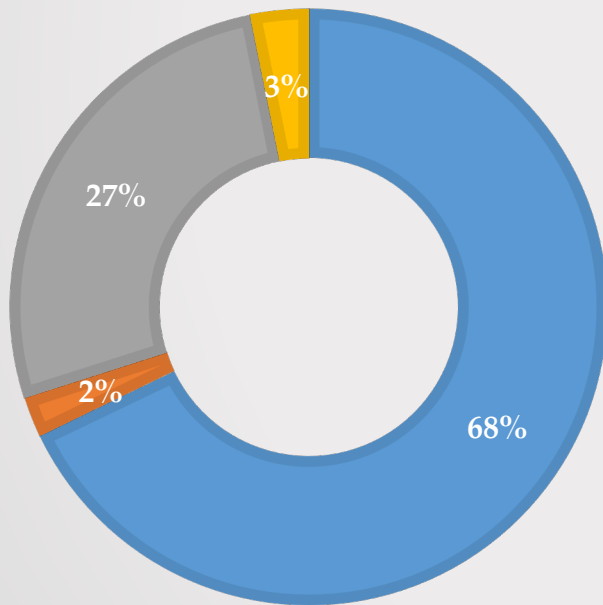
What to do when the testing is
inconclusive?

...

Cohort Diagnostic Rates

PROBAND DIAGNOSTIC RATE

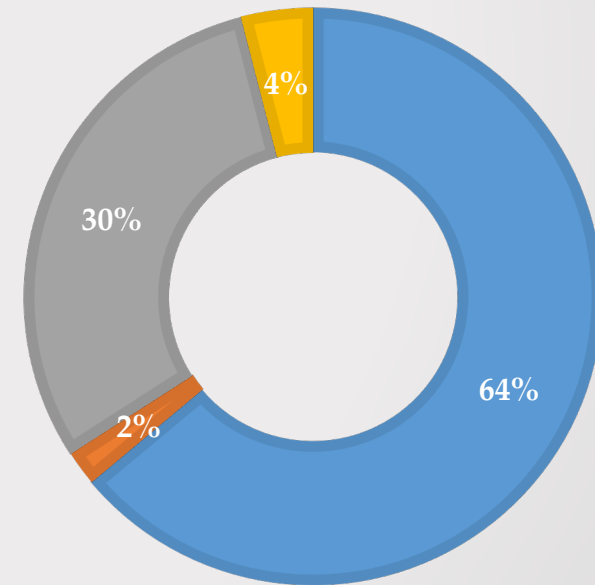
■ Undiagnosed ■ Candidate Diagnosis ■ Final Diagnosis ■ Clinical Diagnosis



2768 Proband
4643 Proband +Family

PROBANDS + AFFECTED FAMILY DIAGNOSTIC RATE

■ Undiagnosed ■ Candidate ■ Final Diagnosis ■ Clinical Diagnosis



New Autoinflammatory Diseases

- Patients who closely resemble an identified disease but test negative for mutations
- Patients with multiple affected family members
- Patients with similar phenotypes that do not fit an identified disease
 - Hypothermia
 - Infections
 - Immune dysregulation
 - Low complements
 - Aseptic meningitis
 - Panniculitis
 - Neutrophilic dermatoses
 - Pericarditis
 - Persistent fevers
 - Medication response vs. lack of response
- Patients with an early age of onset

Further Genetic Testing

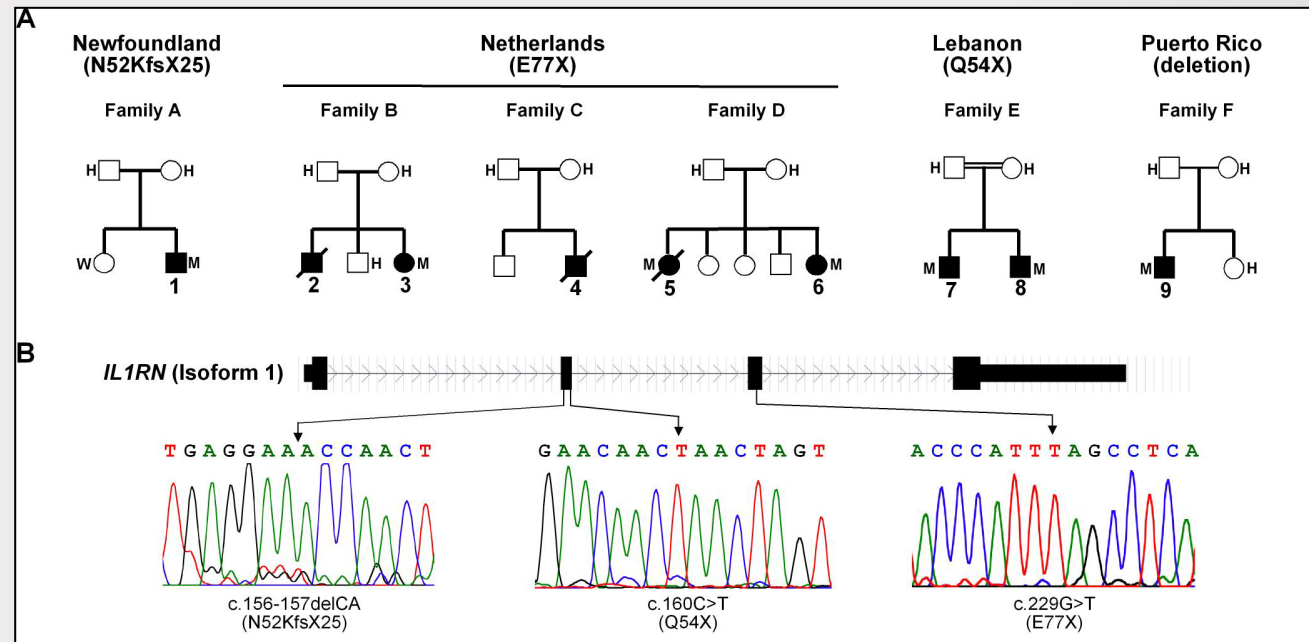
- Whole exome/genome sequencing

- Trio approach

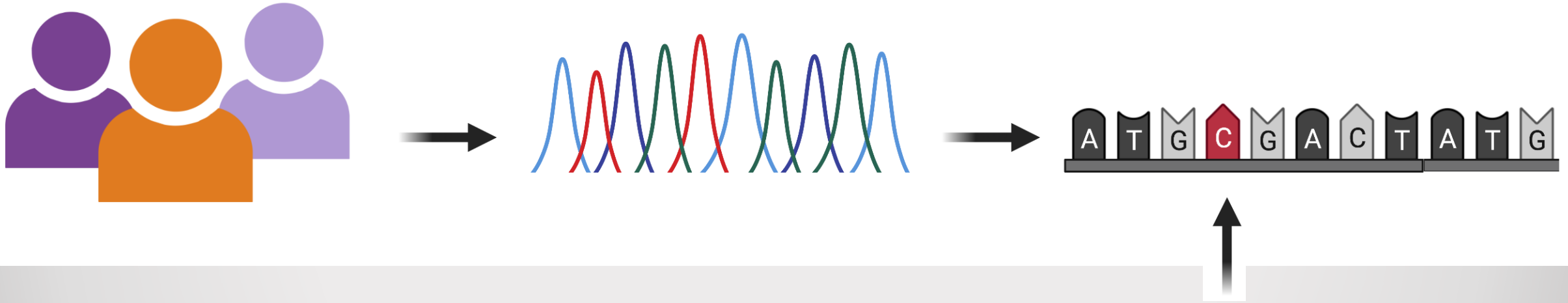
- Affected vs Unaffected

- Deep sequencing

- Somatic mutations



Phenotype-First Approach

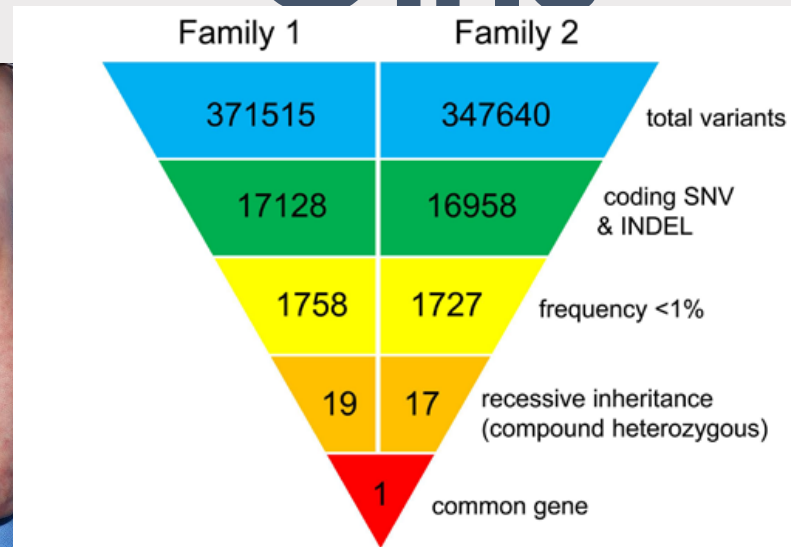


Sequence patients
with similar phenotypes

Identify possible
disease-causing variants



ale of 2 L Girls



Deficiency of Adenosine Deaminase 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

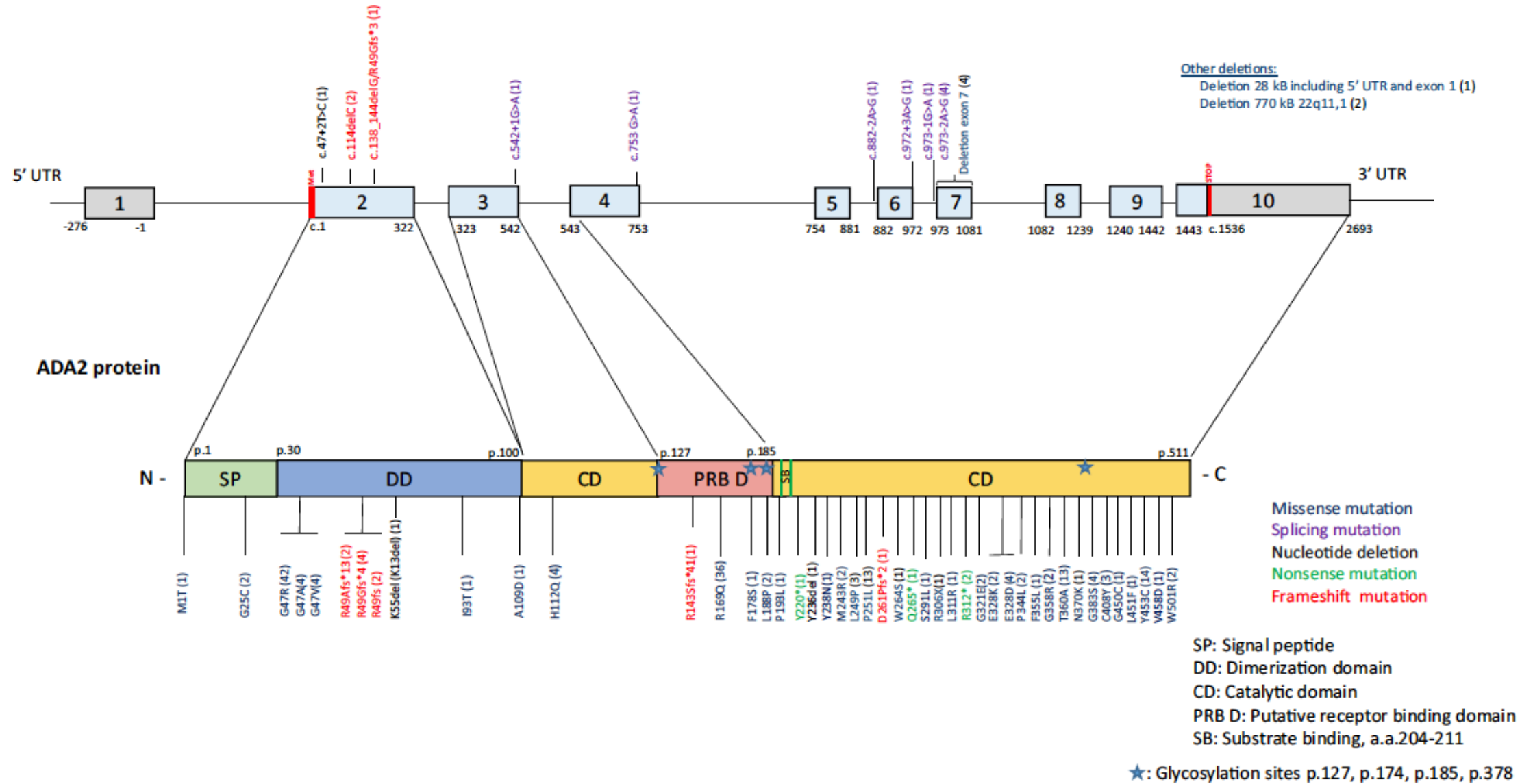
Early-Onset Stroke and Vasculopathy
Associated with Mutations in ADA2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutant Adenosine Deaminase 2
in a Polyarteritis Nodosa Vasculopathy

ADA2/CECR1 gene; NM_001282225.1; NP_001269154.1; ENS00000093072



What is ADA2?

ADA1

- Monomer
- Intracellular
- High affinity for adenosine
- Expressed in:
 - T and B lymphocytes

ADA2

- Homodimer, highly glycosylated
- Secreted protein
- Much lower affinity for adenosine
- Expressed in:
 - Myeloid cells
 - Monocytes
 - NK cells,
 - T and B lymphocytes
- May have growth factor activity

Active ADA2 concentration in plasma

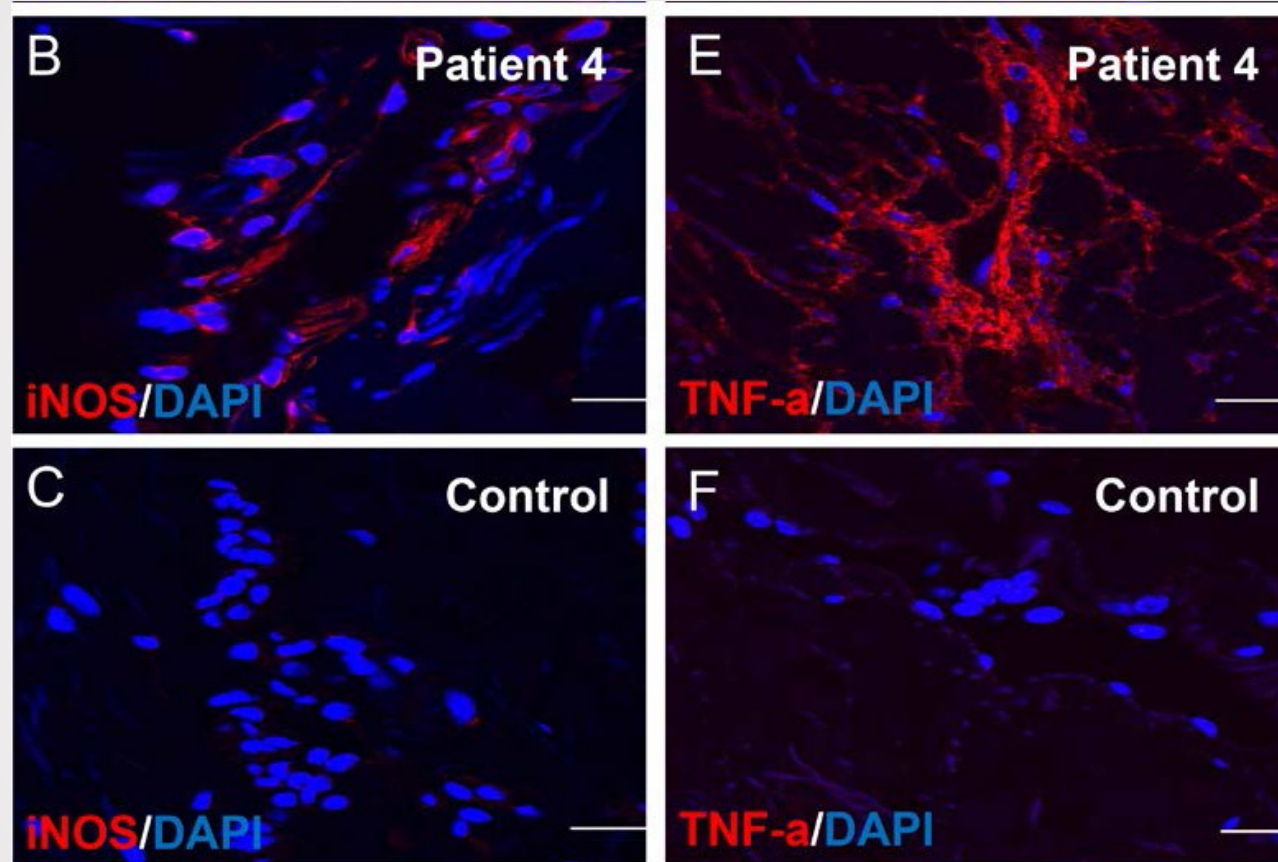
Y-axis: Active ADA2 concentration (ng/ml)

X-axis: Patients, Parents, Siblings, Adult controls, Pediatric controls

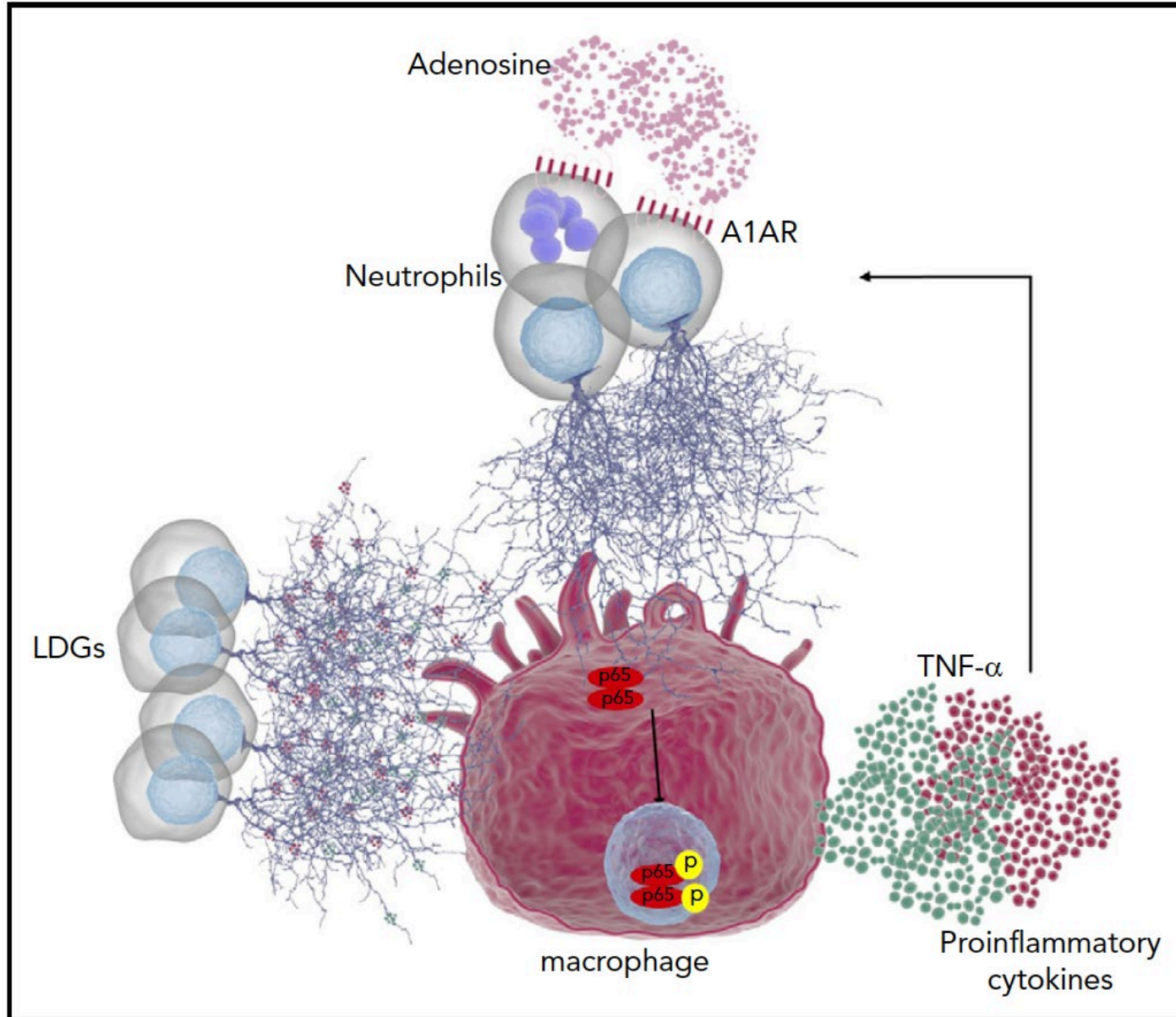
Statistical significance: $p < 0.0001$ (comparing Patients to Parents/Siblings, and Parents/Siblings to Pediatric controls)

Group	Active ADA2 concentration (ng/ml)
Patients	~0
Parents	~45
Siblings	~75
Adult controls	~115
Pediatric controls	~210

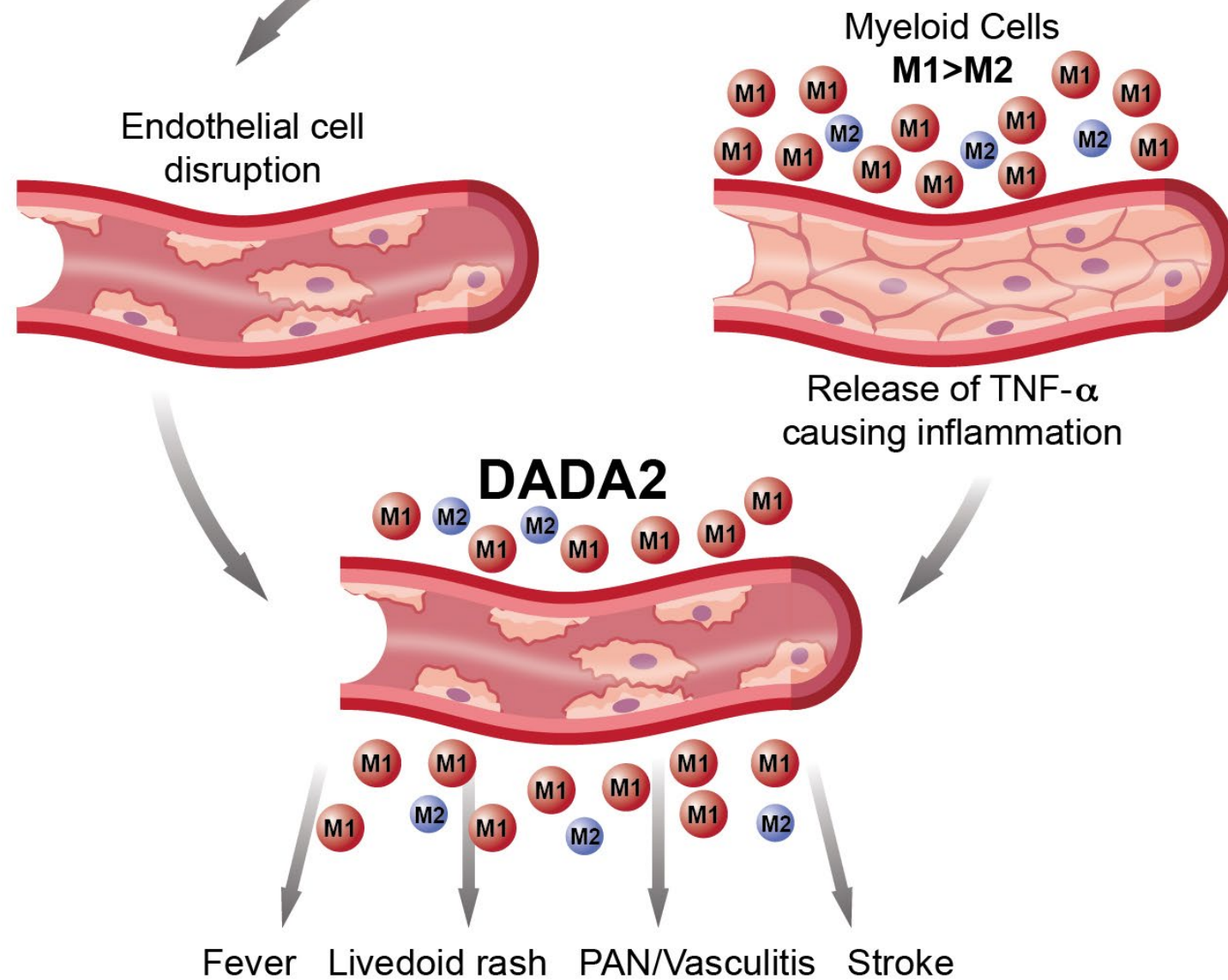
Inflammation in ADA2 Deficiency



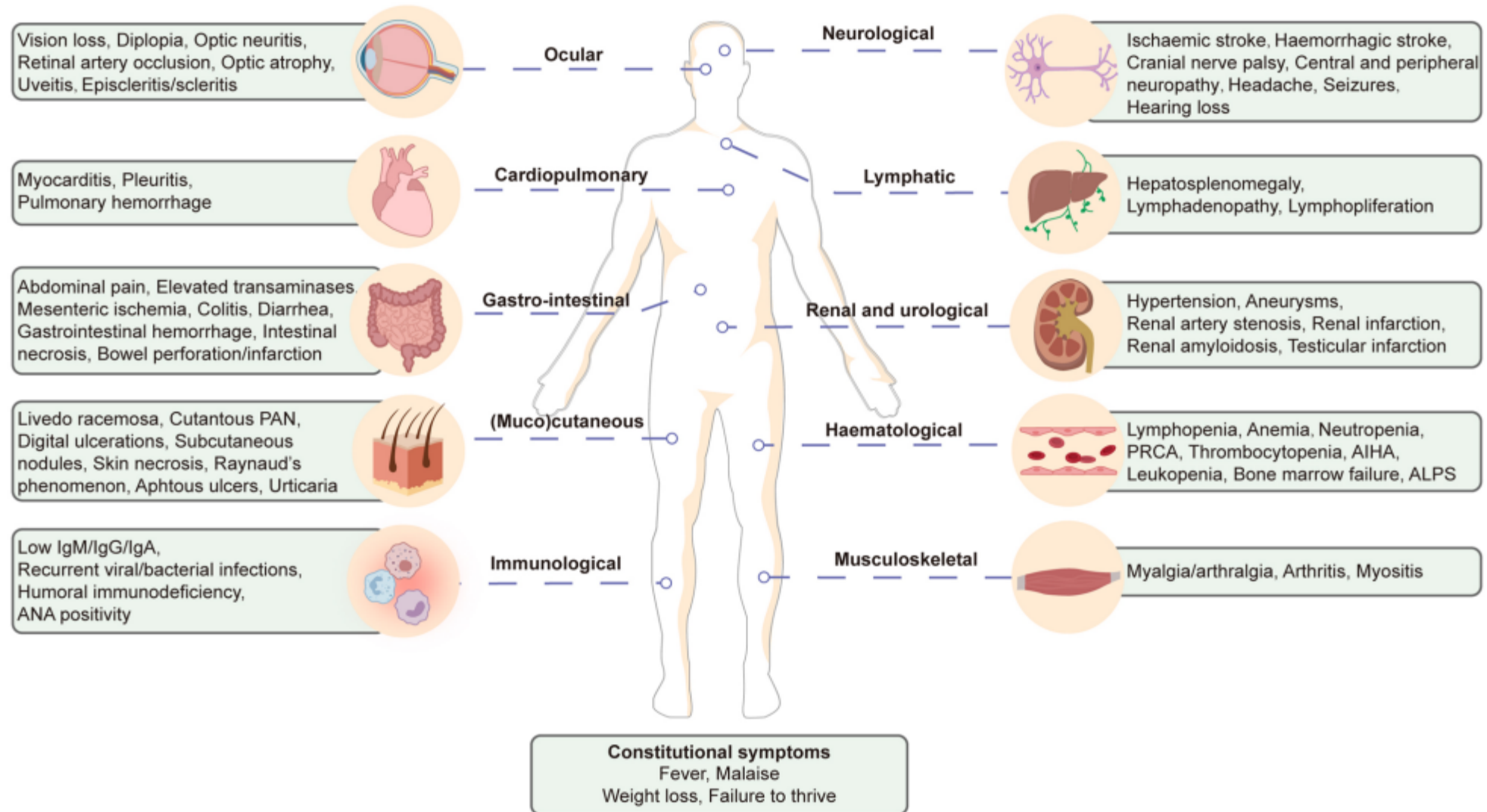
Skin



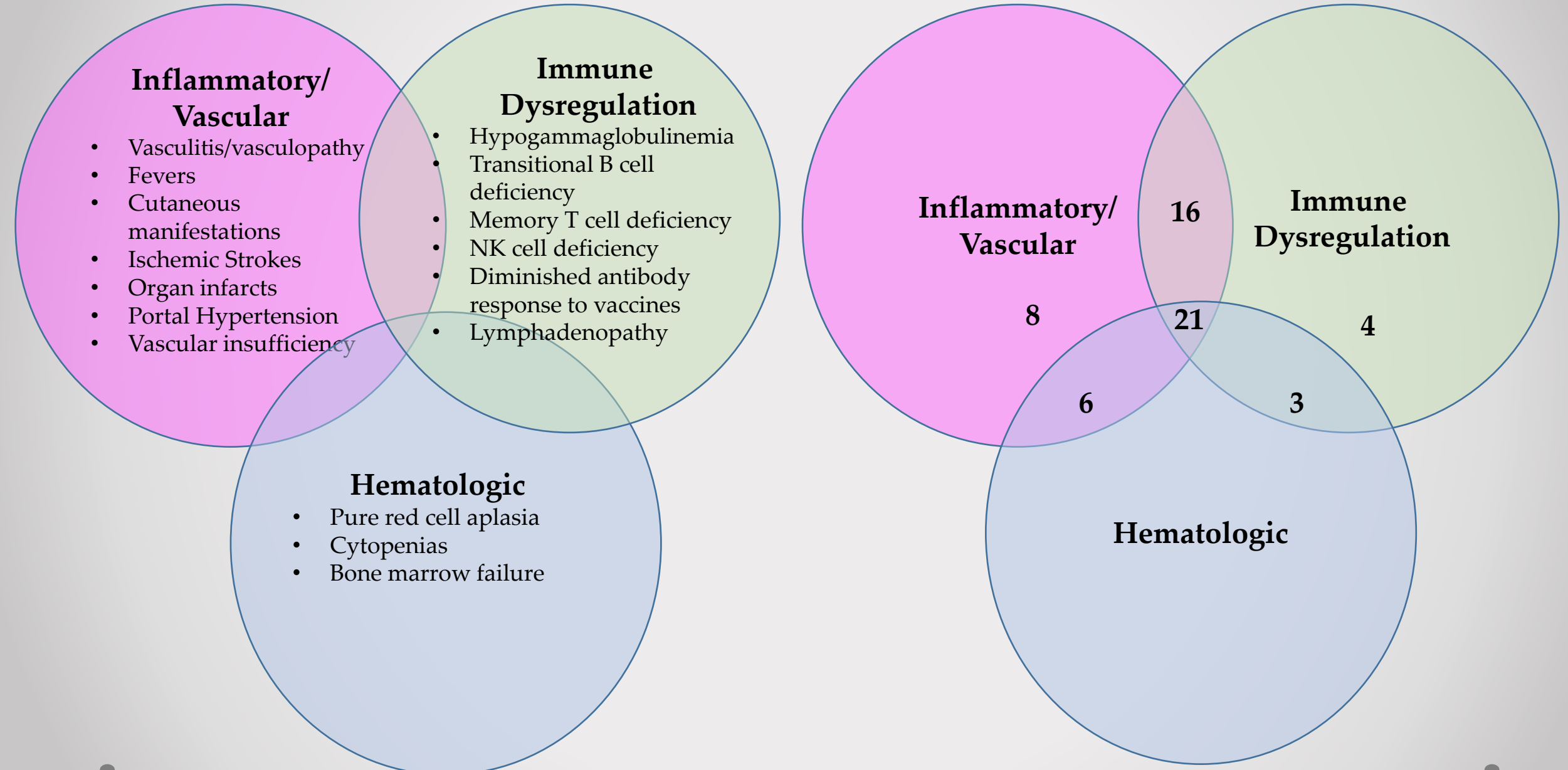
**low
ADA2**



A Multi-Specialty Disease



Phenotypic Variability

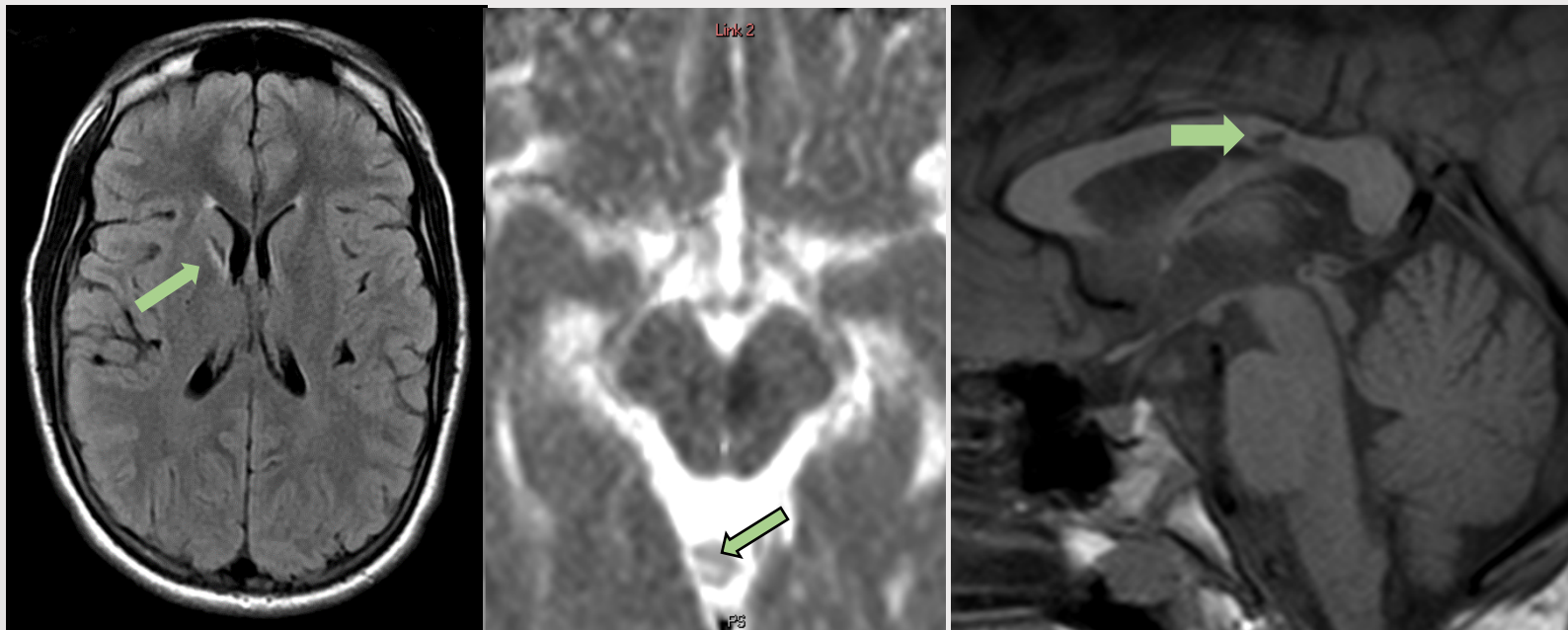


Cutaneous Vasculitis

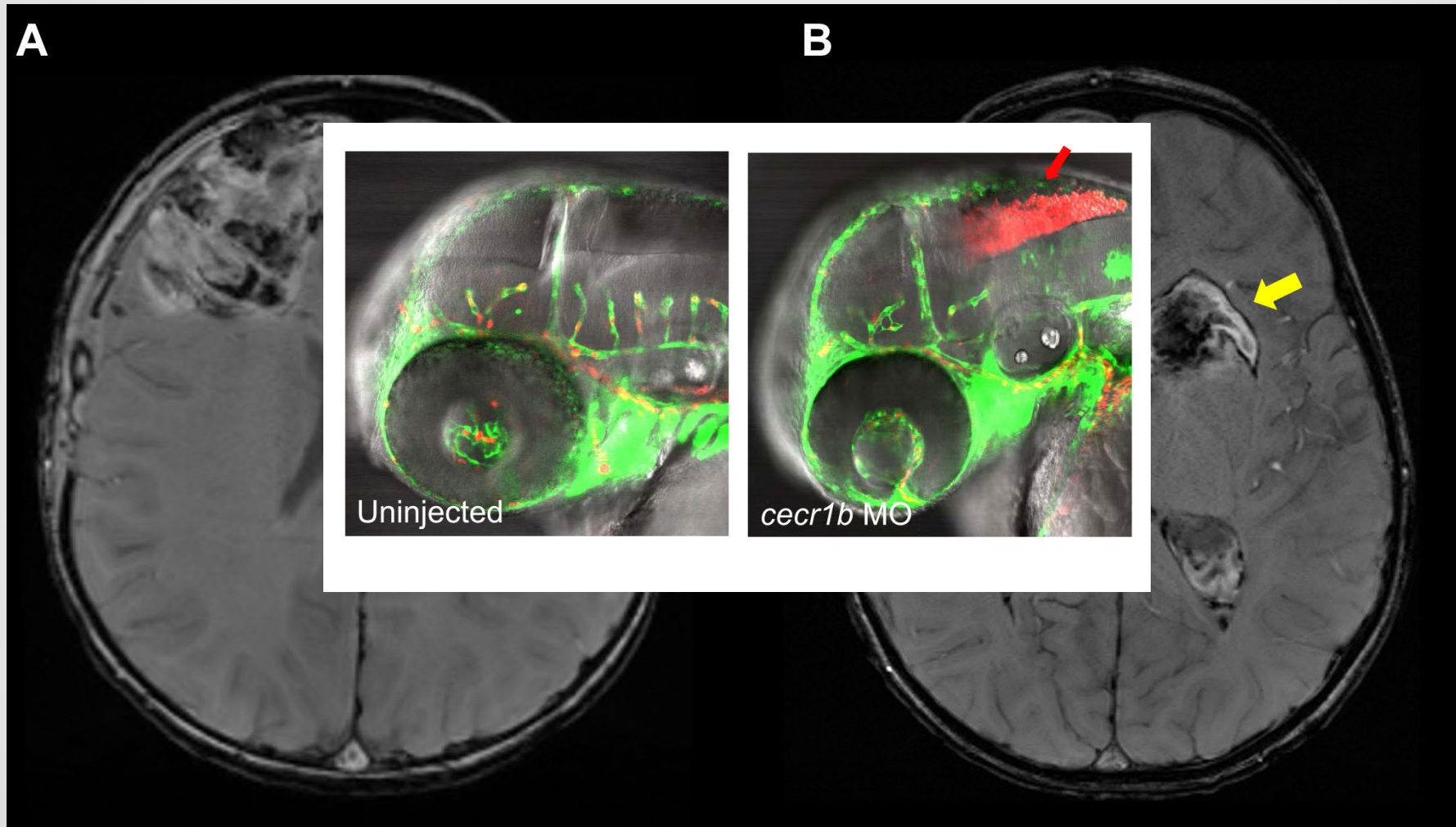


Ischemic Strokes

- Lacunar strokes



Hemorrhagic Strokes in DADA2



Peripheral Vascular Disease in DADA2

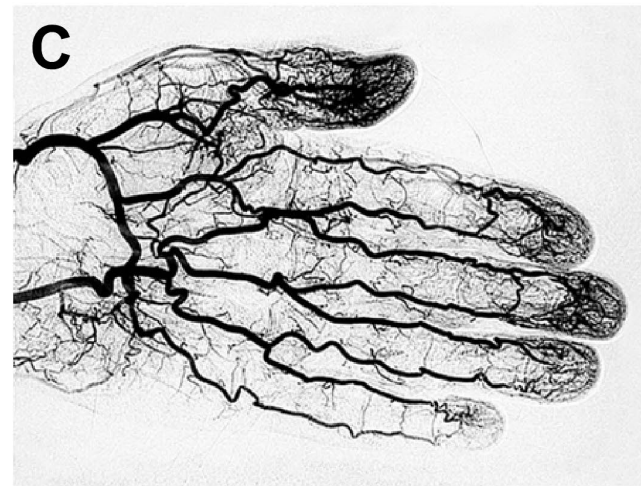


Zhou et al. *NEJM*, 2014



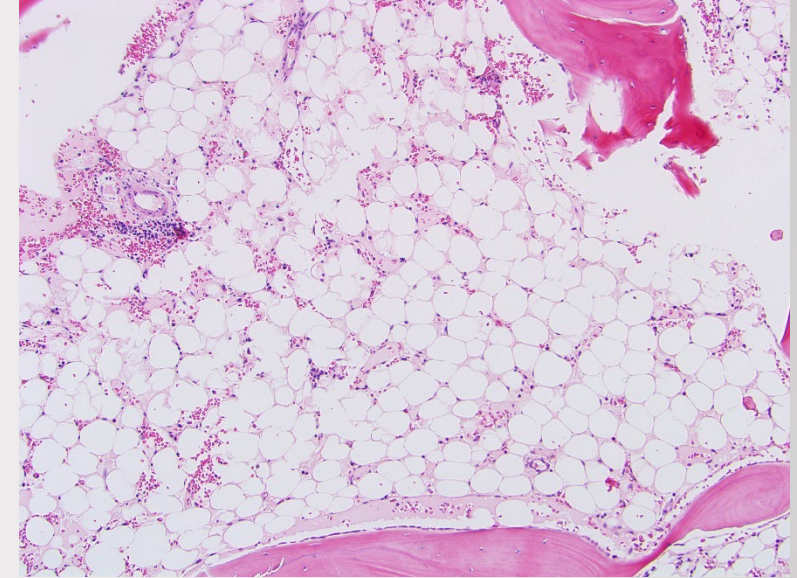
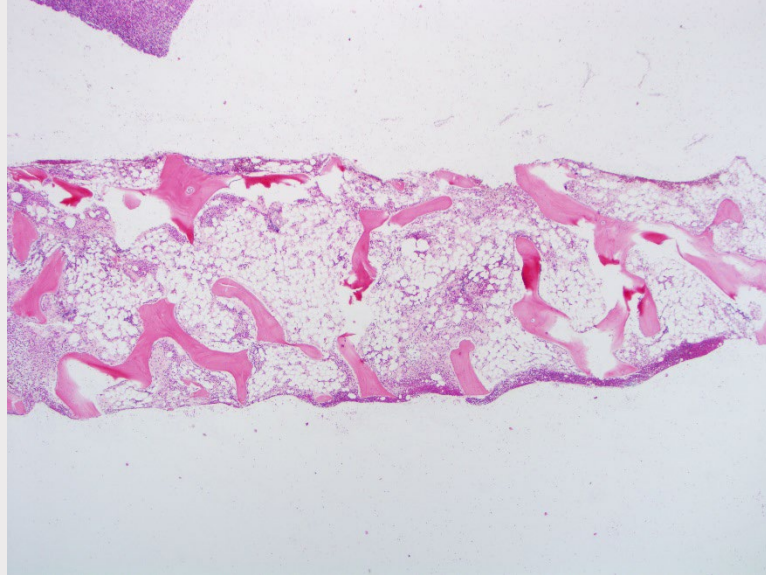
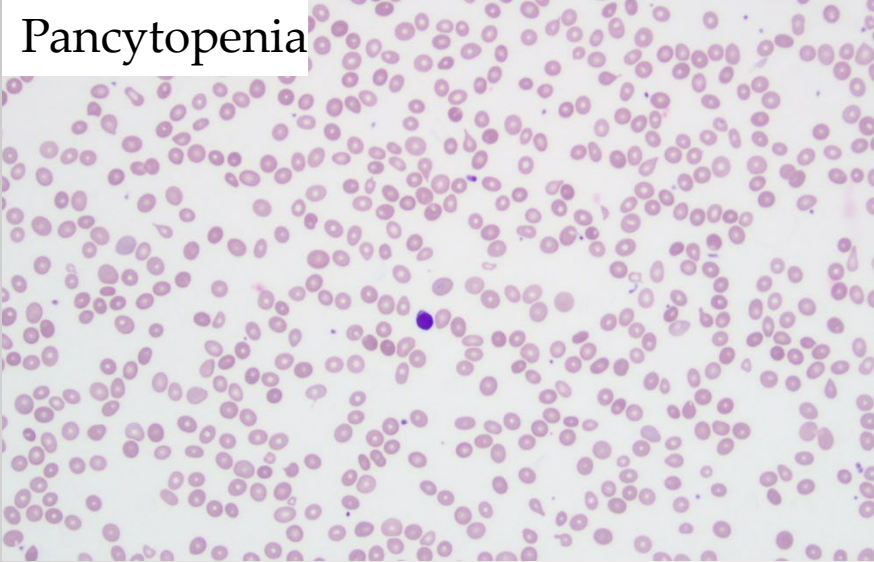
Navon-Elkan et al, *NEJM*, 2014

Peripheral Vascular Disease in DADA2

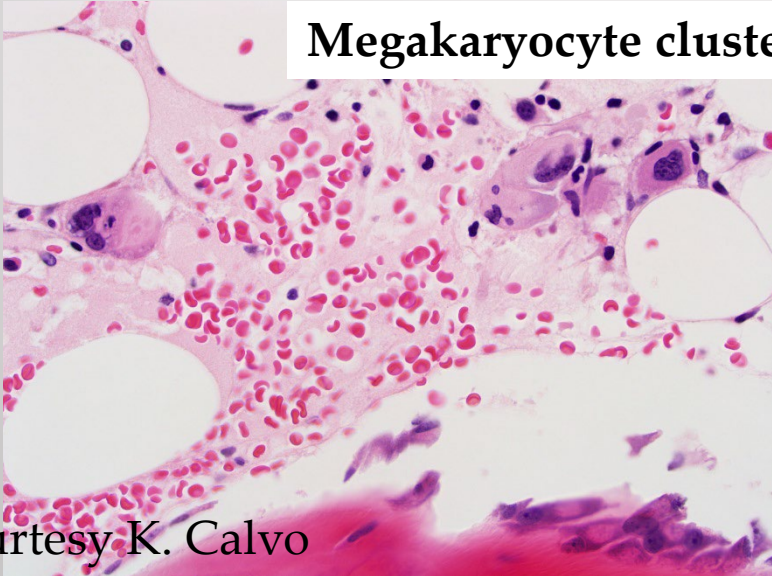


The Hypocellular Model (trilineage failure)

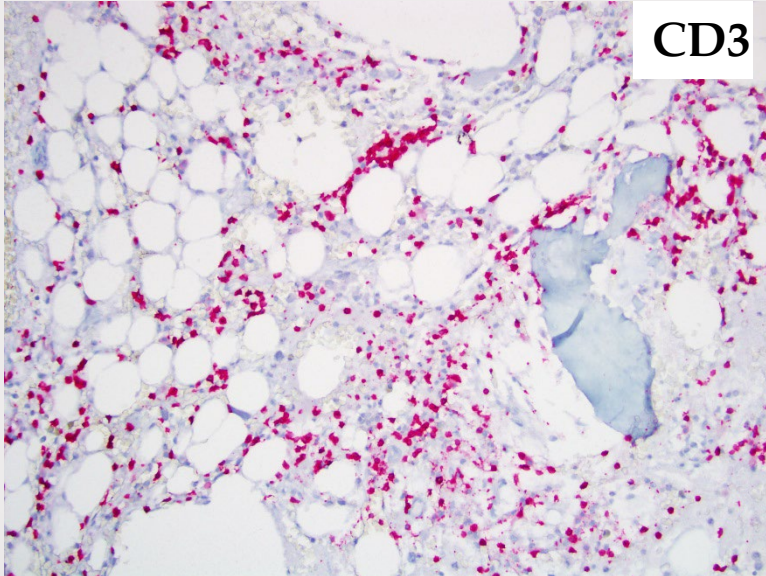
Pancytopenia



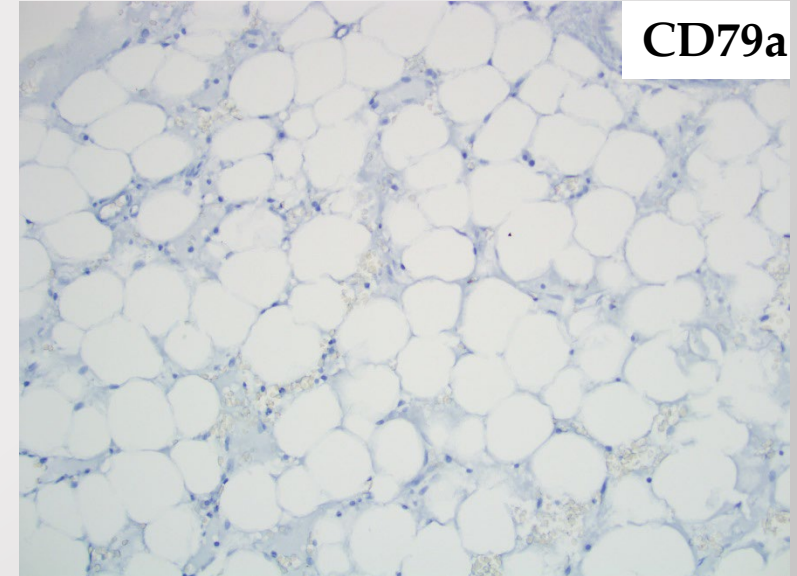
Megakaryocyte clusters



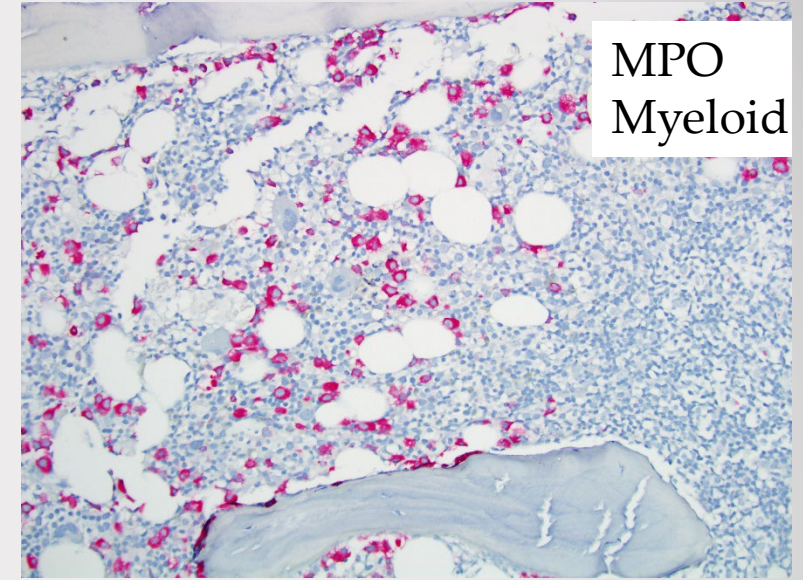
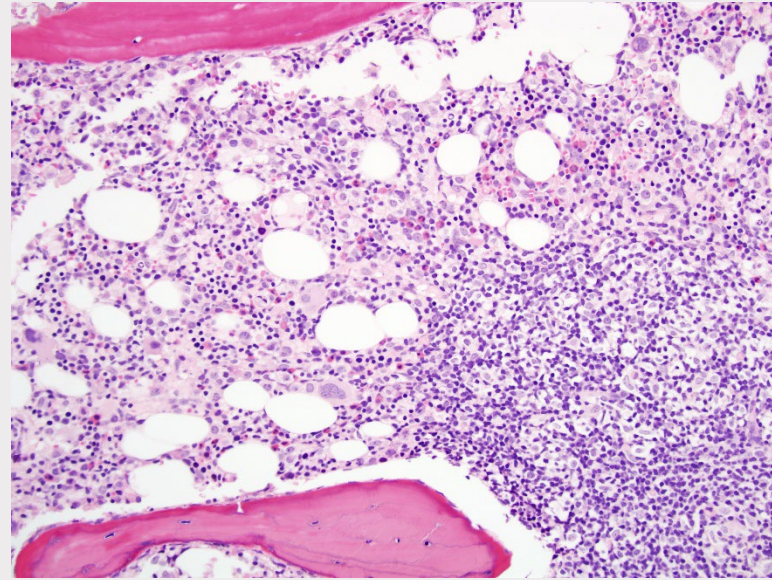
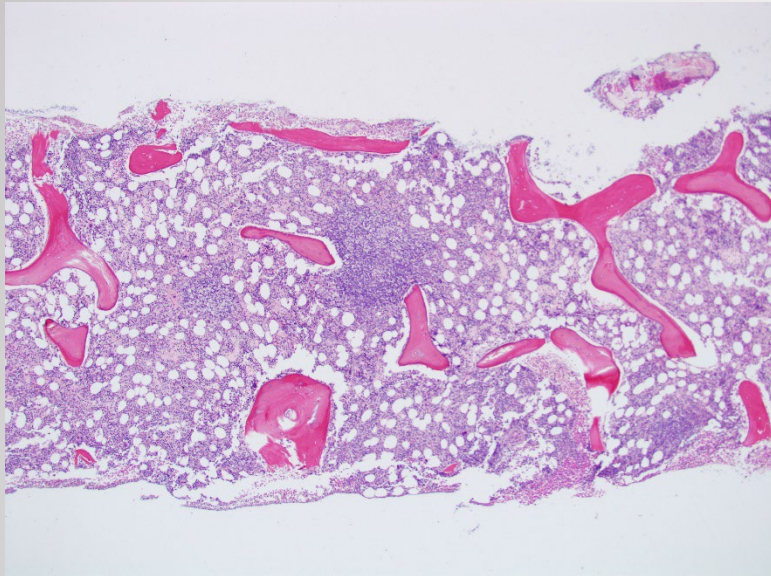
CD3



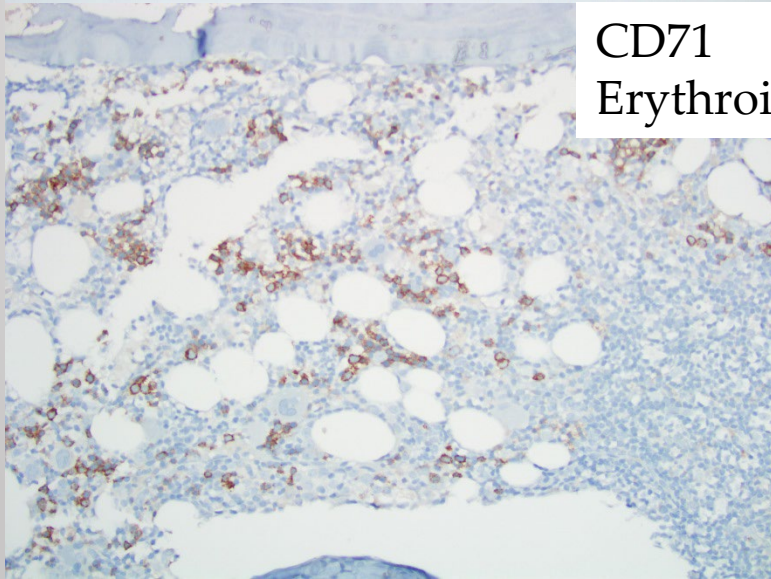
CD79a



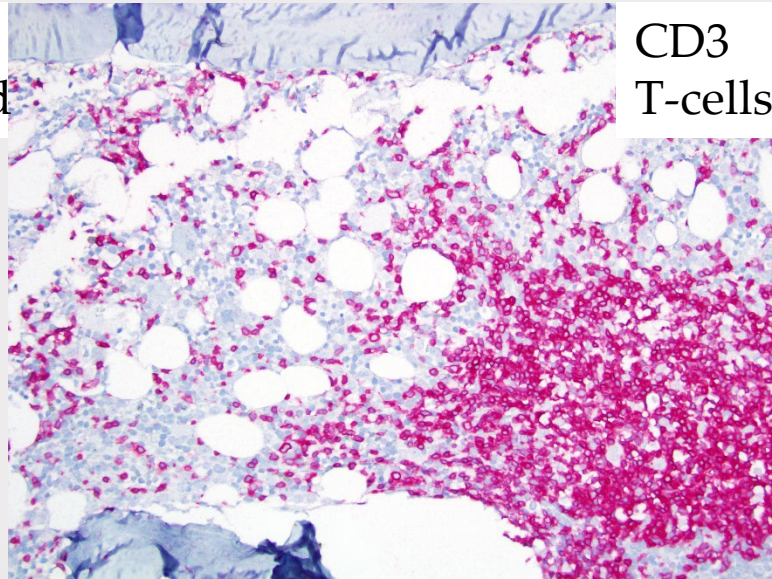
The Hypercellular/Inflammatory Model



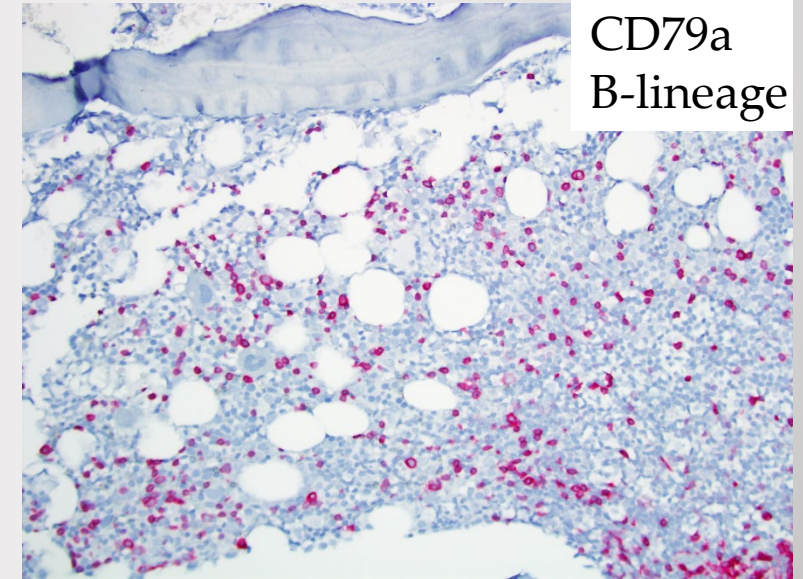
MPO
Myeloid



CD71
Erythroid



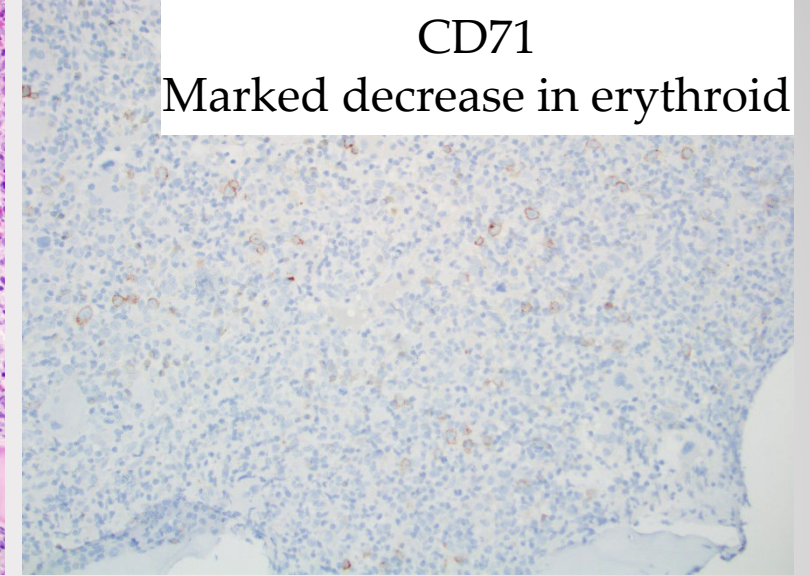
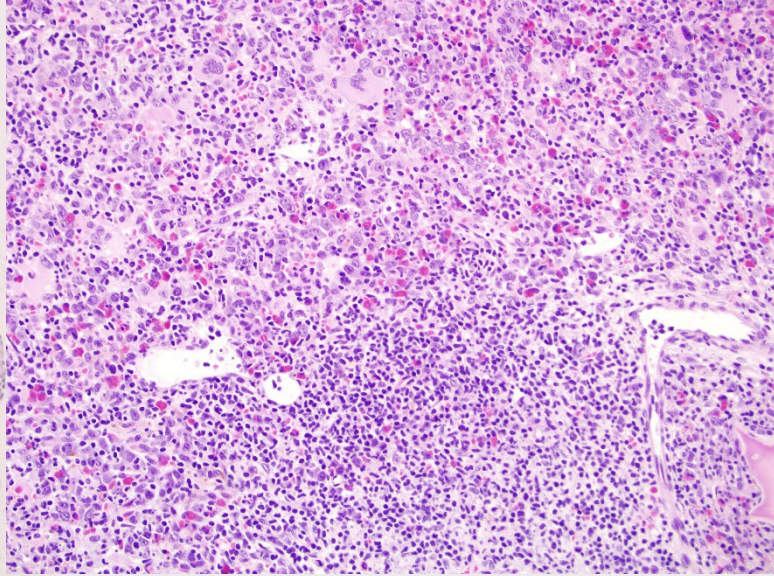
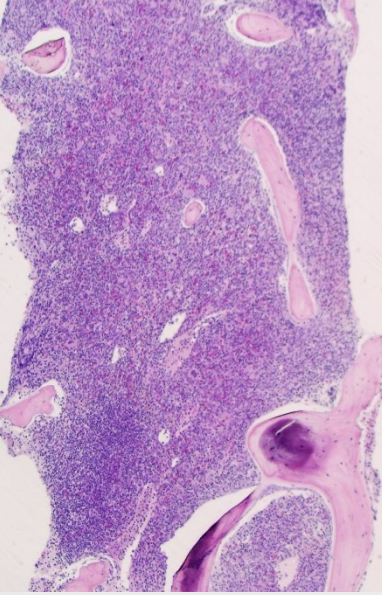
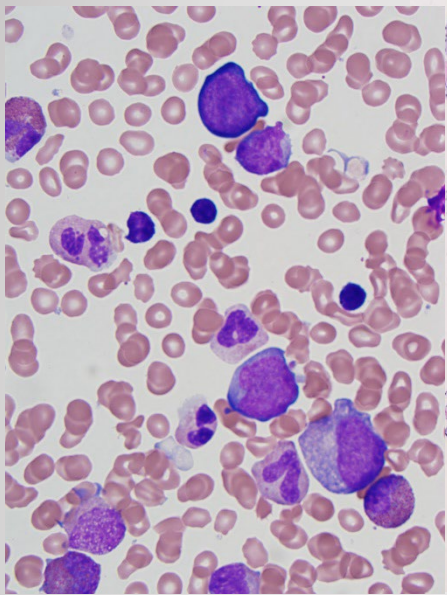
CD3
T-cells



CD79a
B-lineage

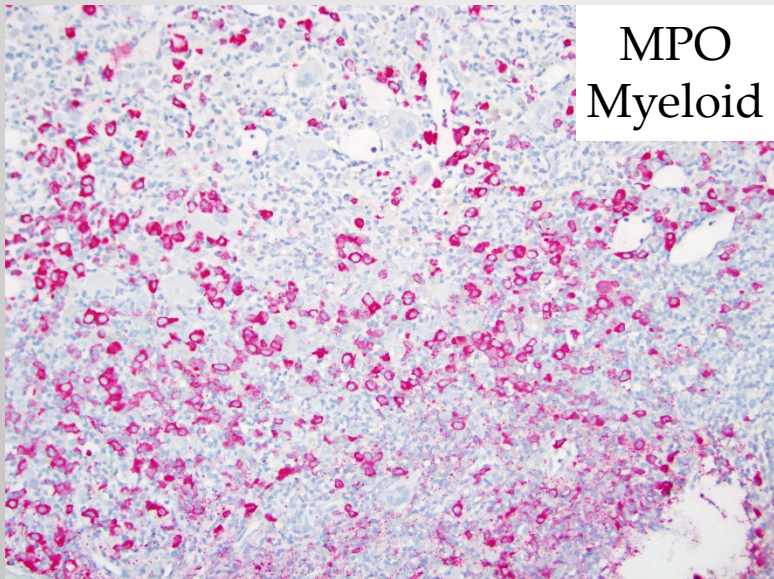
The Combination Marrow

Pure Red Cell Aplasia + Immune Mediated Neutropenia

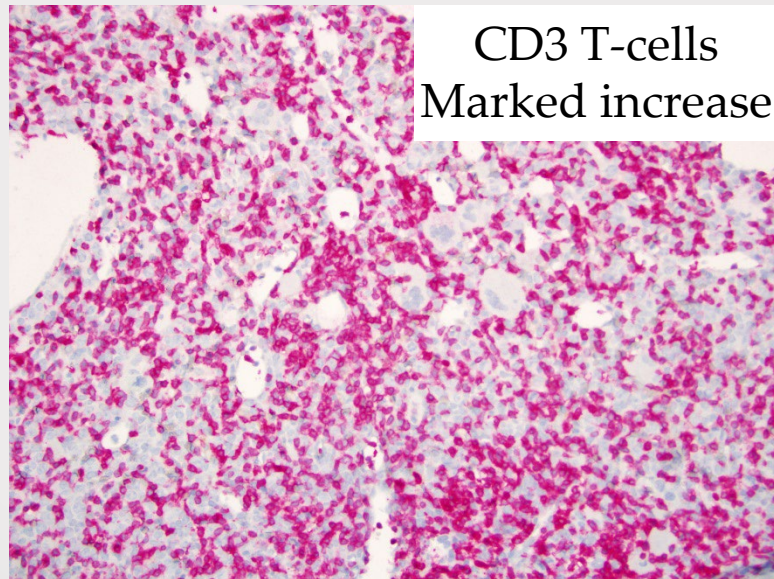


CD71

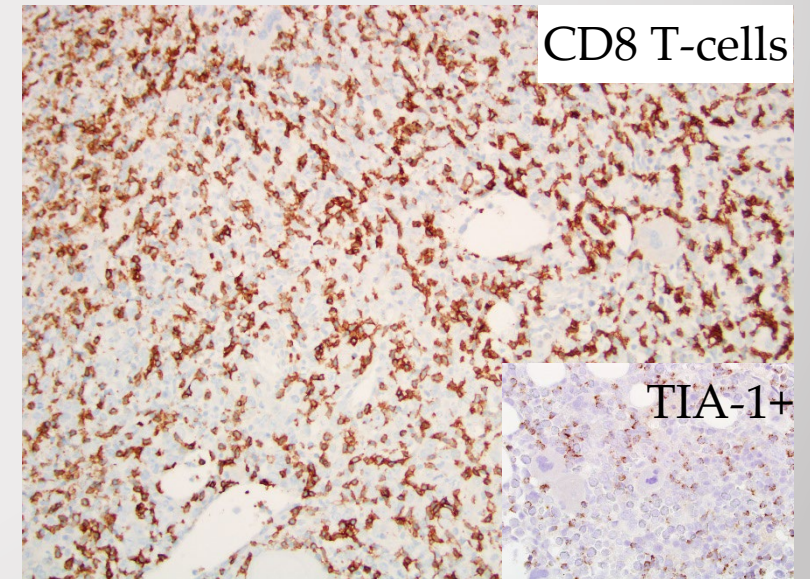
Marked decrease in erythroid



MPO
Myeloid



CD3 T-cells
Marked increase



CD8 T-cells

TIA-1+

Treatment of DADA2

- Anti-TNF Agents
- Highly protective in DADA2 patients with a history of stroke
- Ombrello et al, *NEJM*, 2019

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CORRESPONDENCE

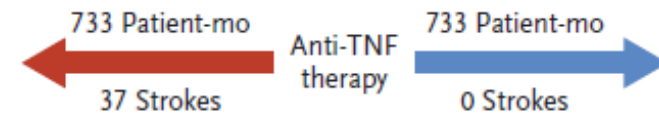


Treatment Strategies for Deficiency of Adenosine Deaminase 2

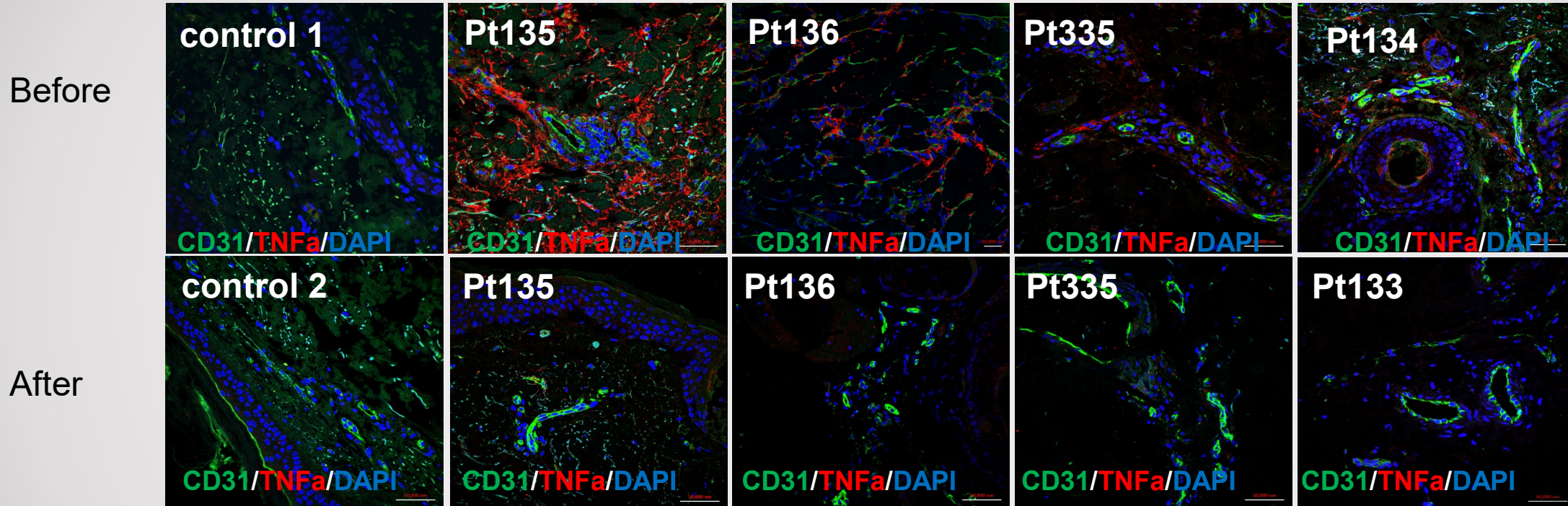
B No. of Strokes and Recurrence Rate in 15 Study Patients

	Patient-Mo	No. of Strokes	Recurrence Rate
Before Anti-TNF Initiation	2077	55	0.025
After Anti-TNF Initiation	733	0	0.000

C No. of Strokes in 15 Study Patients with Matched Timeline

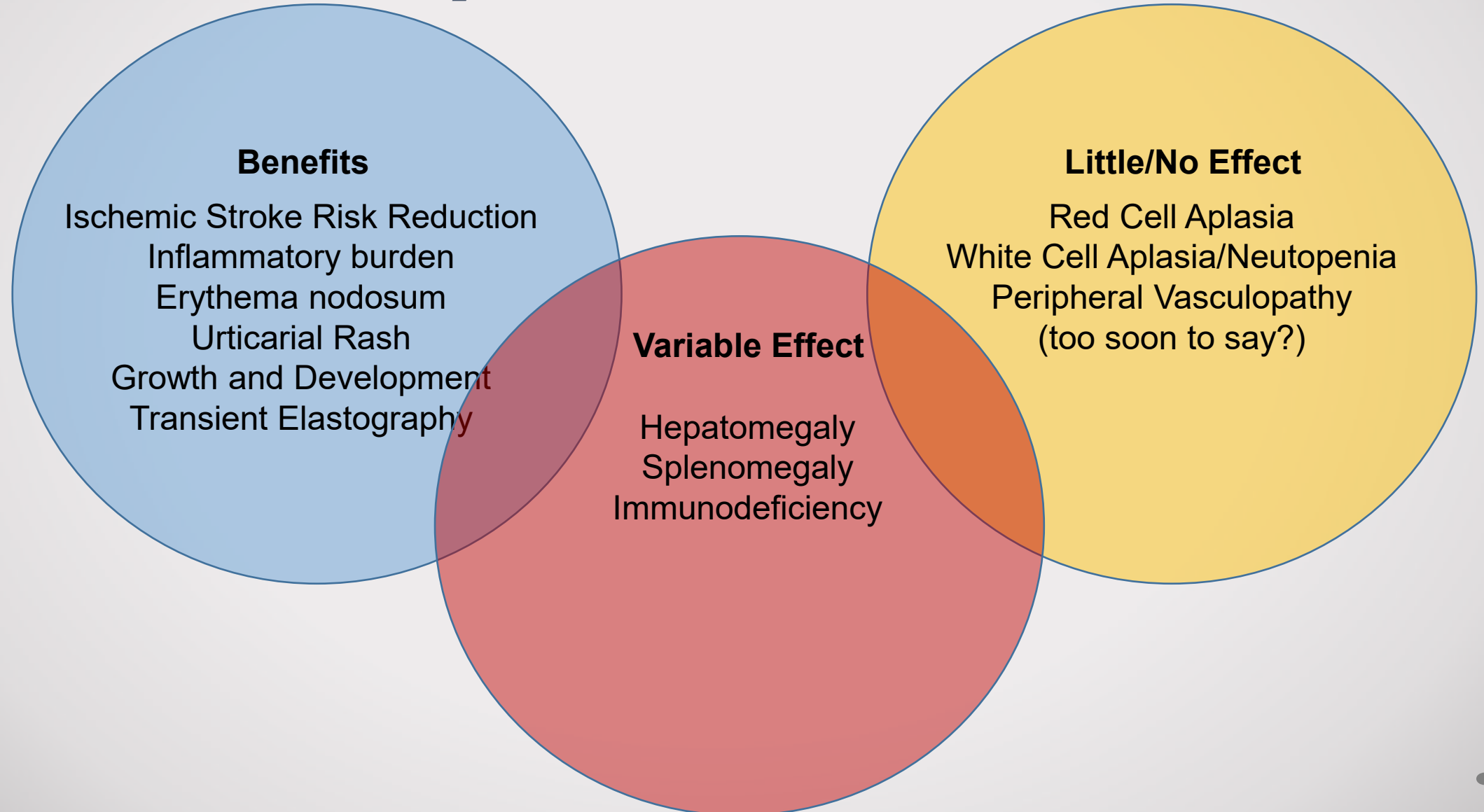


Immunologic Effects of Anti-TNF Treatment in DADA2



Deutch et al., *J Allergy Clin Immunol*, 2022

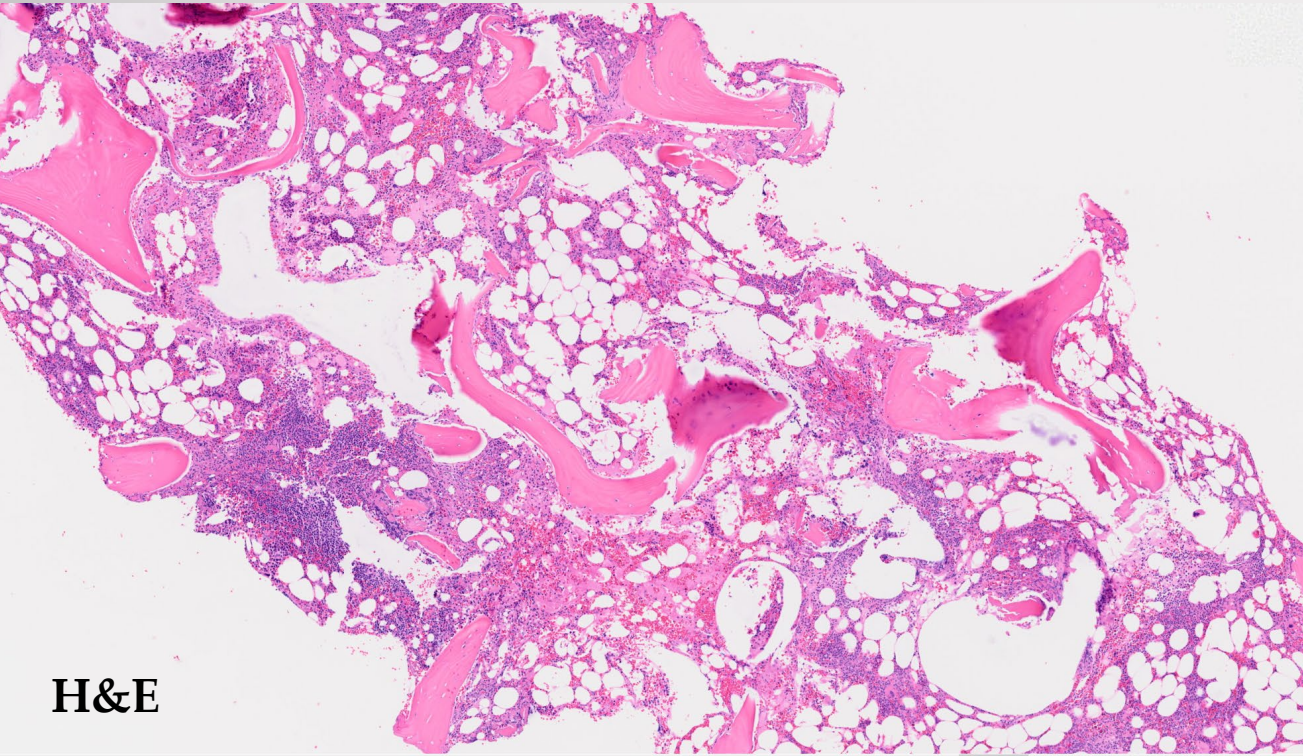
Summary of Anti-TNF Effects



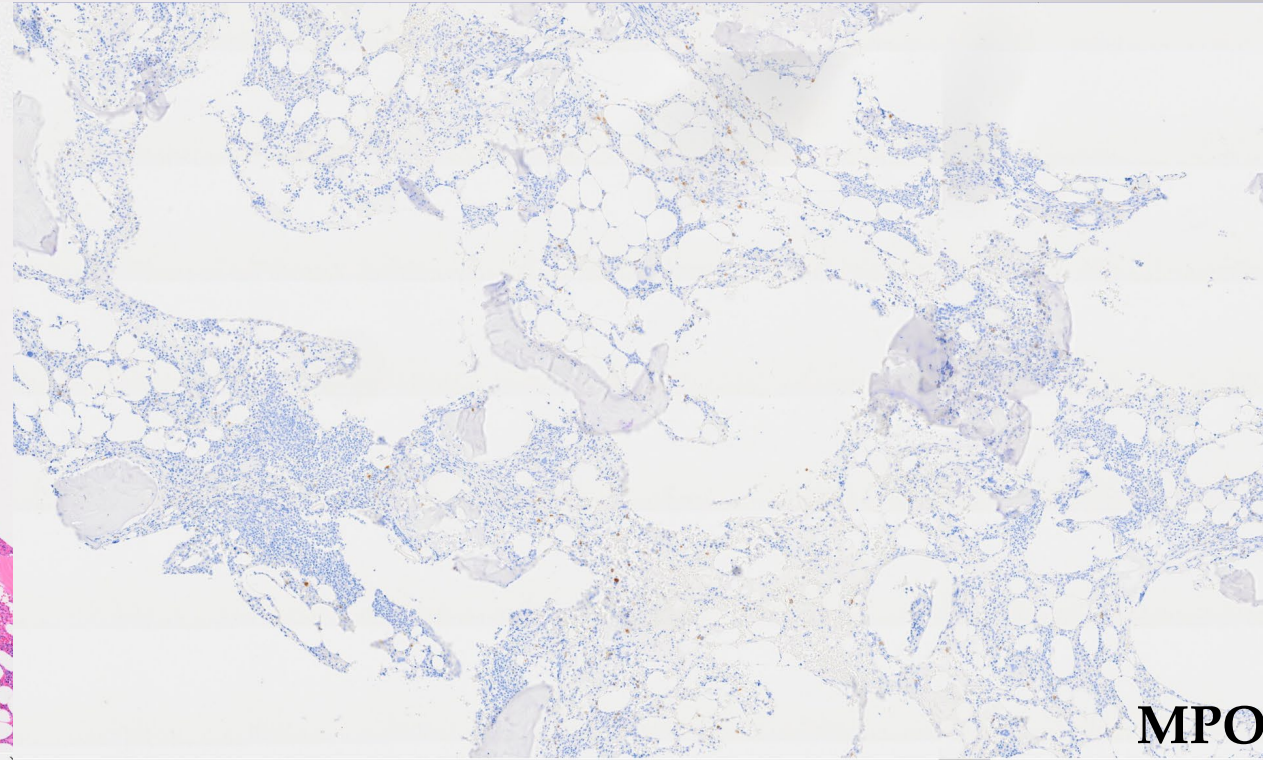
But what about the hematologic
manifestations?

...

57-year-old female with DADA2 and severe neutropenia, ANC=0.0 K/mcL

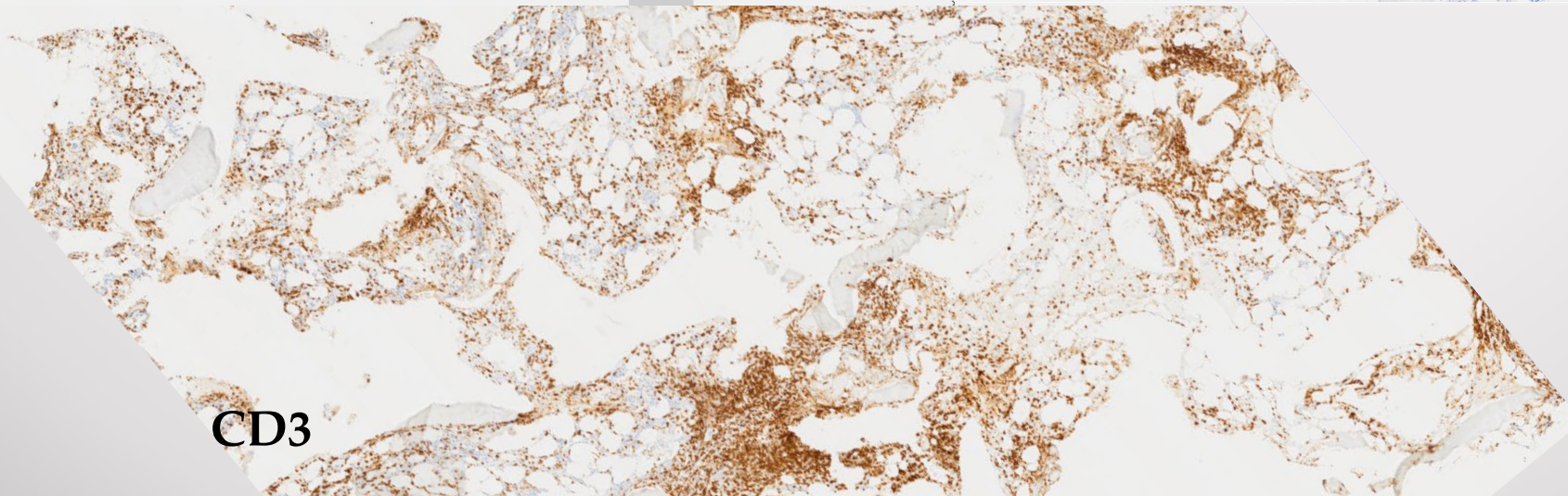


H&E



MPO

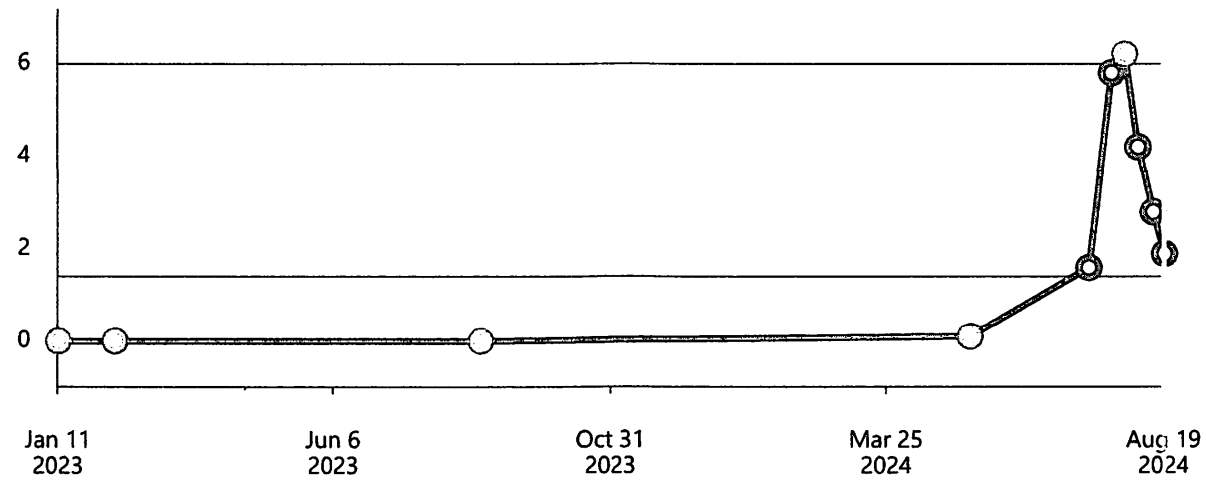
Myeloid aplasia



CD3

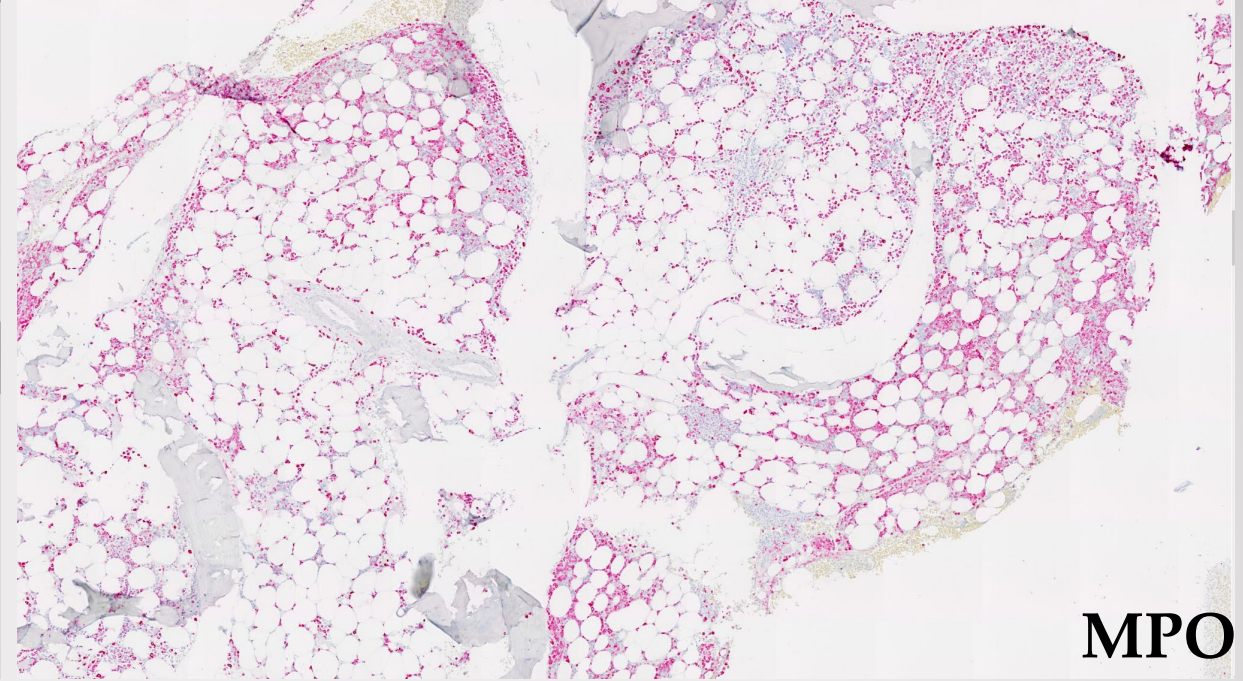
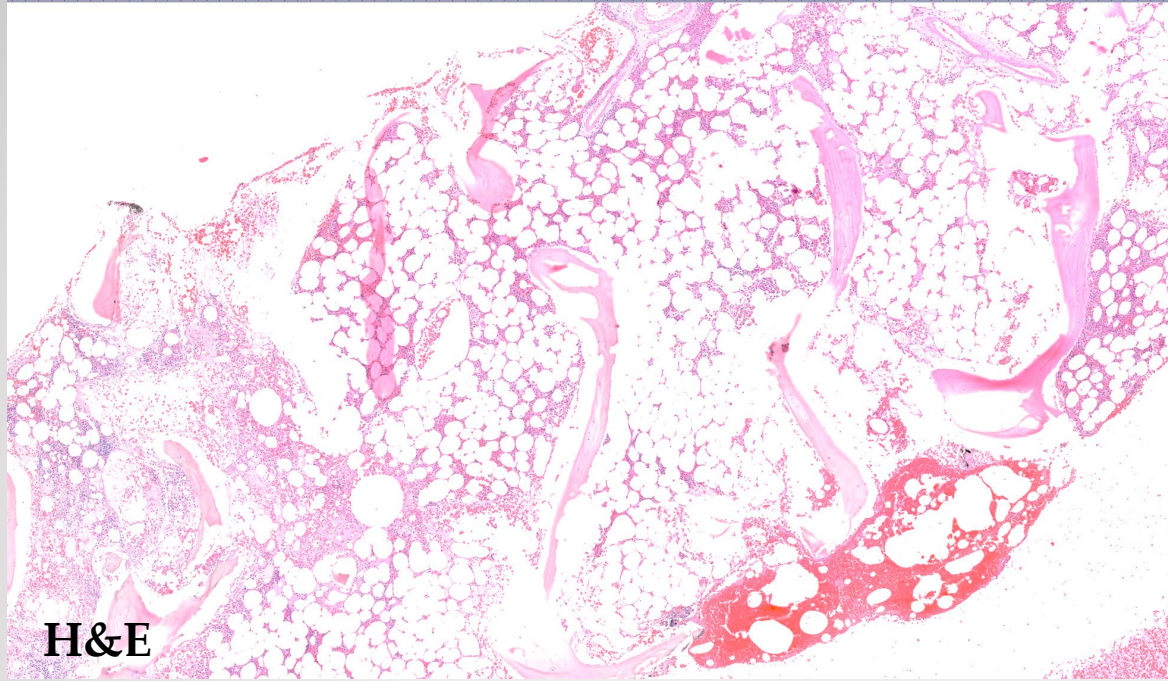
ANC

Normal range: 1.4 - 6.0 K/uL

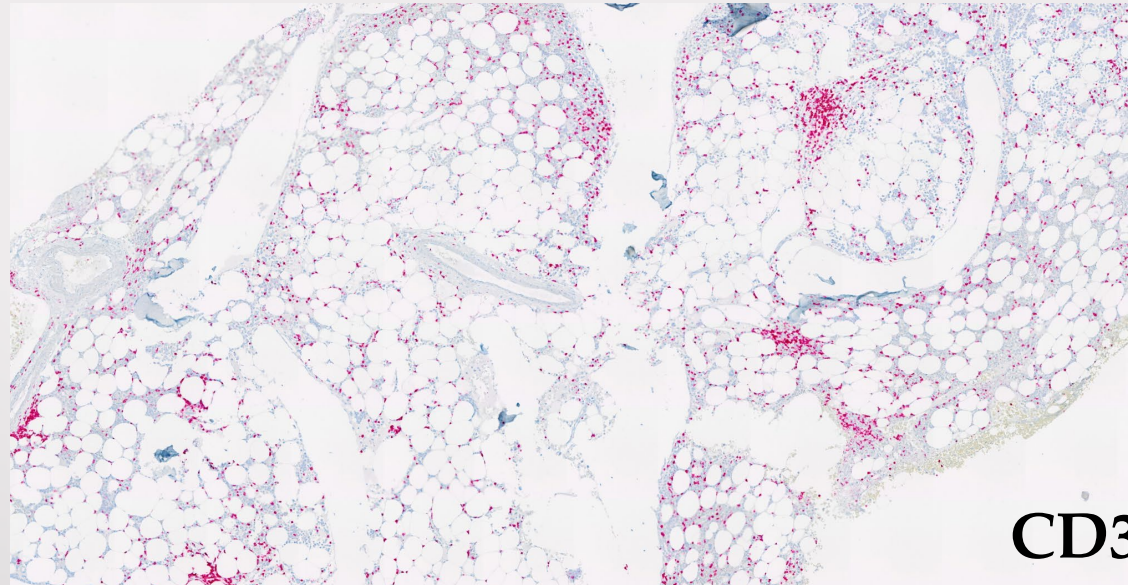


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After treatment with anti-TNF, cyclosporine, prednisone 10 mg ANC 1.96 K/mcL



Restoration of myelopoiesis



How Many People Have DADA2?

- NIH Cohort: 80 patients
- Worldwide: Approximately 600-700 cases

Comprehensive analysis of *ADA2* genetic variants and estimation of carrier frequency driven by a function-based approach

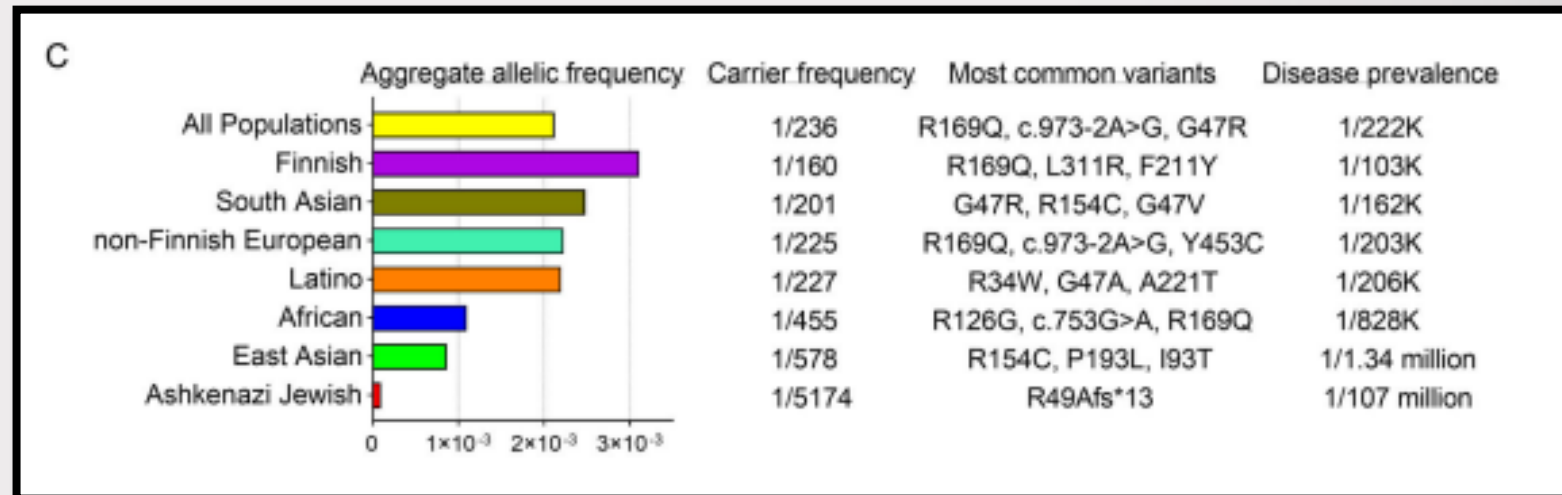
Hyuk Jee, BS^{#1}, Zhengping Huang, MD^{#2,3}, Samantha Baxter, MS CGC⁴, Yuelong Huang, PhD³, Maria L. Taylor, BS¹, Lauren A. Henderson, MD, MMsc¹, Sofia Rosenzweig, BS⁵, Aman Sharma, MD FRCP⁶, Eugene P. Chambers, MD^{7,8}, Michael S. Hershfield, MD⁹, Qing Zhou, PhD¹⁰, Fatma Dedeoglu, MD¹, Ivona Aksentijevich, MD⁵, Peter A. Nigrovic, MD^{1,3}, Anne O'Donnell-Luria, MD PhD^{4,11}, Pui Y. Lee, MD PhD^{1,3,#}

Jee, *J Allergy Clin Immunol*, 2022



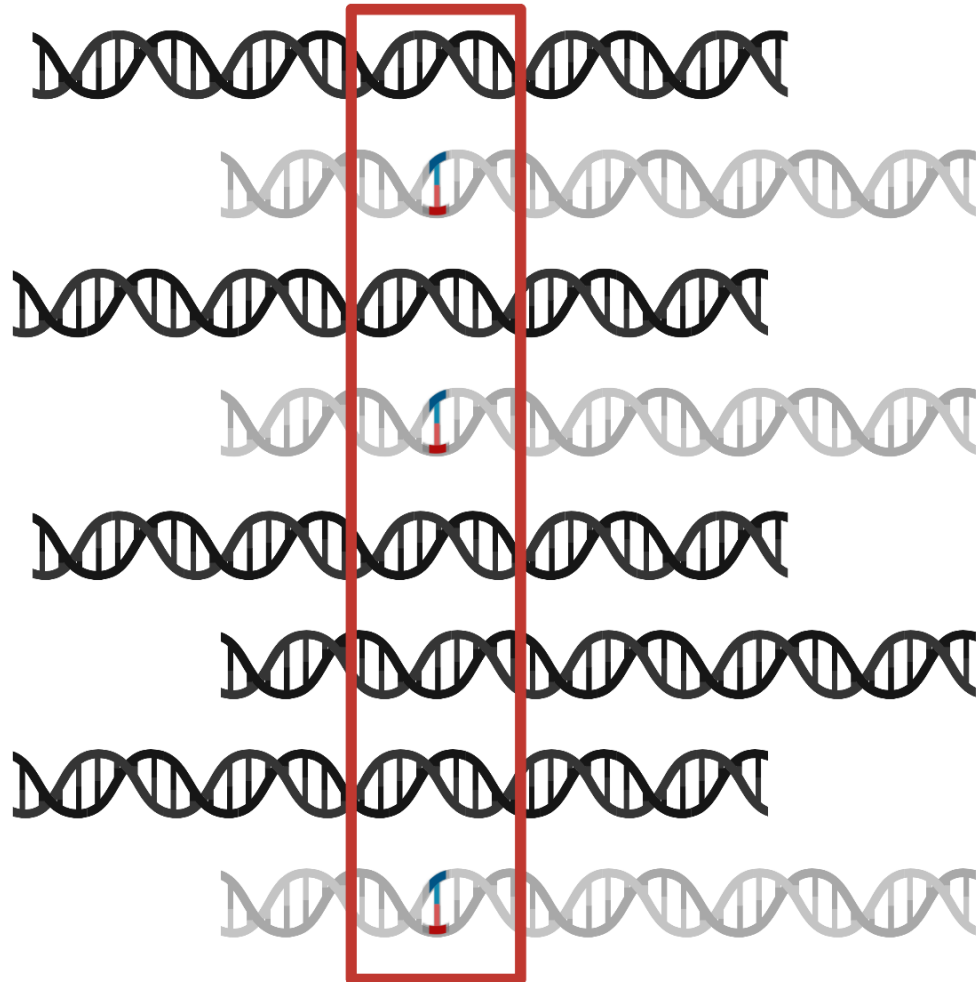
How Many People Have DADA2?

- Carrier Rate:
 - 1:236 individuals
- Disease Prevalence:
 - 1:222,164
- WORLDWIDE CASES:
 - 30,000



Jee, *J Allergy Clin Immunol*, 2022

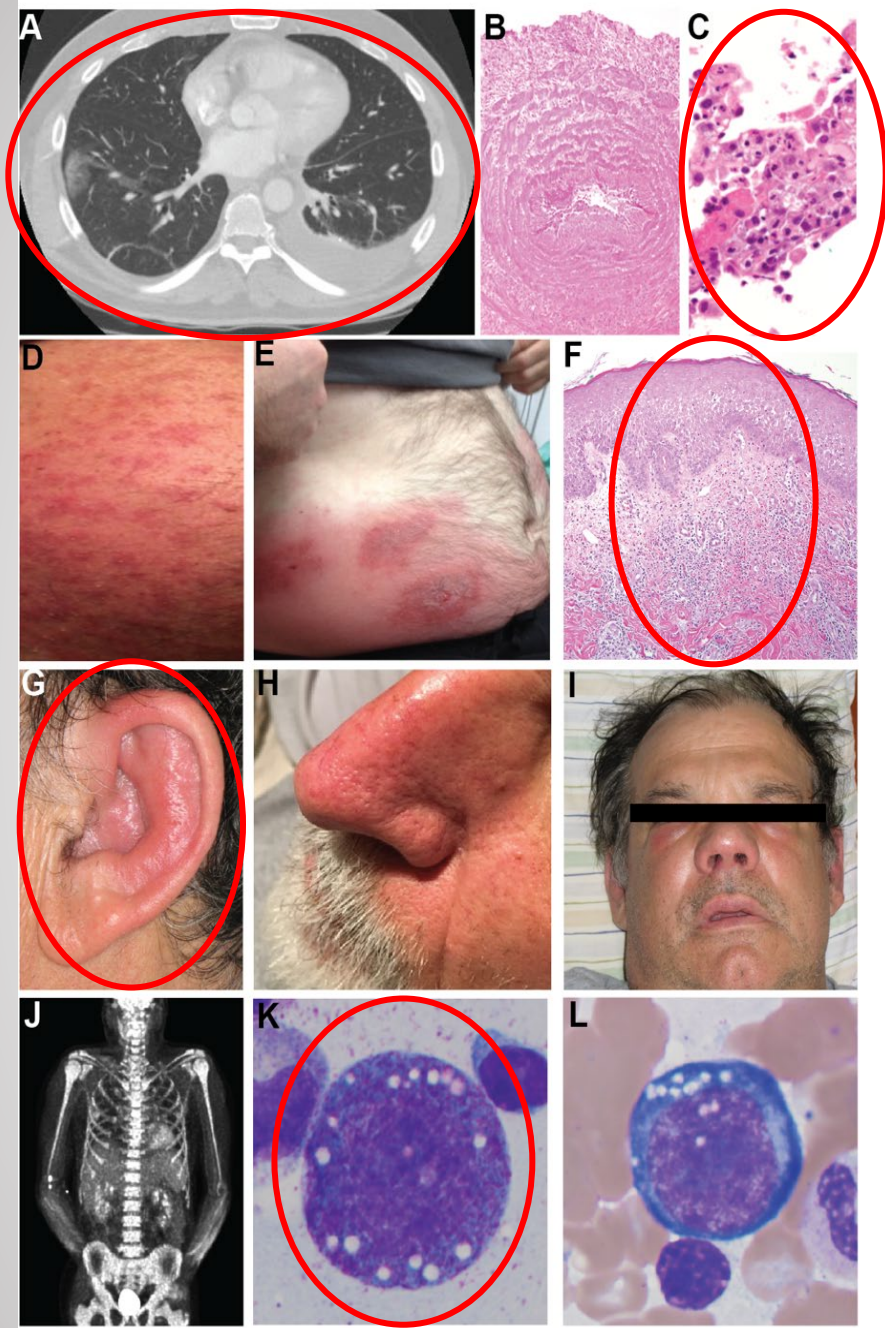
Genotype-First Approach



ORIGINAL ARTICLE

Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar, L. Xu, H. Oda, W. Goodspeed, K.S. Barron, M. Nehrebecky, A. Jones, R.S. Laird, N. Deutch, D. Rowczenio, E. Rominger, K.V. Wells, C.-C.R. Lee, W. Wang, M. Trick, J. Mullikin, G. Wigerblad, S. Brooks, S. Dell'Orso, Z. Deng, J.J. Chae, A. Dulau-Florea, M.C.V. Malicdan, D. Novacic, R.A. Colbert, M.J. Kaplan, M. Gadina, S. Savic, H.J. Lachmann, M. Abu-Asab, B.D. Solomon, K. Retterer, W.A. Gahl, S.M. Burgess, I. Aksentijevich, N.S. Young, K.R. Calvo, A. Werner, D.L. Kastner, and P.C. Grayson



V

acuoles

E

1 ubiquitin-activating enzyme

X

- linked

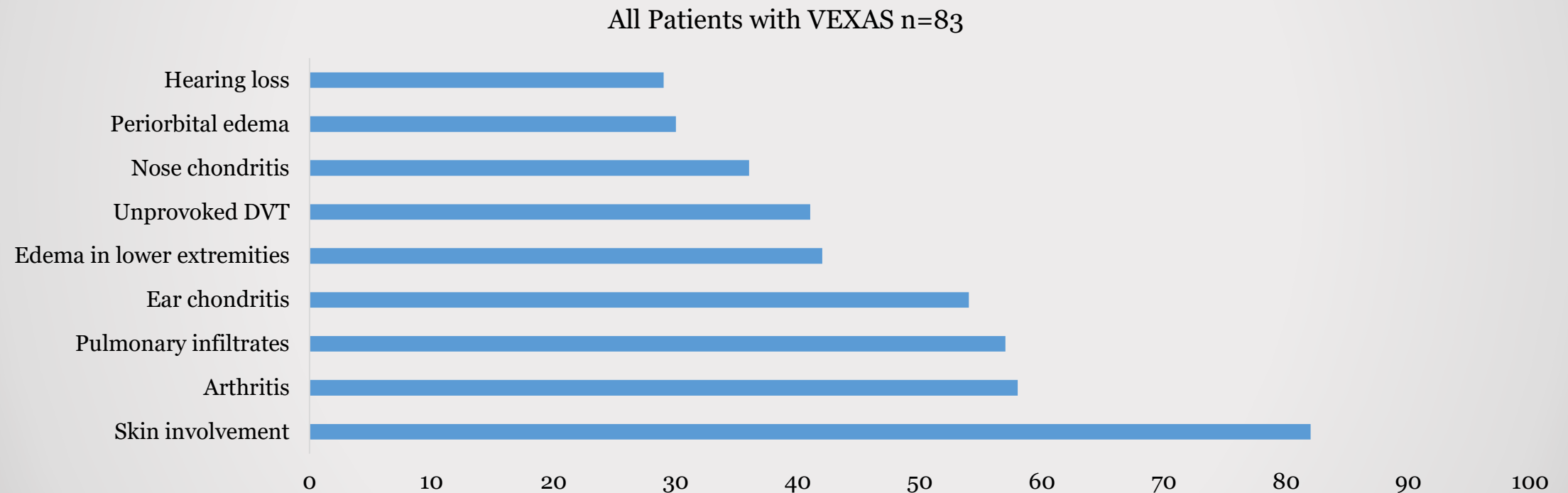
A

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S

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Clinical Manifestations of All VEXAS Patients



Treatments

- Responsive to steroids
 - Increase dose as disease progresses
 - Glucocorticoids = long term side effects
- Partially Responsive:
 - Tocilizumab: temporizing steroid sparing effects (Japan & NIH)
 - JAKi: Ruxolitinib (French & NIH)
 - Hypomethylating agents (azacitidine) if bone marrow involvement
- Avoid use of IL-1 inhibitors (i.e. anakinra) = severe skin reactions at injection site
- Transplant

Summary

- Think autoinflammatory when patients have recurrent febrile episodes with other systemic symptoms that are not explained by infection/autoimmune/malignancy
- Think autoinflammatory when the diagnosis doesn't fit (JIA/PAN/SLE)—round pegs in square holes
- Detailed family history
- Consider genetic testing (candidate gene vs panel vs whole exome/genome sequencing)
- Common treatments include glucocorticoids, cytokine inhibitors

Take-Home Message

- Don't get overwhelmed, you are not alone!
- Feel free to reach out to me at anytime!
 - Amanda.Ombrello@nih.gov





Patrycja Hoffmann
NHGRI



Lorena Wilson
NHGRI



Deb Stone
NHGRI



Natalie Deutch
NHGRI



Tina Romeo
NHGRI



Dan Kastner
NHGRI

The NIH DADA2 Team

Camilo Toro

Ariane Soldatos

Theo Heller

Jenna Bergerson

Dimana Dimitrova

Kathy Calvo

Ivona Aksentijevich