Horror Autoinflammaticus: Autoimmune Disease Research in the NHGRI Intramural Research Program

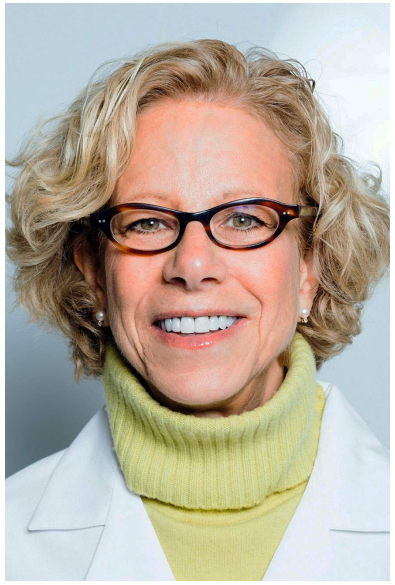
Dan Kastner, MD, PhD
Scientific Director, Division of Intramural Research
National Human Genome Research Institute, NIH
March 4, 2021

Essentials of the NIH Intramural Research Program

- Budgets appropriated by Congress and administered through the Institutes/Centers
- Institutional commitment to researchers over projects
- Rigorous quadrennial heavily retrospective review by Boards of Scientific Counselors
- Long-term studies that require stable funding
- High-risk, high-reward projects that would be difficult to do with R01 funding
- Specialized resources

Nuts and Bolts of the NHGRI IRP

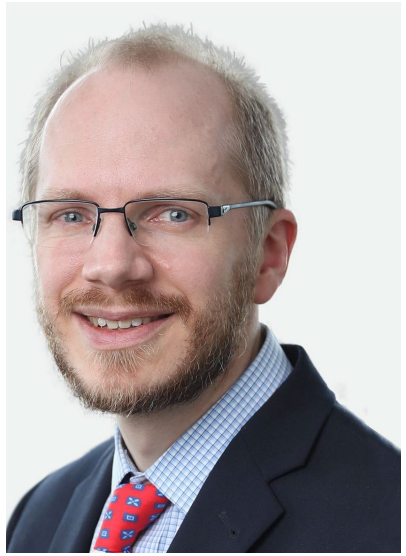
- 24 Tenured Senior-Investigators, 3 Tenure-Track Investigators, 3 Senior Scientists, 2 Senior Clinicians, 12 Associate Investigators, 9 Adjunct Investigators, 1 Scientist Emeritus
- ~ 625 total staff
- FY2020 appropriated budget of ~$120.7M
- 7 buildings on the NIH campus, plus off-campus facilities in Rockville and Baltimore



Diana Bianchi

Les Biesecker

Francis Collins



Josh Denny

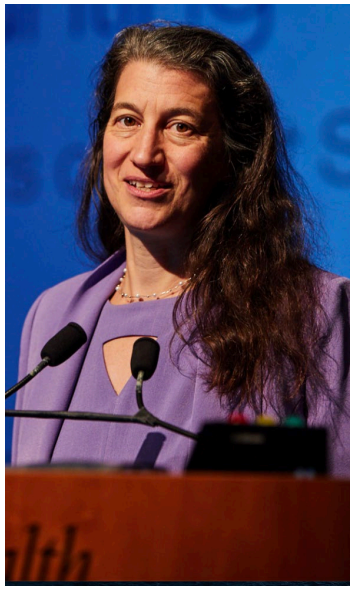
Bill Gahl

Gary Gibbons

Dan Kastner

Elaine Ostrander

Charles Rotimi



Julie Segre

Our Newest Senior Faculty Member

Lindsey A. Criswell, MD, MPH, DSc
Director, NIAMS

Our Newest Tenure-Track Investigator

Neil A. Hanchard, MBBS, D Phil

The Future of Genomics

Adam Phillippy, PhD

Two Flavors of Immunity

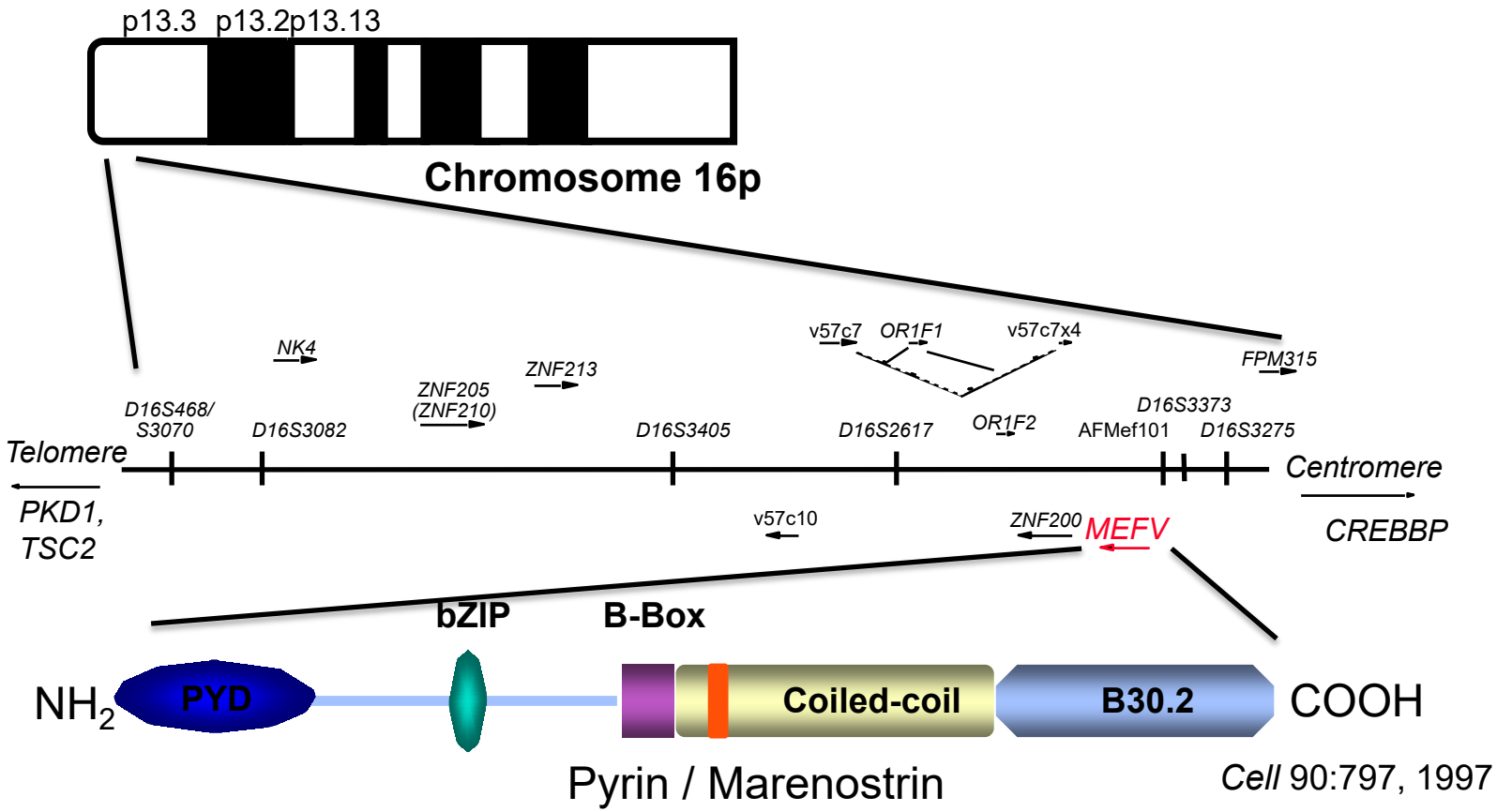
Adaptive Immunity

- T and B lymphocytes are the major players
- Receptors somatically rearrange and mutate
- Autoimmune diseases characterized by high-titer autoantibodies and/or antigen-specific T cells

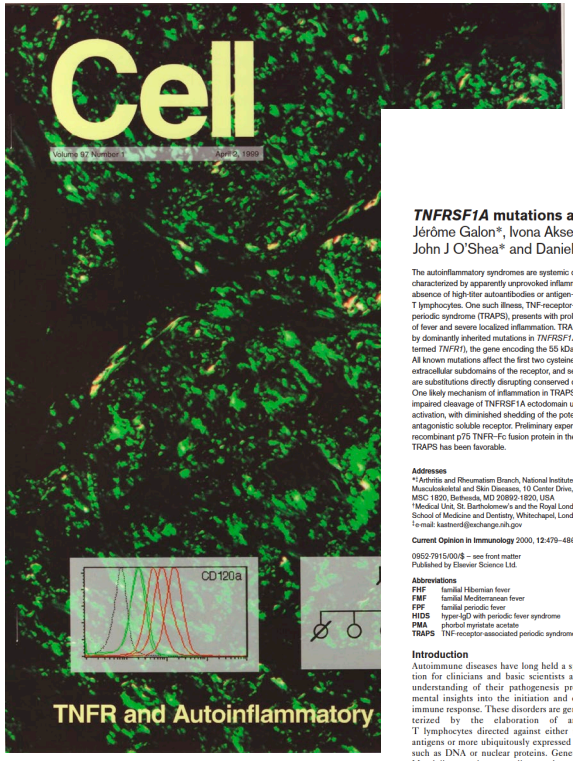
Innate Immunity

- Myeloid-lineage cells are the major effectors
- Receptors are hard-wired in the germline genome
- Autoinflammatory diseases are characterized by seemingly unprovoked inflammation without high-titer autoantibodies or antigen-specific T cells

Positional Cloning of *MEFV,* the Gene Mutated in Familial Mediterranean Fever (FMF)



Cell 90:797, 1997



479

TNFRSF1A mutations and autoinflammatory syndromes

Jérôme Galon*, Ivona Aksentijevich*, Michael F McDermott†, John J O'Shea* and Daniel L Kastner‡

The autoinflammatory syndromes are systemic disorders characterized by apparently unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T lymphocytes. One such illness, TNF-receptor-associated periodic syndrome (TRAPS), presents with prolonged attacks of fever and severe localized inflammation. TRAPS is caused by dominantly inherited mutations in *TNFRSF1A* (formerly termed *TNFR1*), the gene encoding the 55 kDa TNF receptor. All known mutations affect the first two cysteine-rich extracellular subdomains of the receptor, and several mutations are substitutions directly disrupting conserved disulfide bonds. One likely mechanism of inflammation in TRAPS is the impaired cleavage of TNFRSF1A ectodomain upon cellular activation, with diminished shedding of the potentially antagonistic soluble receptor. Preliminary experience with recombinant p75 TNFR–Fc fusion protein in the treatment of TRAPS has been favorable.

Addresses
*†‡ Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, 10 Center Drive, Room 9N228, MSC 1820, Bethesda, MD 20892-1820, USA
†Medical Unit, St. Bartholomew's and the Royal London Hospital School of Medicine and Dentistry, Whitechapel, London E1 1BB, UK
‡e-mail: kastnerd@exchange.nih.gov

Current Opinion in Immunology 2000, **12**:479–486

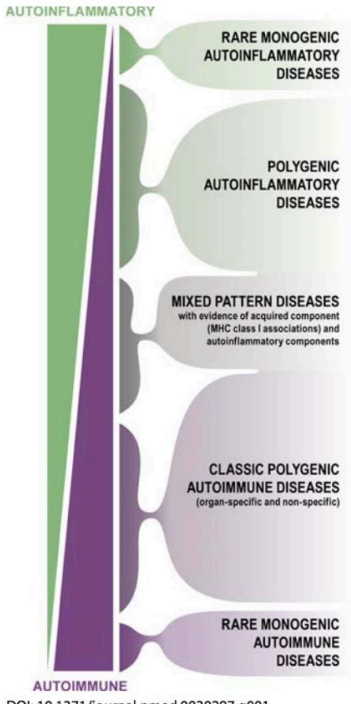
0952-7915/00/$ – see front matter
Published by Elsevier Science Ltd.

Abbreviations

FHF	familial Hibernian fever
FMF	familial Mediterranean fever
FPF	familial periodic fever
HIDS	hyper-IgD with periodic fever syndrome
PMA	phorbol myristate acetate
TRAPS	TNF-receptor-associated periodic syndrome

Introduction

Autoimmune diseases have long held a special fascination for clinicians and basic scientists alike, since an understanding of their pathogenesis provides fundamental insights into the initiation and control of the immune response. These disorders are generally characterized by the elaboration of antibodies or T lymphocytes directed against either tissue-specific antigens or more ubiquitously expressed determinants, such as DNA or nuclear proteins. Genetic analysis of Mendelian autoimmune diseases has provided new insights into the biologic role of known genes — such as the *Fas* gene in the autoimmune lymphoproliferative syndrome (ALPS) [1–3] — or may uncover heretofore unknown regulatory pathways, as in autoimmunepolyendocrinopathy–candidiasis–ectodermal-dystrophy (APECED) [4,5]. Dissection of genetically more complex autoimmune disorders, such as systemic lupus



DOI: 10.1371/journal.pmed.0030297.g001

ANNUAL REVIEWS **Further**

Click here for quick links to Annual Reviews content online, including:

- Other articles in this volume
- Top cited articles
- Top downloaded articles
- Our comprehensive search

Horror Autoinflammaticus: The Molecular Pathophysiology of Autoinflammatory Disease*

Seth L. Masters,[1] Anna Simon,[2] Ivona Aksentijevich,[1] and Daniel L. Kastner[1]

[1]The National Institute of Arthritis and Musculoskeletal Institutes of Health, Bethesda, Maryland 20892 and Medicine, Radboud University Nijmegen Medical email: masterss@mail.nih.gov, a.simon@aig.umcn.n kastnerd@mail.nih.gov

Annu. Rev. Immunol. 2009. 27:621–68

The *Annual Review of Immunology* is online at immunol.annualreviews.org

This article's doi: 10.1146/annurev.immunol.25.022106.141627

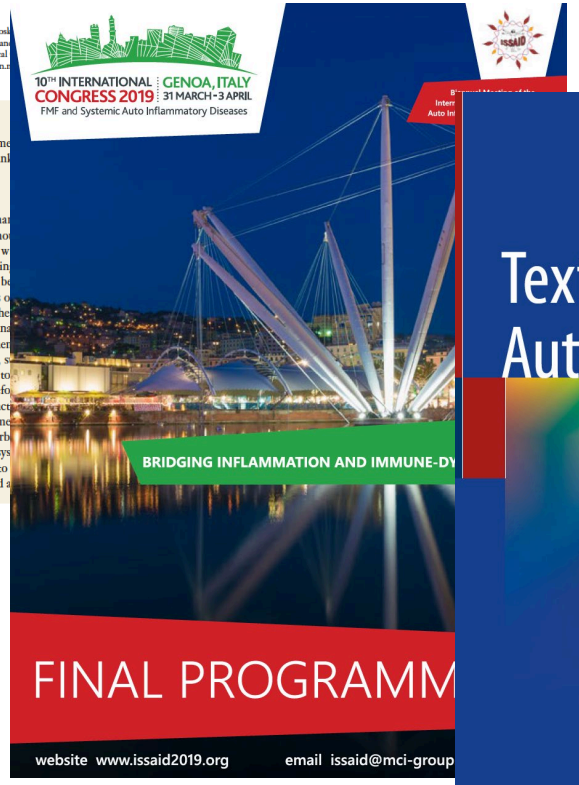
0732-0582/09/0423-0621$20.00

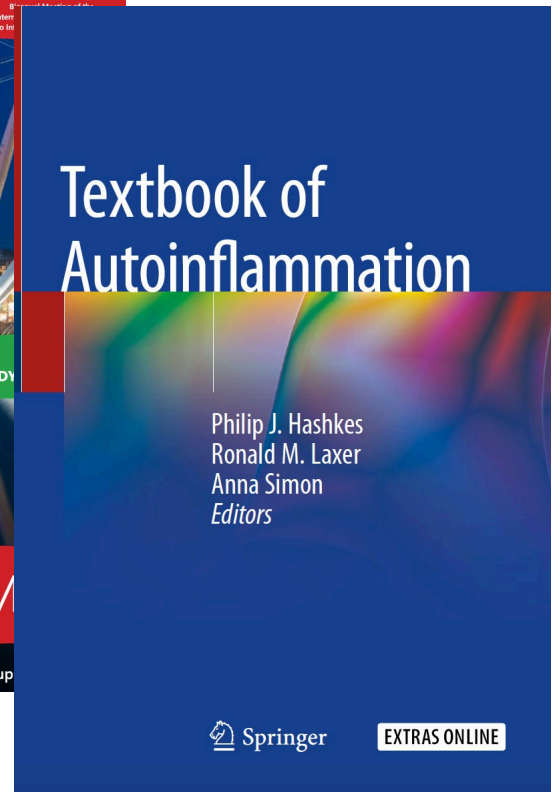
Key Words

innate immunity, IL-1β, inflammasome
pulmonary fibrosis, Crohn's disease, ank
atherosclerosis

Abstract

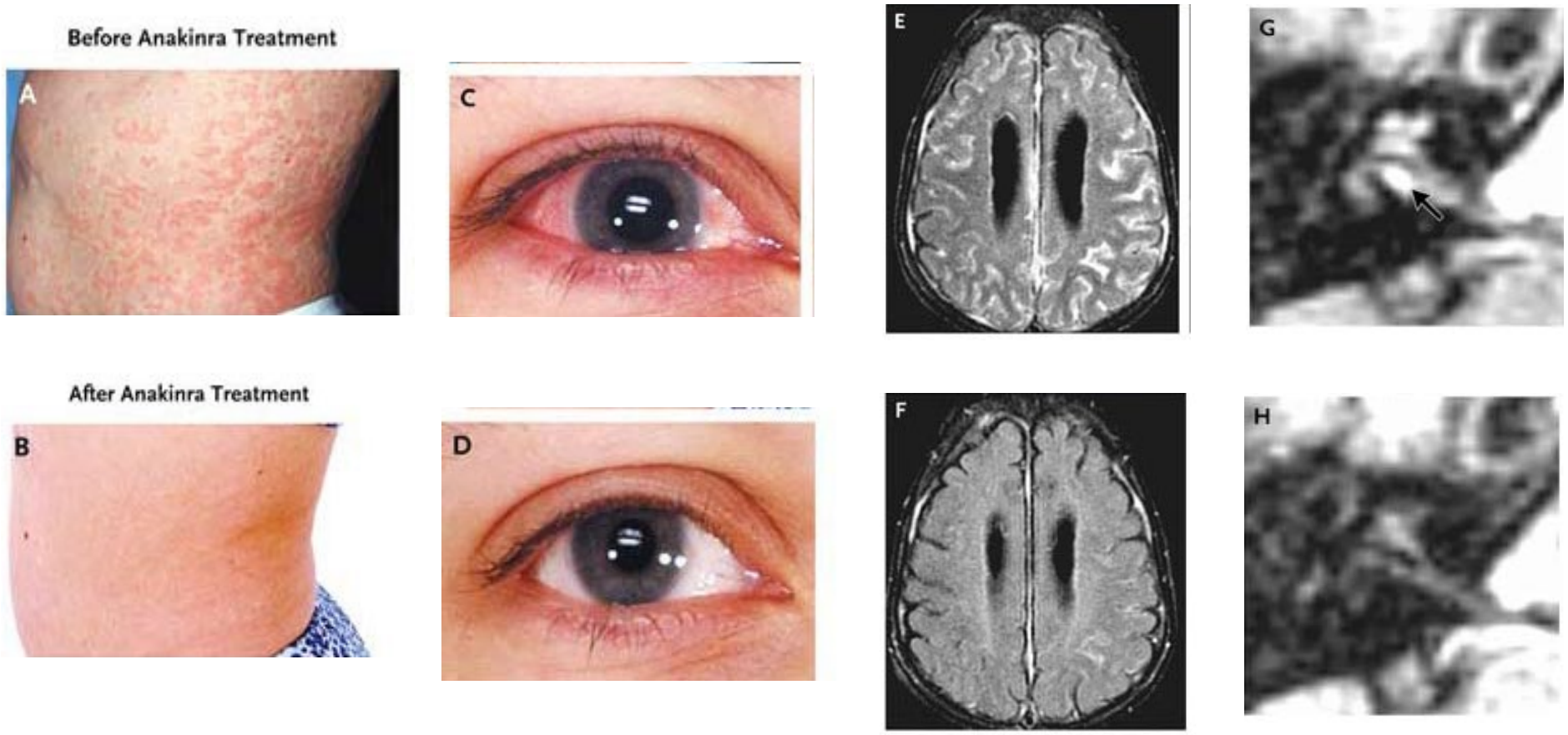
The autoinflammatory diseases are char
voked episodes of inflammation, witho
antigen-specific T cells. The concept w
the identification of the genes underlyin
dromes. This nosology has taken root b
in our knowledge of the genetic basis o
autoinflammatory diseases, and with the
derive from genetic variants of the inna
propose an updated classification scher
sights garnered over the past decade, s
tion that has served well but is opaque to
therapeutic interrelationships now befo
of autoinflammatory disease: IL-1β acti
mopathies), NF-κB activation syndrome
complement regulatory diseases, disturb
macrophage activation syndromes. A sys
physiology will bring greater clarity to
new hypotheses both at the bench and a





ORIGINAL ARTICLE

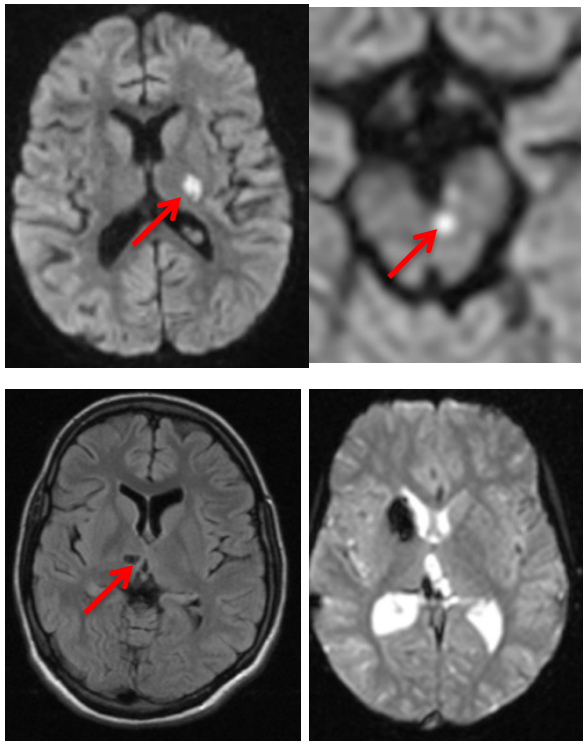
Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1β Inhibition

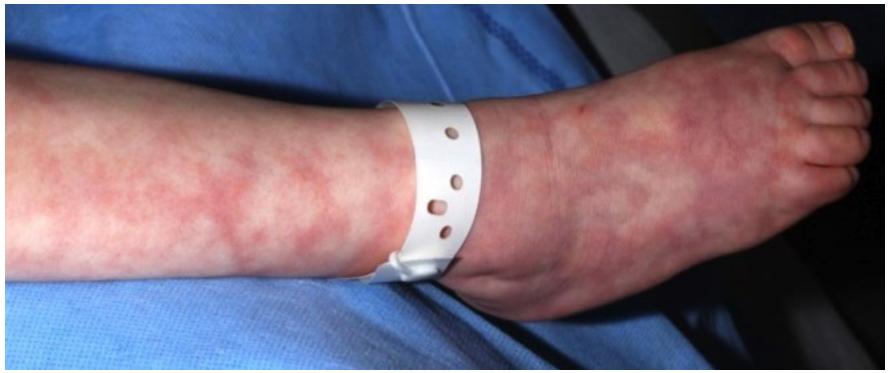


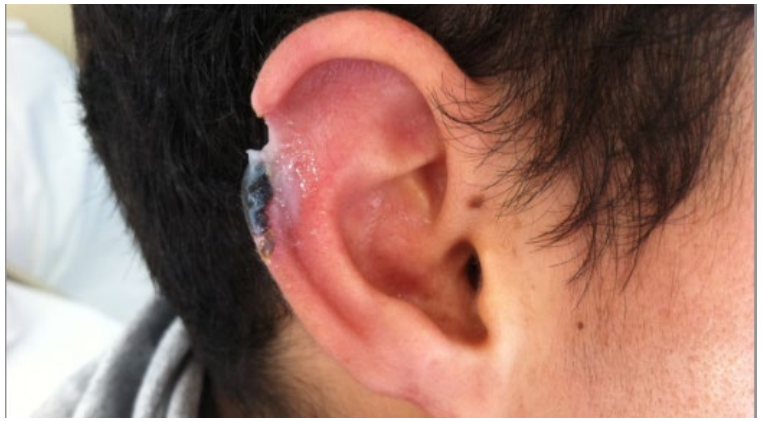
Goldbach-Mansky R et al. N Engl J Med 2006;355:581-592

ORIGINAL ARTICLE

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2



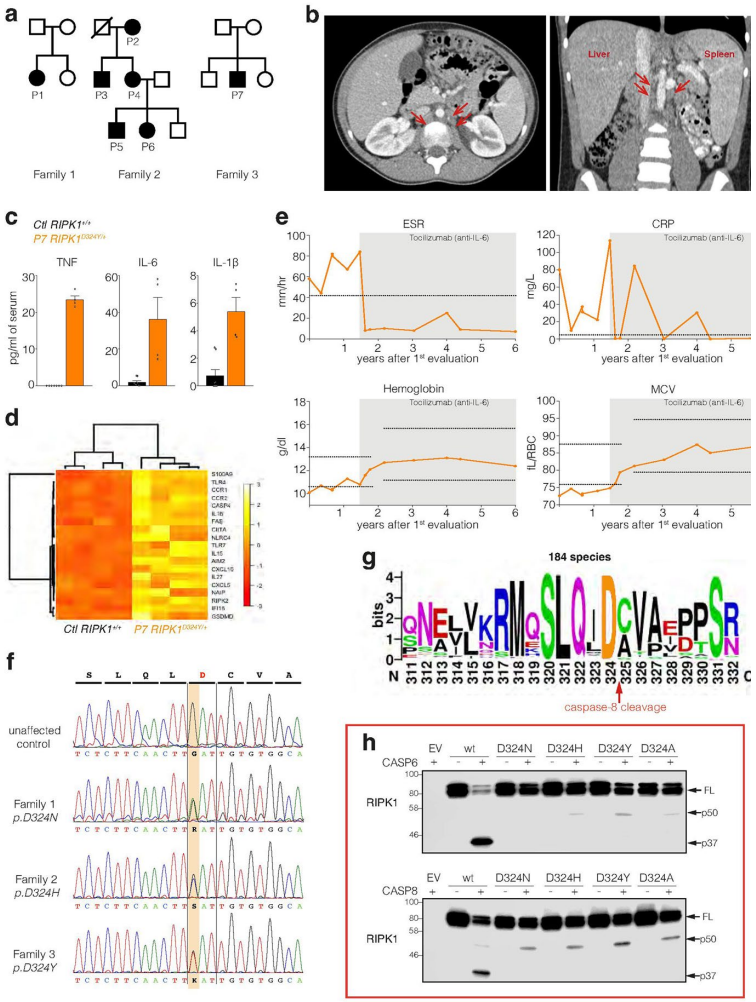




Zhou et al. *NEJM* 370:911, 2014

Article

Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease



Laloui, Boyden, Oda, et al.,
Nature 577:103, 2020

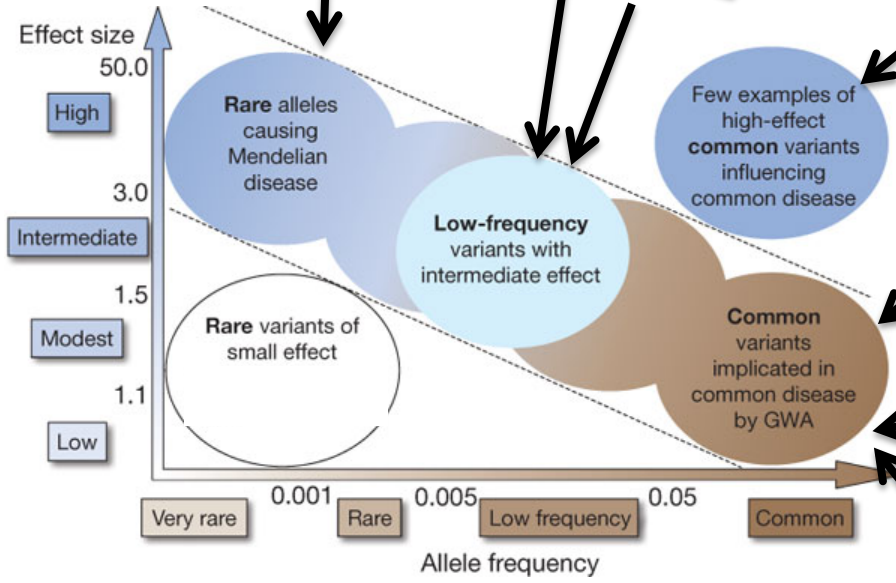
Genetic Architecture of Behçet's Disease

TNFAIP3
(Haploinsufficiency of A20)

MEFV
IL23R
TLR4
NOD2

HLA-B*51

ERAP1



IL10
IL23R

CCR1
STAT4
KLRC4

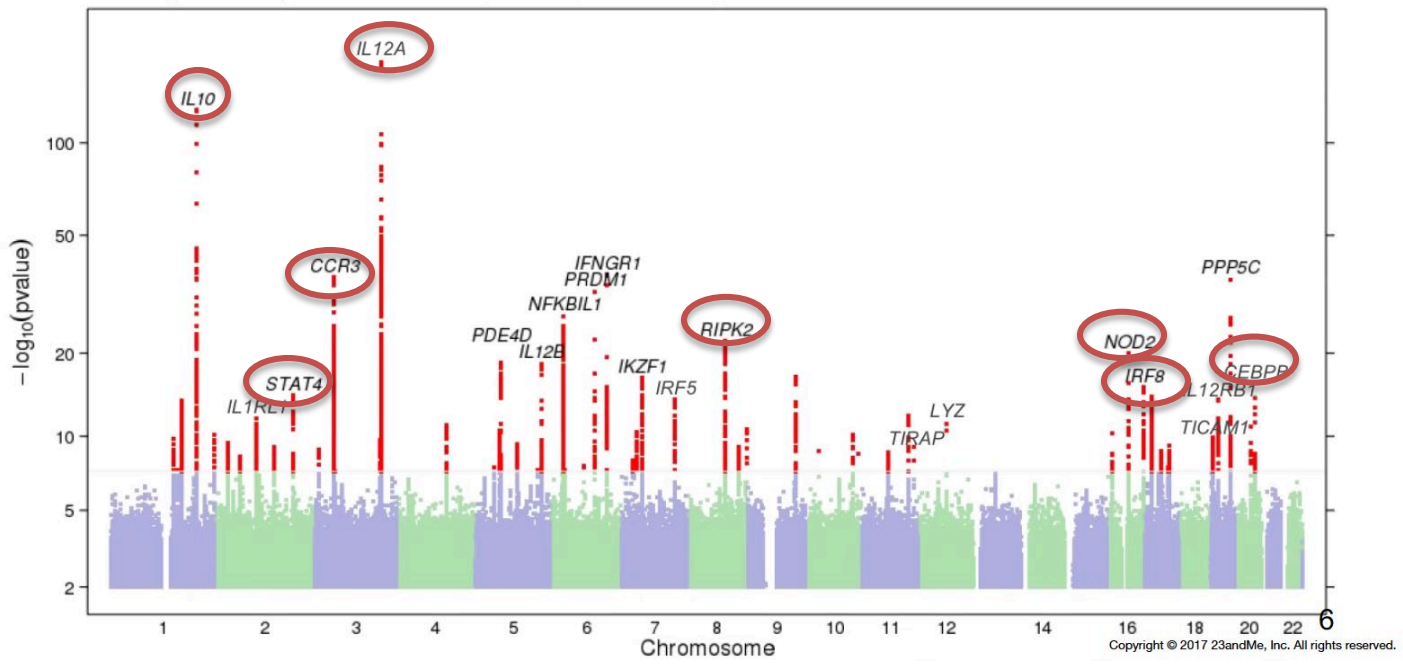
IL12A
IL1A-IL1B
IRF8
CEPB-PTPN1
ADO-EGR2
RIPK2
LACC1
FUT2

Remmers et al., *Nat Genet* 42:698, 2010
Kirino et al., *Nat Genet* 45:202, 2013
Kirino et al., *PNAS* 110:8134, 2013
Ombrello et al., *PNAS* 111:8867, 2014
Zhou et al. *Nat Genet* 48:67, 2016
Takeuchi et al. *Nat Genet* 49:438, 2017

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



Sathirapongsasuti et al., 23andMe, Inc., ASHG 2017

Genetic risk variants for PFAPA

SNP	Nearest gene	Risk allele	OR_{meta}	p_{meta} (Bonferroni corrected)
rs17753641	*IL12A*	G	2.13	$6x10^{-9}$
rs7574070	*STAT4*	A	1.51	0.0001
rs1518110	*IL10*	A	1.45	0.003
rs7616215	*CCR1-CCR3*	T	1.38	0.02

Behçet's spectrum disorders (BSD)

Recurrent aphthous ulcers

PFAPA

Behçet's disease

Manthiram et al. *PNAS* 117:14405, 2020

HLA Associations across the Spectrum

	Recurrent aphthous ulcers	PFAPA	Behçet's disease
Top *HLA* associations	*HLA-DRB1*0103* **OR 1.33**	*HLA-DQB1*0603, HLA-DRB1*1301, HLA-DQA1*0103* **OR 2.13**	*HLA-B*5101* **OR 3.0**

stronger *HLA* associations

HLA may be a factor that affects phenotype along the spectrum.
Microbial antigens may modulate the disease.

Manthiram et al. *PNAS* 117:14405, 2020

nature immunology

ARTICLES

https://doi.org/10.1038/s41590-020-0705-6

Ancient familial Mediterranean fever mutations in human pyrin and resistance to *Yersinia pestis*

Yong Hwan Park[1,11,13], Elaine F. Remmers[1,13], Wonyong Lee[1], Amanda K. Ombrello[1], Lawton K. Chung[2], Zhao Shilei[3,4,5], Deborah L. Stone[1], Maya I. Ivanov[2], Nicole A. Loeven[2,12], Karyl S. Barron[6], Patrycja Hoffmann[1], Michele Nehrebecky[1], Yeliz Z. Akkaya-Ulum[7], Erdal Sag[8], Banu Balci-Peynircioglu[7], Ivona Aksentijevich[1], Ahmet Gül[9], Charles N. Rotimi[10], Hua Chen[3,4,5], James B. Bliska[2,12], Seza Ozen[8], Daniel L. Kastner[1]✉, Daniel Shriner[10] and Jae Jin Chae[1]✉

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

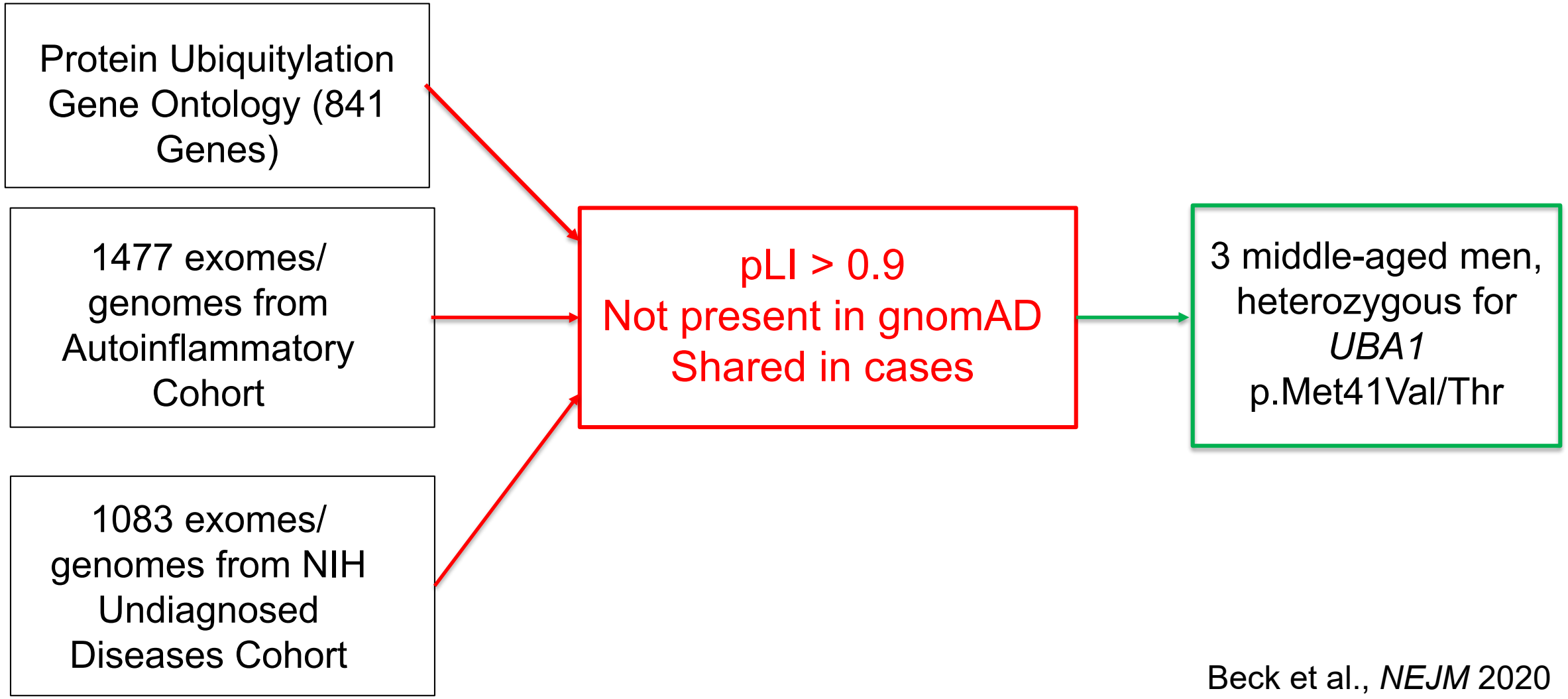
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

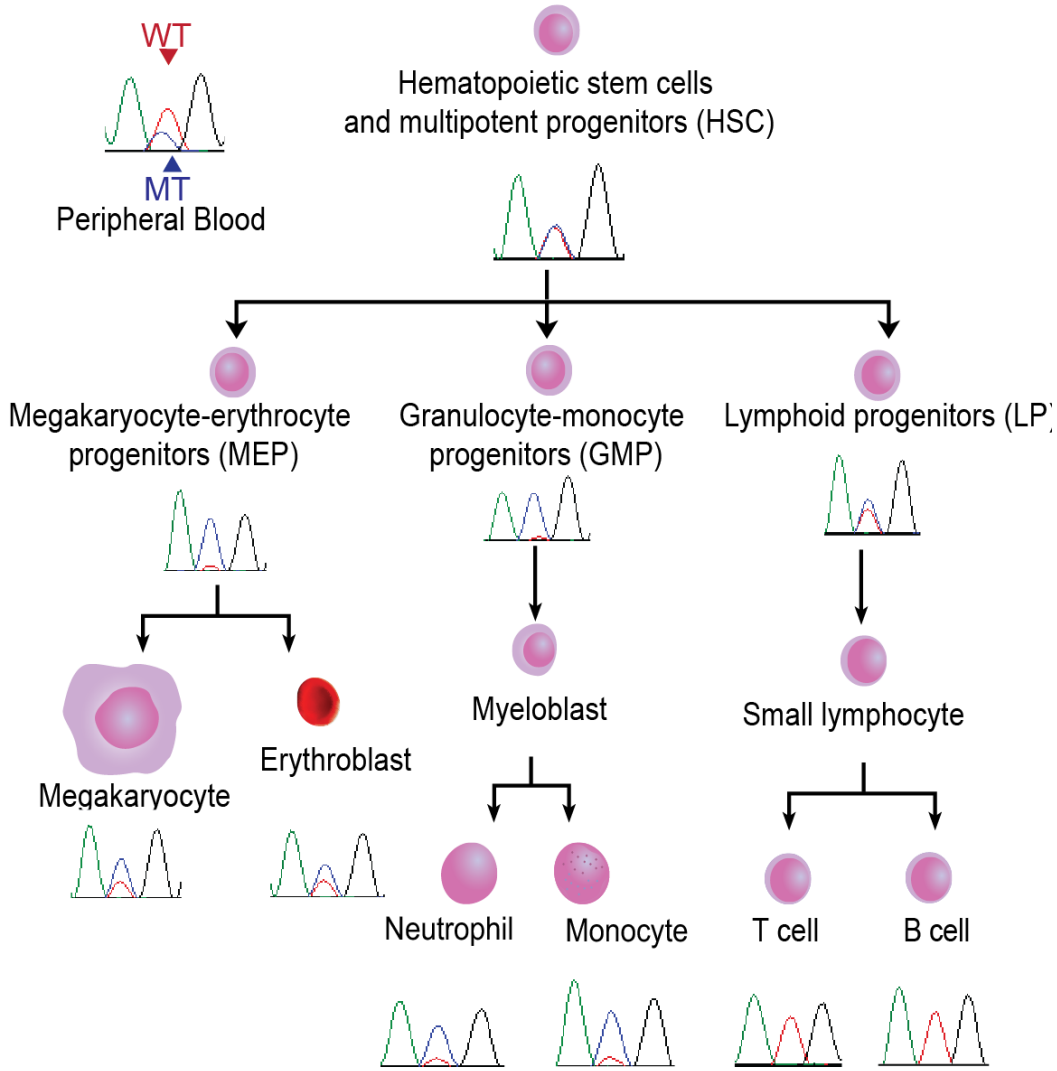
D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar, L. Xu, H. Oda, W. Goodspeed, K.S. Barron, M. Nehrebecky, A. Jones, R.S. Laird, N. Deuitch, 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

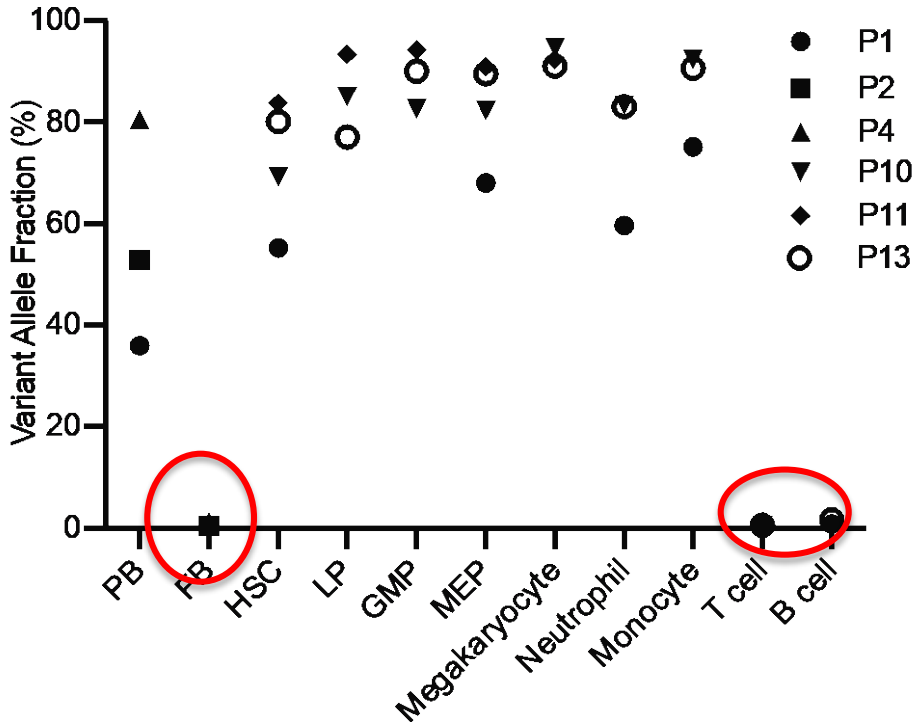
Genotype First!



Beck et al., *NEJM* 2020

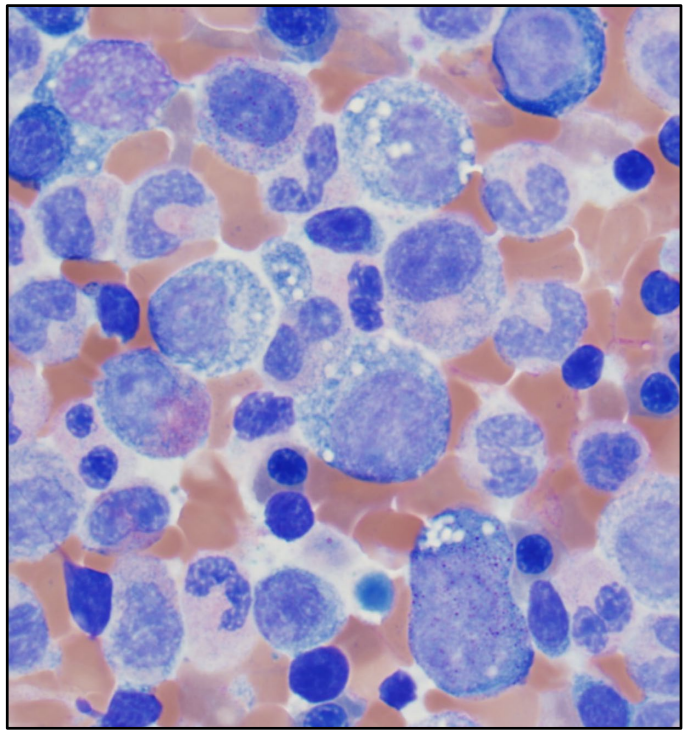
Identification of Myeloid-Restricted Somatic *UBA1 M*utations



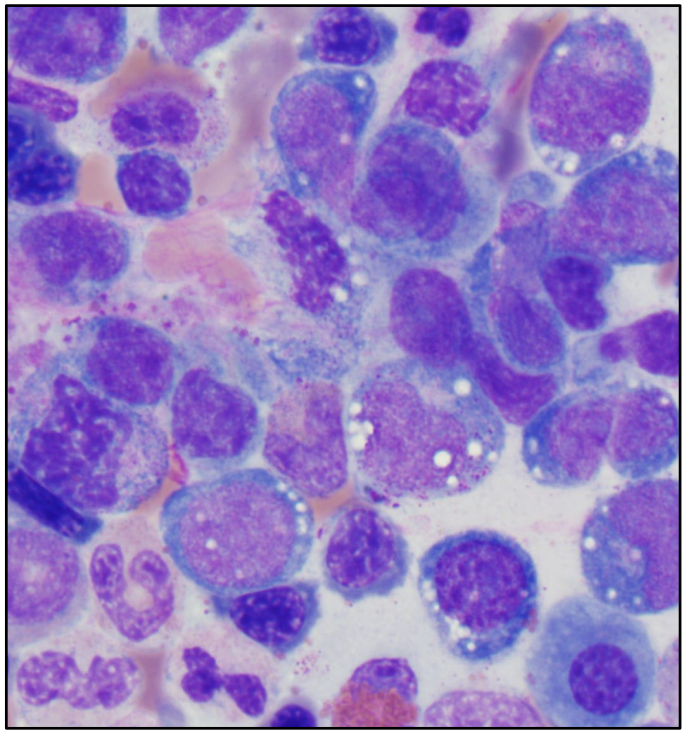


Beck et al., *NEJM* 2020

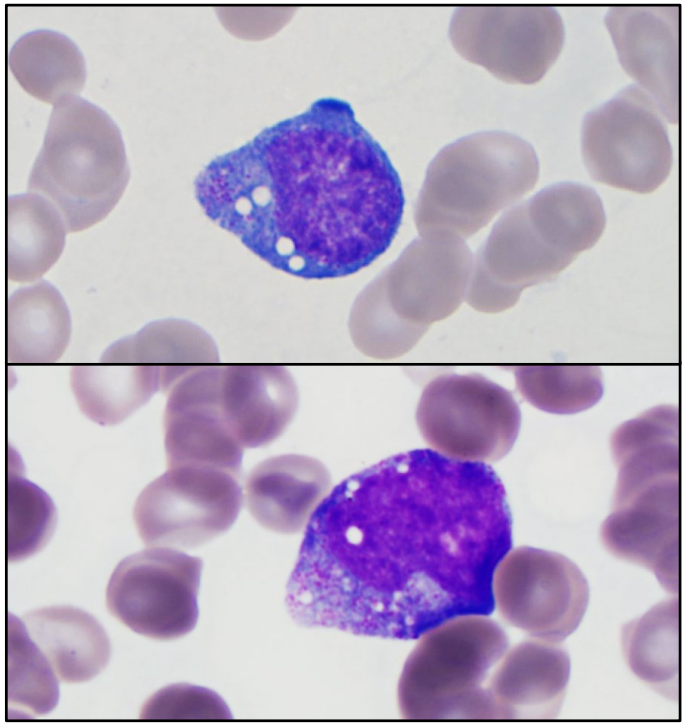
Bone Marrow-Resident Myeloid Cells in *UBA1* Patients Exhibit Striking Vacuoles



P1- 54 y/o male
Bone Marrow



P2- 61 y/o male
Bone Marrow



P3- 74 y/o male
Bone Marrow

Beck et al., *NEJM* 2020

The Clinical Spectrum of 25 Patients with *UBA1* p.Met41 Somatic Mutations

Male gender	**25 (100%)**
Age at onset, median (range)	**64 (45 – 80)**
Deceased	**10 (40%)**
Fever	**23 (92%)**
Skin involvement	**22 (88%)**
Pulmonary infiltrate	**18 (72%)**
Ear/nose chondritis	**16 (64%)**
Venous thromboembolism	**11 (44%)**
Macrocytic anemia	**24 (96%)**
Bone marrow vacuoles	**18/18 (100%)**

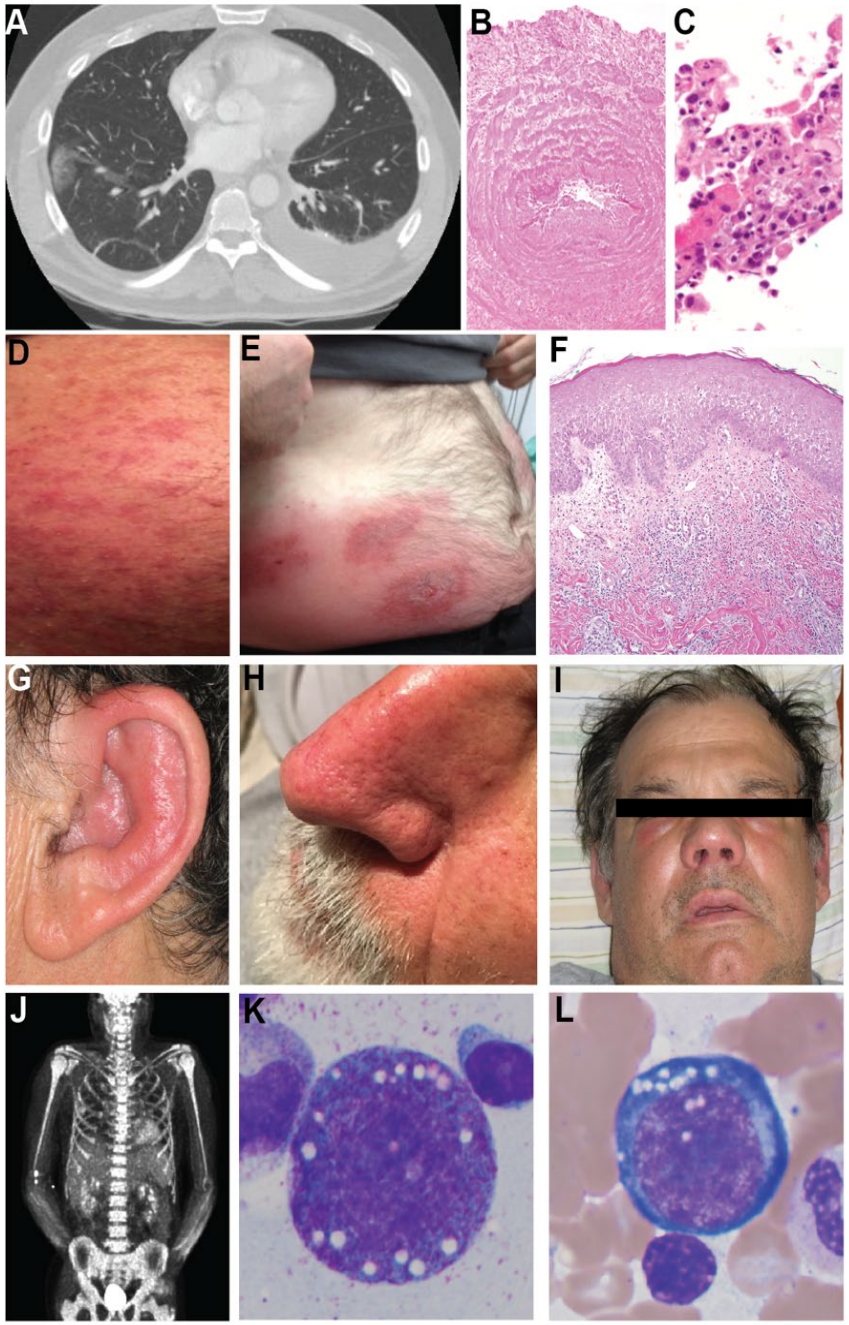
Beck et al., *NEJM* 2020

The Clinical Spectrum of 25 Patients with *UBA1* p.Met41 Somatic Mutations (2)

Meets Diagnostic or Classification Criteria for:

Relapsing polychondritis	**15 (60%)**
Sweet syndrome	**8 (32%)**
Myelodysplastic syndrome	**6 (24%)**
Multiple myeloma (MGUS)	**5 (20%)**
Polyarteritis nodosa	**3 (12%)**
Giant cell arteritis	**1 (4%)**

Beck et al., *NEJM* 2020



V acuoles

E 1 ubiquitin-activating enzyme

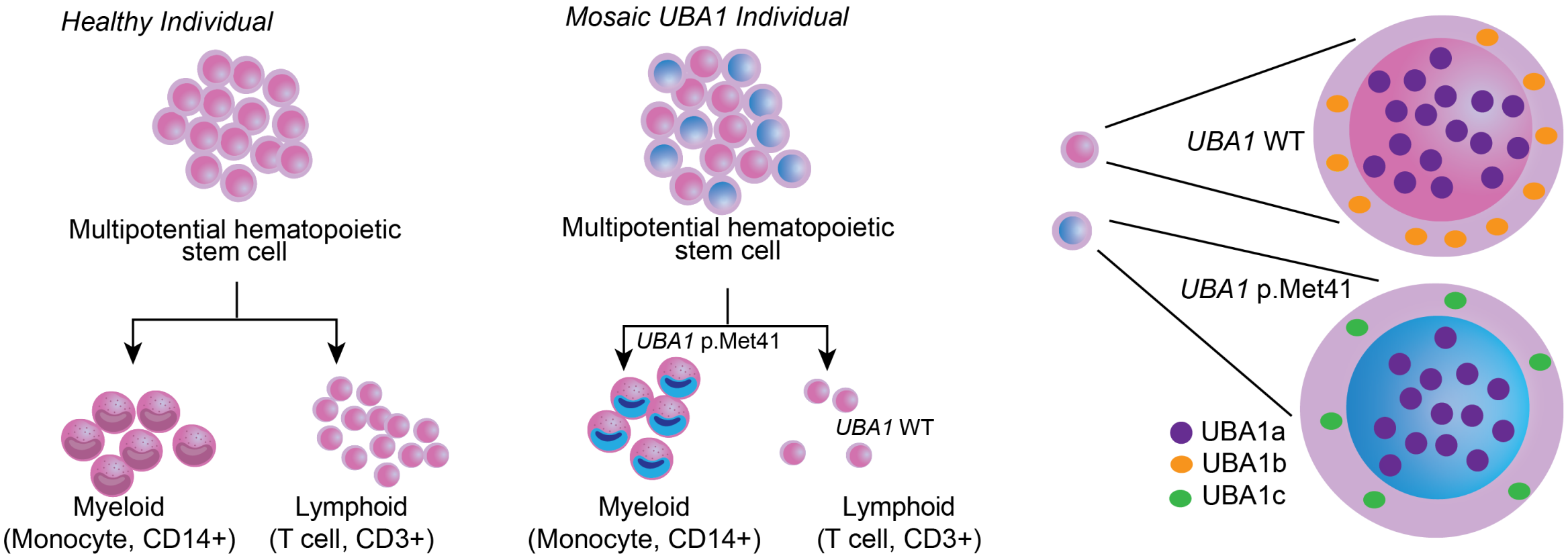
X - linked

A utoinflammatory

S omatic

Beck et al., *NEJM* 2020

VEXAS Model


Healthy Individual
Multipotential hematopoietic stem cell
Myeloid (Monocyte, CD14+)
Lymphoid (T cell, CD3+)
Mosaic UBA1 Individual
Multipotential hematopoietic stem cell
UBA1 p.Met41
UBA1 WT
Myeloid (Monocyte, CD14+)
Lymphoid (T cell, CD3+)
UBA1 WT
UBA1 p.Met41
UBA1a
UBA1b
UBA1c

VEXAS: The Big Picture

- Using a genotype-first strategy, one can define new illnesses based on genetic variants shared among patients carrying distinct clinical diagnoses. This may give rise to a new molecular taxonomy of rheumatic disease.
- Somatic variants for genes encoded on the X-chromosome are probably under-recognized.
- Somatic mutation may account for a significant fraction of adult-onset inflammatory disease.

NIH Clinical Center

dan.kastner@nih.gov
Tina.Romeo@nih.gov, referrals