SOMATIC MUTATIONS IN «BENIGN» DISEASES

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Disclosures: Neal S. Young

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	CRADA						
Incyte	CTA						

CRADA = Collaborative Research and Development Agreeet; CTA = Clinical Trials Agreement

SOMATIC MUTATIONS IN “BENIGN” DISEASE

A CASE

OF

INTERMITTENT HÆMATINURIA,

WITH REMARKS.

By WILLIAM W. GULL, M.D.

This disease is characterised by the passing, at intervals, of urine of a dark colour, looking as if it contained blood; no blood-corpuscles, however, are present. The urine is, in fact, of a red Burgundy-wine colour, and is often turbid, forming a dark-coloured sediment on cooling. It coagulates by heat and nitric acid. The specific gravity is generally higher than that of normal urine. On examining it under the microscope we notice granules scattered or aggregated into masses, granular casts of the tubules, a few degenerated epithelium-cells, and crystals of oxalate of lime. No blood-corpuscles, or, if any, merely a stray or a doubtful one, is to be seen. The granules, when carefully examined, are found to consist chiefly of very small prismatic crystals of hæmatin; and even such granules as are not so distinctly crystalline are, on changing the focus, seen to have a somewhat similar crystalline appearance. When the crystals and granular matter are thrown slightly out of focus their colour changes from the claret hue of hæmatin to a pale green.

One of the most striking points in the clinical history of this affection is its intermittent character, the urine suddenly

Guys Hosp Rep 12:381, 1882

The NEW ENGLAND JOURNAL of MEDICINE

2020; 3893:2628

ORIGINAL ARTICLE

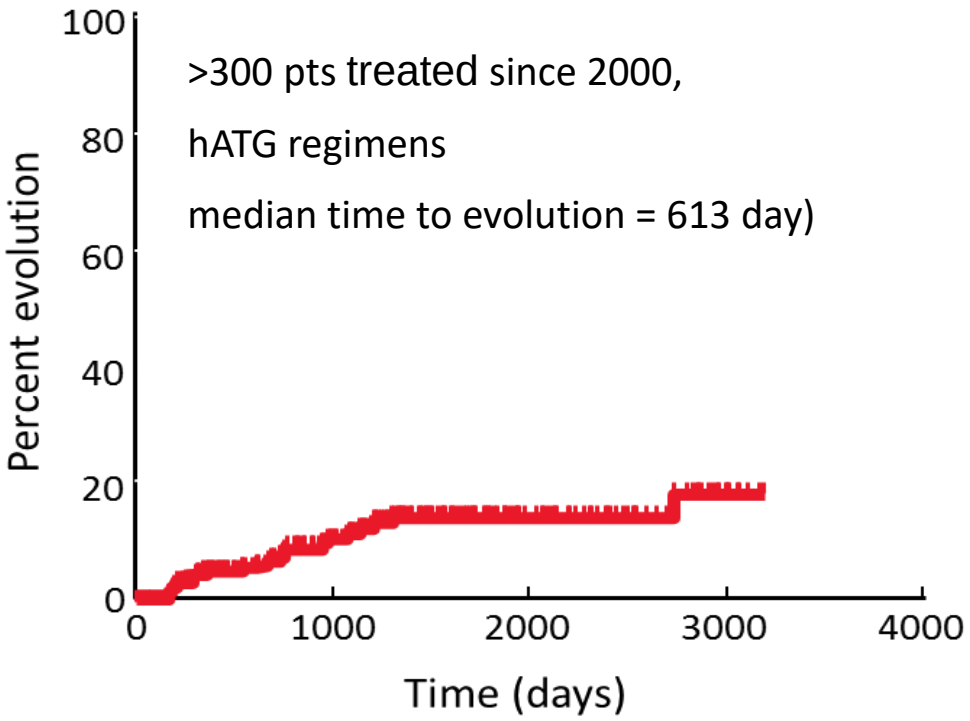
Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

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

Case report, 1882
PNH

Genome-first discovery, 2020
VEXAS

CLONAL EVOLUTION IN SEVERE APLASTIC ANEMIA



>300 pts treated since 2000,

hATG regimens

median time to evolution = 613 day)

Evolution = MDS/AML—
usually 7-, 8+, del13q, del20q

Riddle: **What Do Aplastic Anemia, Paroxysmal Nocturnal Hemoglobinuria (PNH) and "Hypoplastic" Leukemia Have in Common?**

By WILLIAM DAMESHEK

Blood 1967

PERSPECTIVE

The Problem of Clonality in Aplastic Anemia: Dr Dameshek's Riddle, Restated

By Neal S. Young

Blood 1992

Clonality in context: hematopoietic clones in their marrow environment

James N. Cooper and Neal S. Young

Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

Blood 2017

HSC CLONALITY IN APLASTIC ANEMIA

PNH

GPI- clones, >50% AA (PNH/AA)

Specific to immune-mediated marrow failure

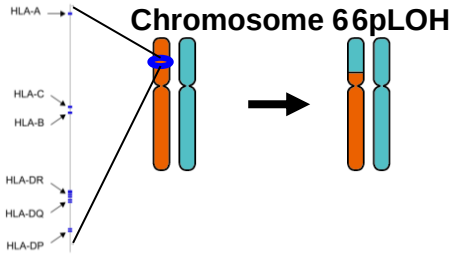
6pLOH/HLA mutations

>20% SAA

Diminished HLA class I expression

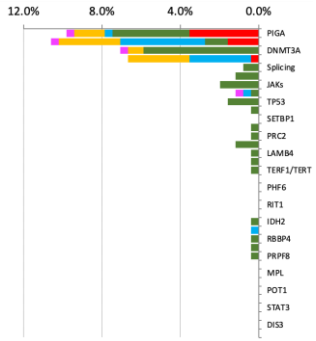
Specific to HLA antigens

Associated with response to IST/outcome



CHIP

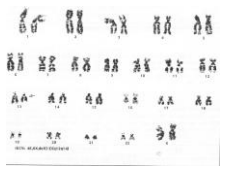
BCOR/L, DNMTS2, ASXL1

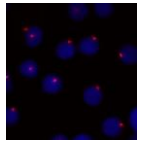


Clonal cytogenetic abnormalities

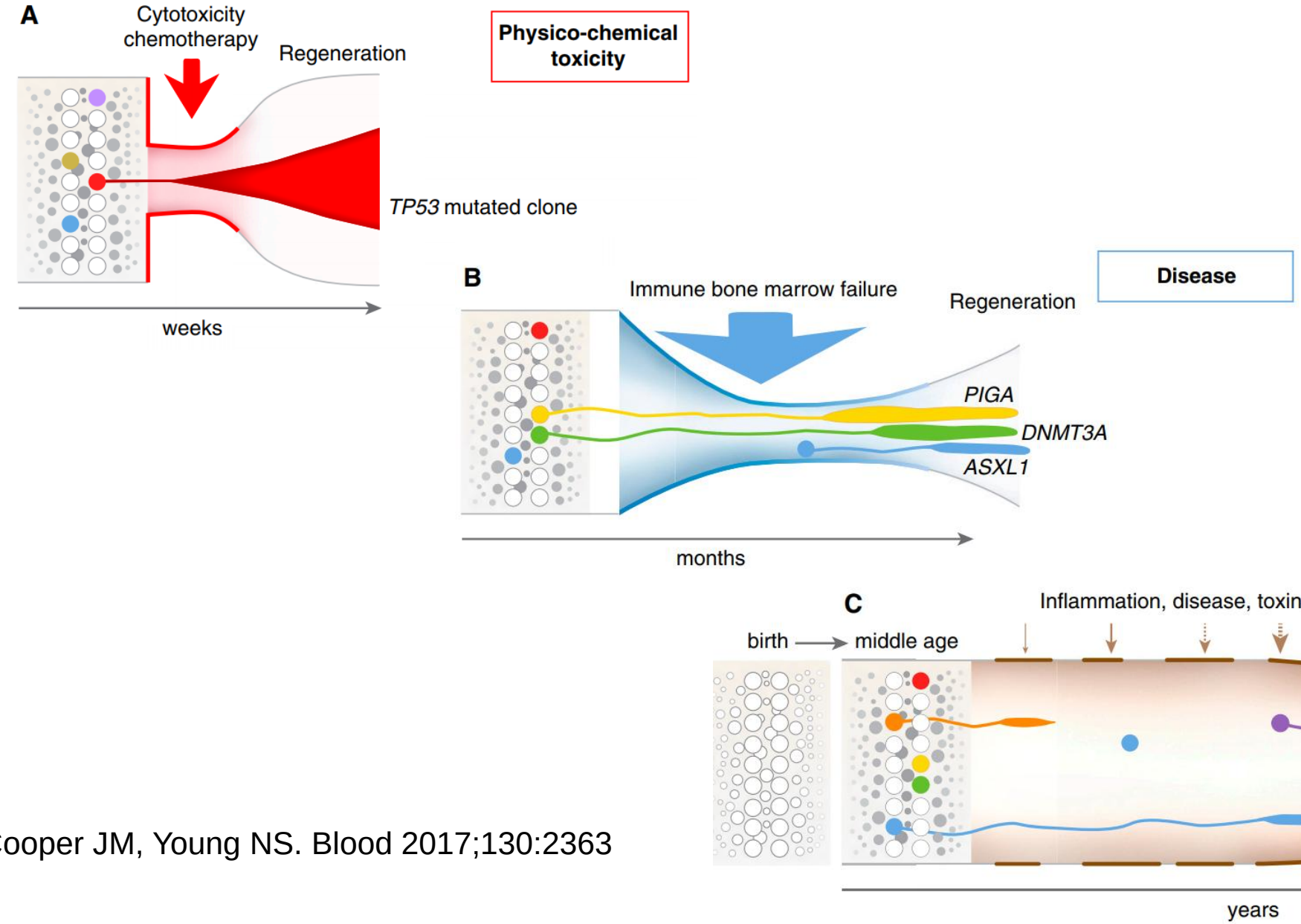
7-; also 8+, 12q-, 15q-

Associate with prognosis



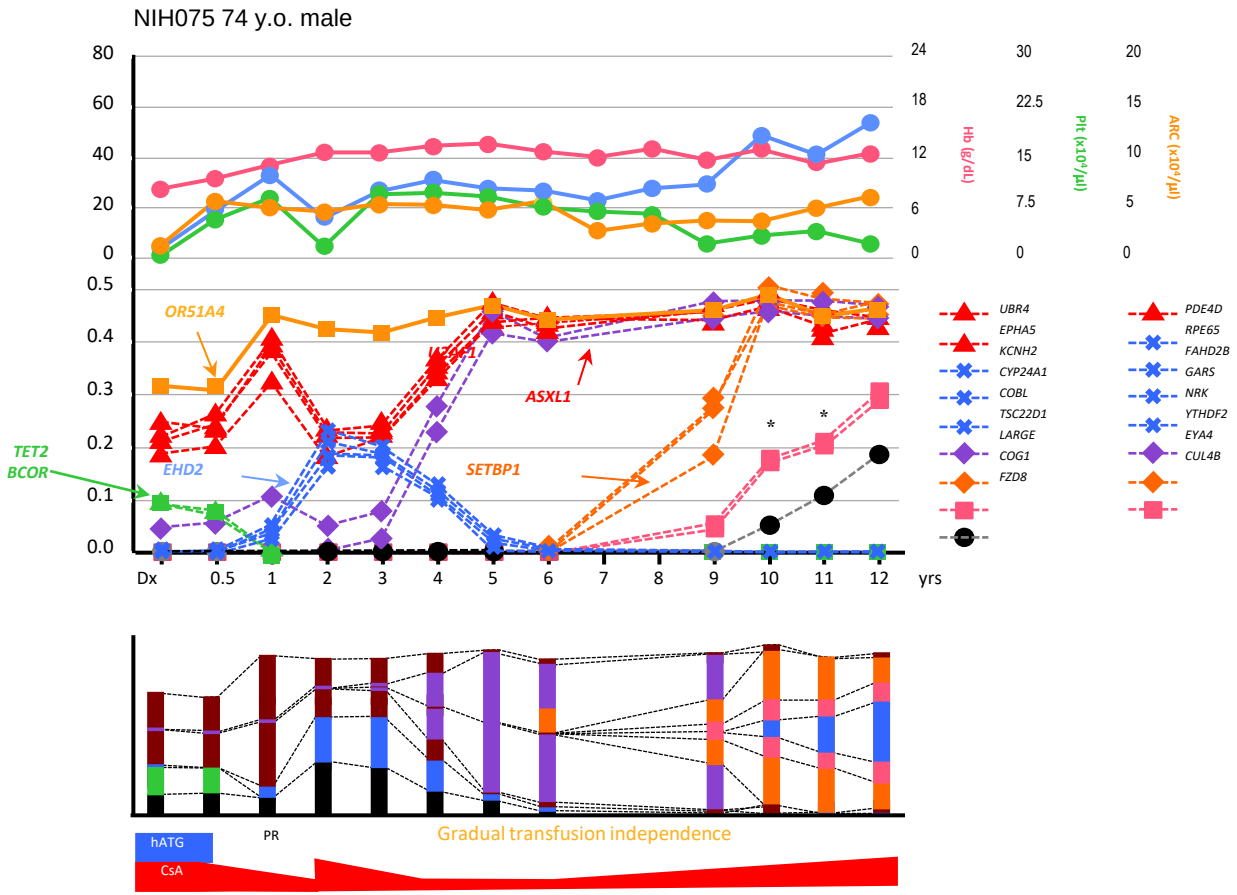


ENVIRONMENT SHAPES CLONALITY OVER TIME



Cooper JM, Young NS. Blood 2017;130:2363

CLONAL HEMATOPOIESIS IN SAA: >12 YEAR COURSE



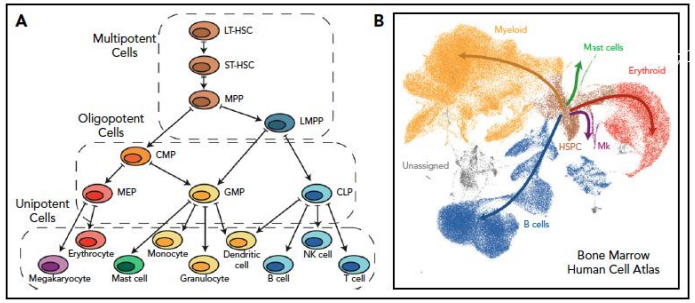
Complicated! Dynamic! Clinically relevant?

SCRNASEQ IN HEMATOLOGY

SINGLE-CELL TECHNOLOGY MEETS HEMATOLOGY

New insights into hematopoietic differentiation landscapes from single-cell RNA sequencing

Sam Watcham, Iwo Kucinski, and Berthold Gottgens

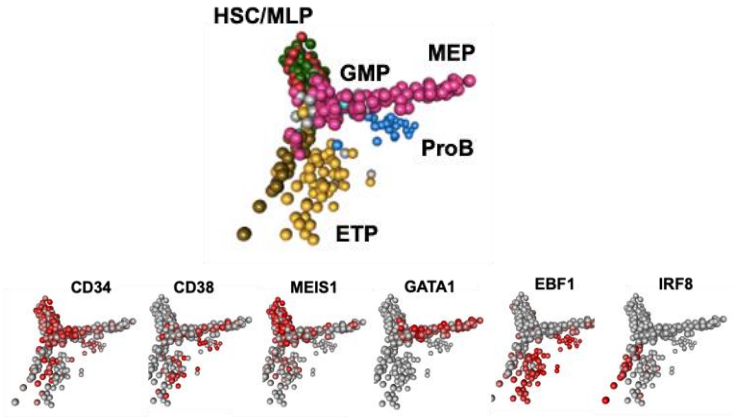


Complex, emergent *system* rather than unidirectional *hierarchy*

Single-cell genomics in acquired bone marrow failure syndromes

Zhijie Wu and Neal S. Young

Blood 2023; 142:1193



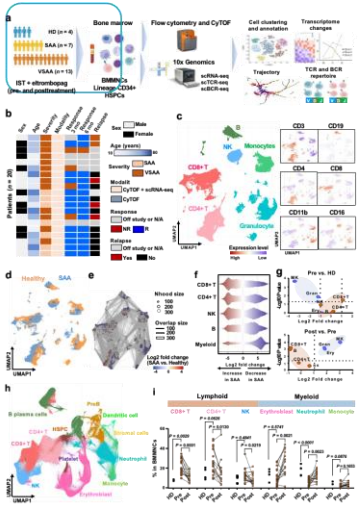
scRNAseq to:

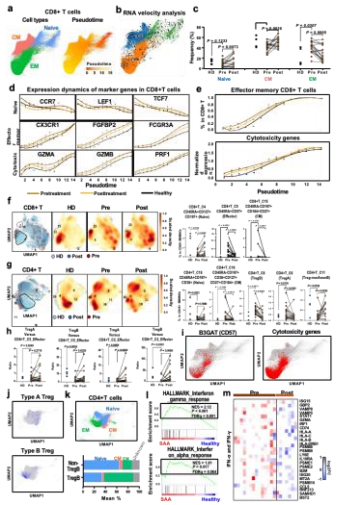
- define **normal hematopoiesis** (**marrow**) in human and mouse
- examine relationships of **mRNA, lncRNA**, chromatin structure, proteins
- define abnormal cells (**aneuploid**, **mutated**)
- explore constitutional genetic deficiencies (**GATA2**, **DADA2, telomere disease**)
- test drug mechanisms (**alemtuzumab**, ATG)
- determine cell-cell interactions (immune-HSCP in **AA**, low risk MDS)
- assess environmental perturbations (HGFs, cytokines, 0_2 , stroma)

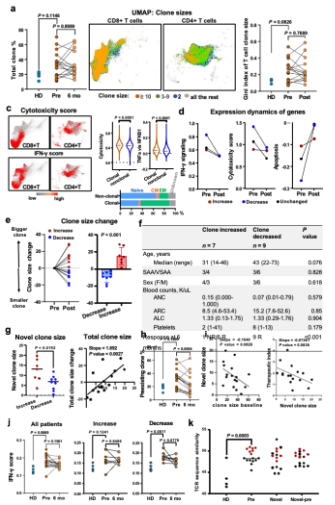
RNA sequencing + proteomics + DNA/chromatin

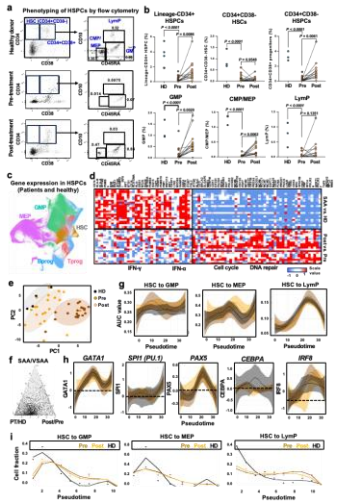
IMMUNE AA AT SINGLE CELL RESOLUTION

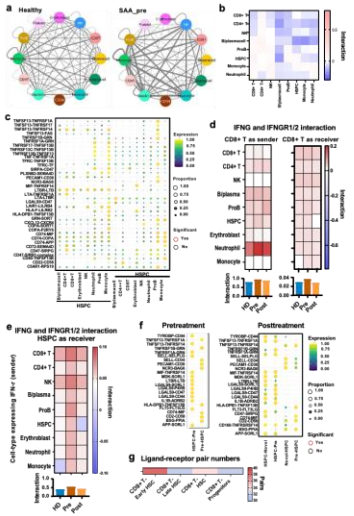
Minimal in vitro perturbation
Multidimensional
Conserved heterogeneity
Imputed functionality
Cell number flexible

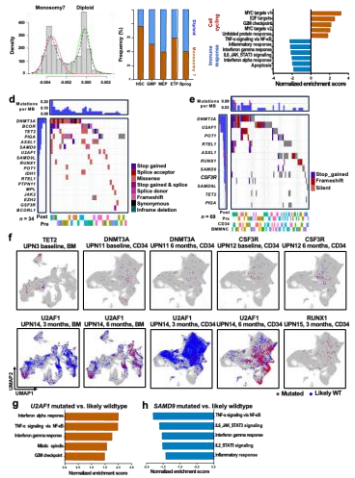










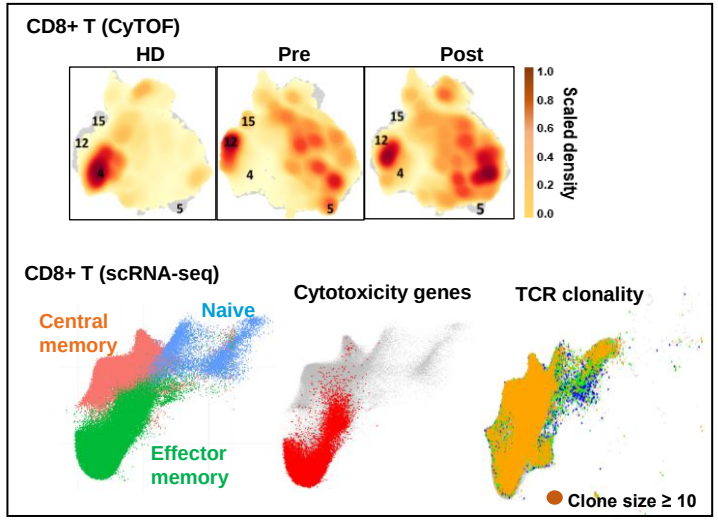


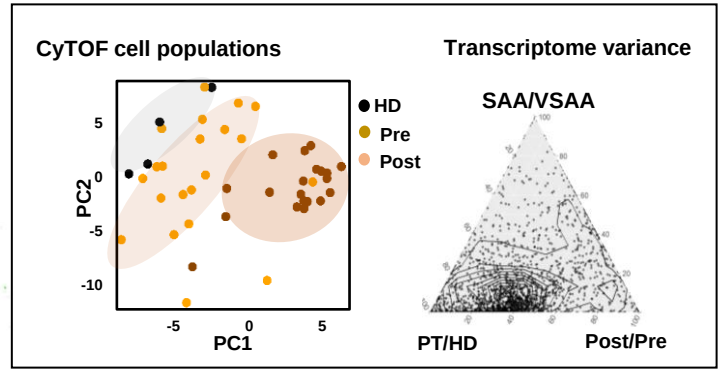
N = 20, pre- and post-triple rx
scRNAseq, TCR/BCR,
mutation/aneuploidy
CyTOF (Kordasti),
conventional flow cytometry, cytokines
GWAS for germline variants

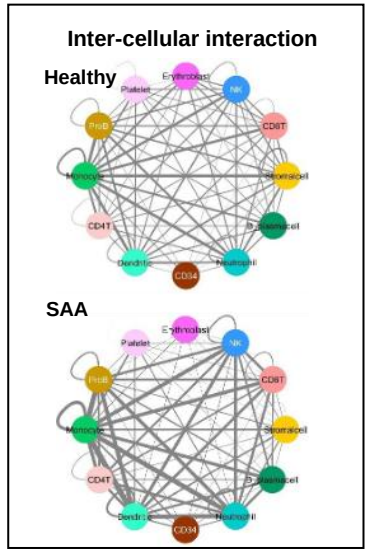
Wu Z et al, under review; ASH oral 2024

OBSERVATIONS/IMPUTATIONS FROM SINGLE CELL ANALYSES IN AA

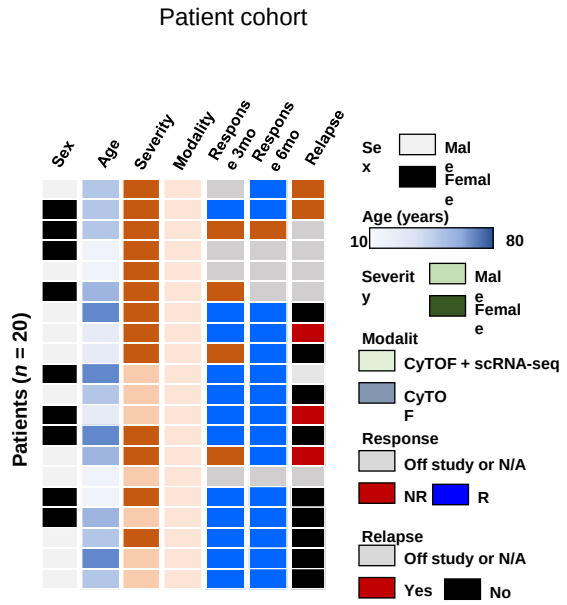
Dominance of CD8 effector memory cells in all immune AA. HSC target cells.
Multiple distinct CD8 subsets, private TCRs, prominent IFNγ signal
Complex CD8 T cell clonal dynamics, emergence of new clones correlates with clinical outcomes
Regulatory T cells in distinct subsets
Marked cell-cell interactions: among hematopoietic-immune cells, primitive-mature cell types
Incomplete resolution of immune abnormalities with therapy
Recovery of multi-potential progenitors, not stem cells
Linkage to germline immune system variants (*SIPR5, NFKB1, IRF5)* and IFN pathways

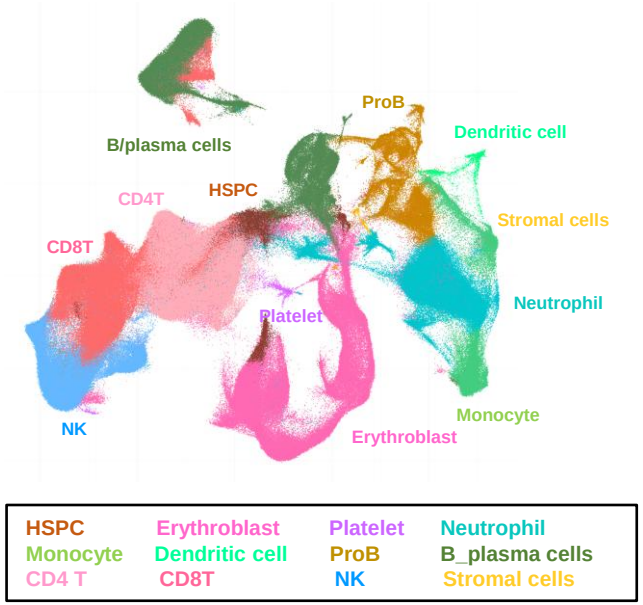


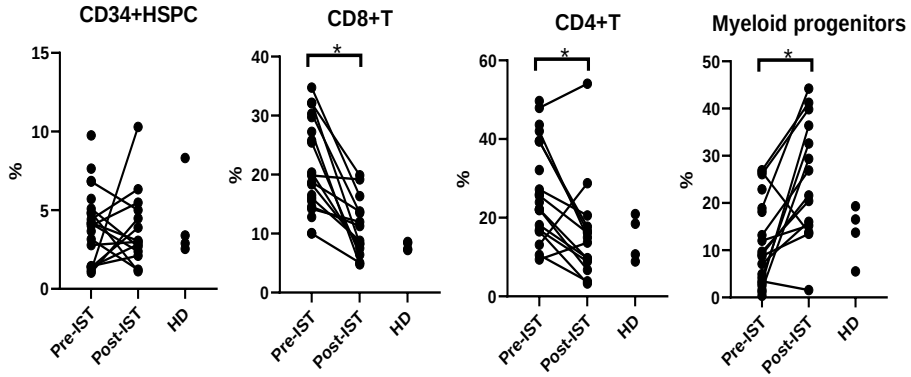




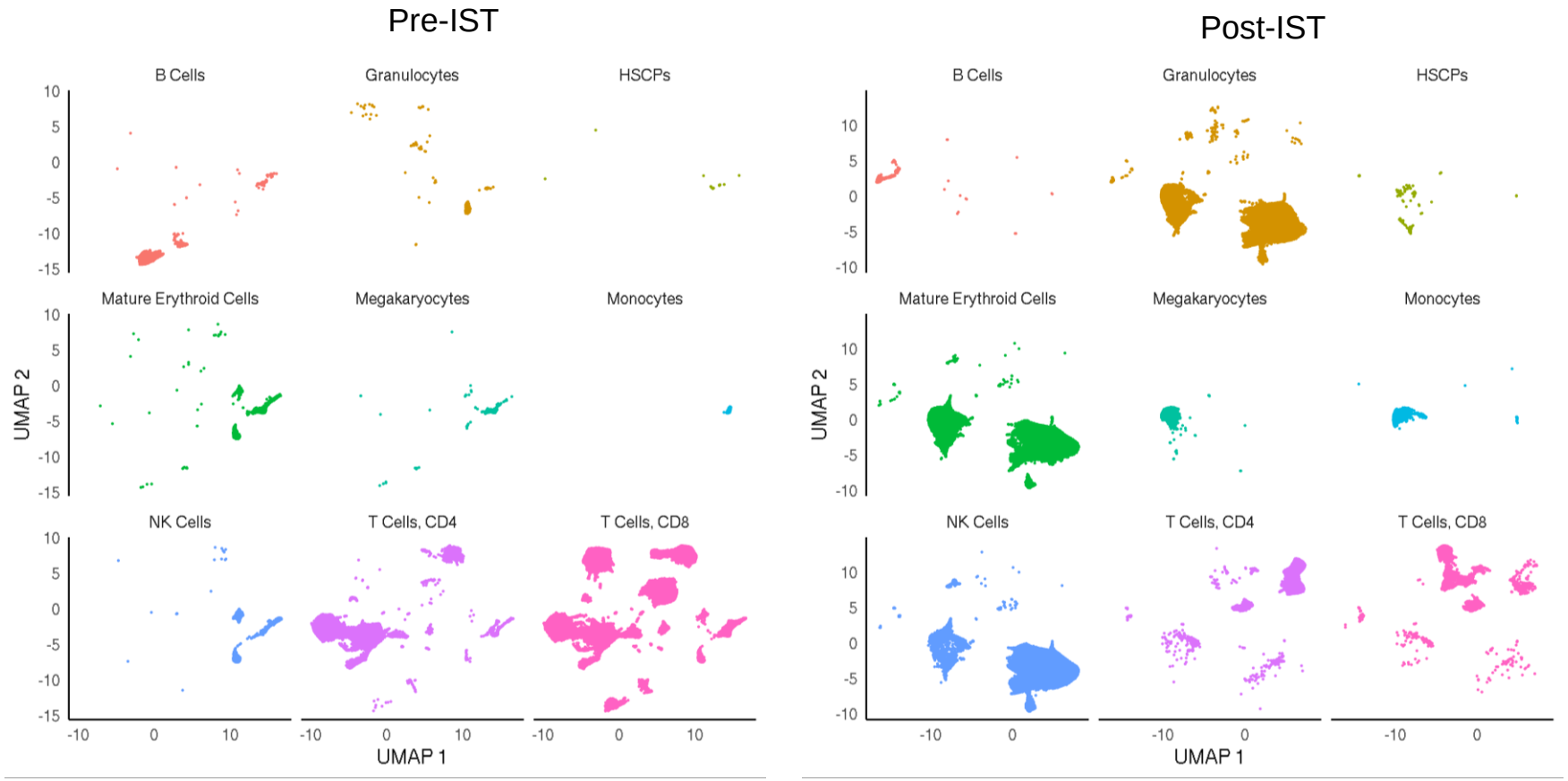
SEVERE APLASTIC ANEMIA:
TRANSCRIPTOMES OF INDIVIDUAL CELLS, PRE- AND POST-IST





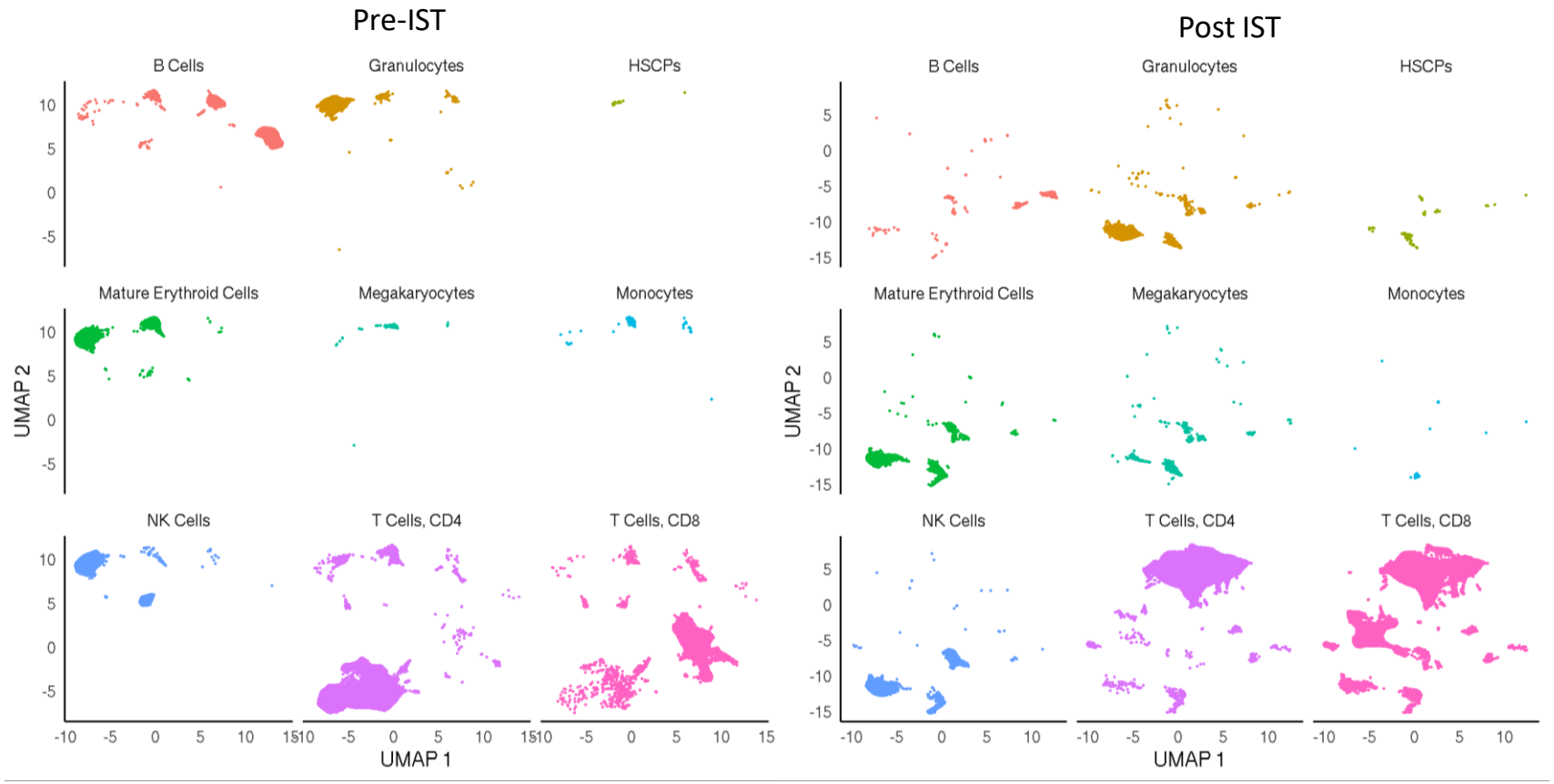


TIME-OF-FLIGHT CYTOMETRY OF APLASTIC BONE MARROW
RESPONDING PATIENT



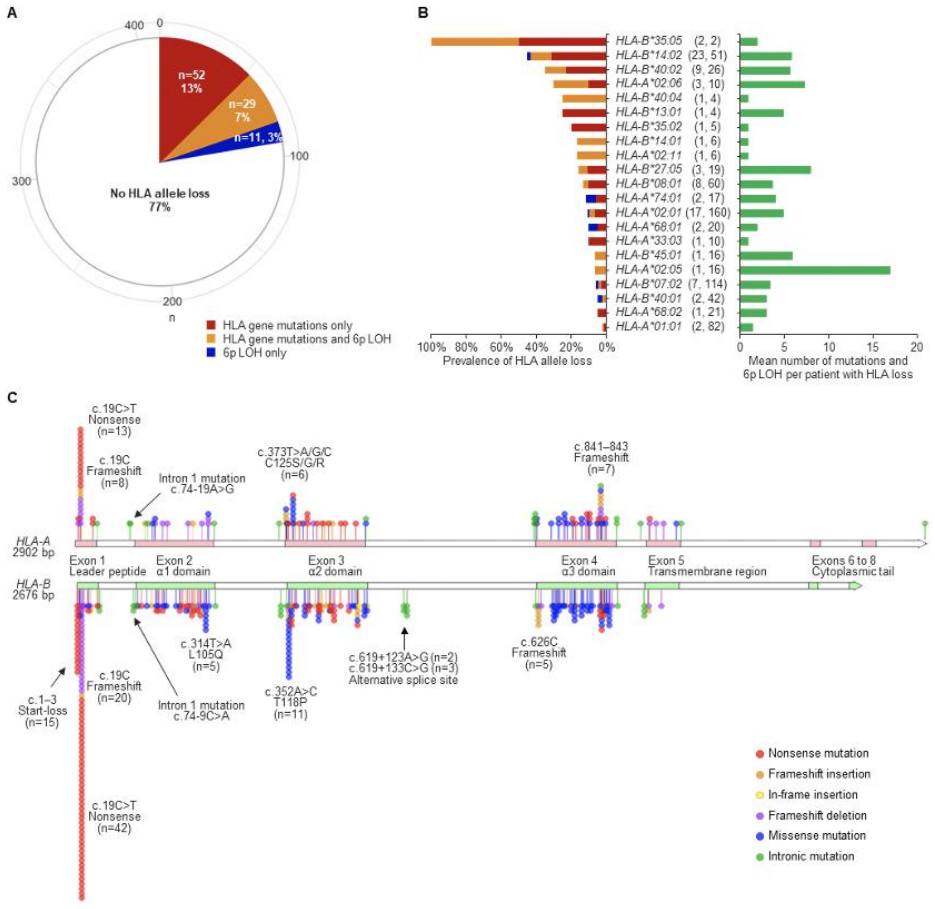
AA-responder

TIME-OF-FLIGHT CYTOMETRY OF APLASTIC BONE MARROW
NON-RESPONDING PATIENT



AA-non-responder

HLA ”ESCAPE” MUTATIONS ARE COMMON IN AA



N=544

Loss detected by flow cytometry +/- sequencing

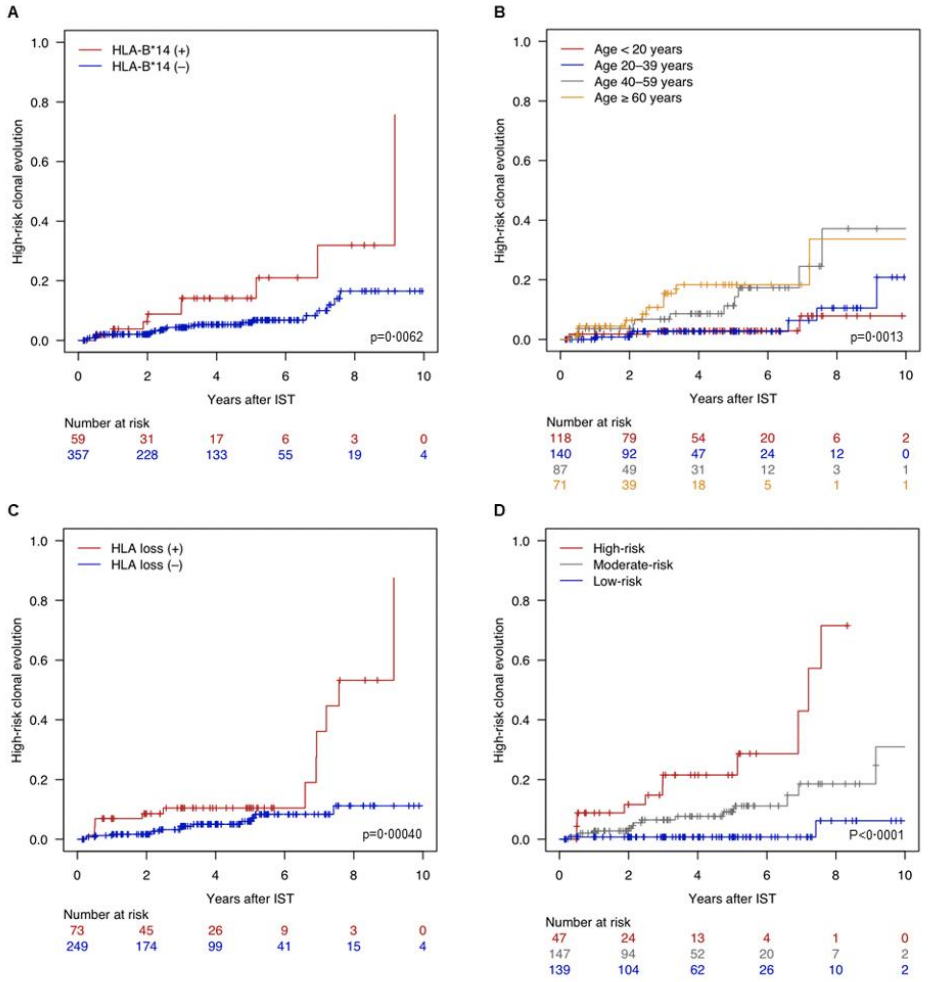
Highest associations:
- **DRB1*15**
- **B14*02**
- **B40*02**
- [DRB13* under-represented]

Somatic loss = **22%** patients

Strong association: **high risk clonal evolution**

Zaimoku Y et al, 2021; Blood 138:2799

HLA: CLINICAL CORRELATION WITH HIGH RISK CLONAL EVOLUTION



Age (>40 yrs)
B40 presence
HLA somatic loss

VEXAS IS A NEWLY DISCOVERED DISEASE

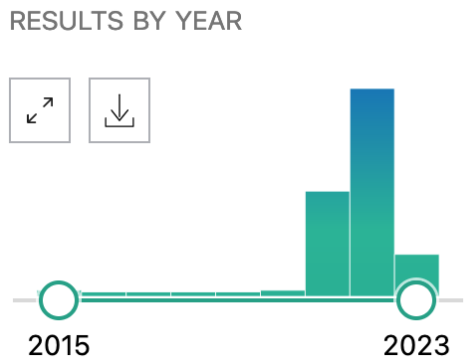
V = vacuoles
E = E1 ubiquitin
X = X chromosome
A = autoinflammatory
S = somatic

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

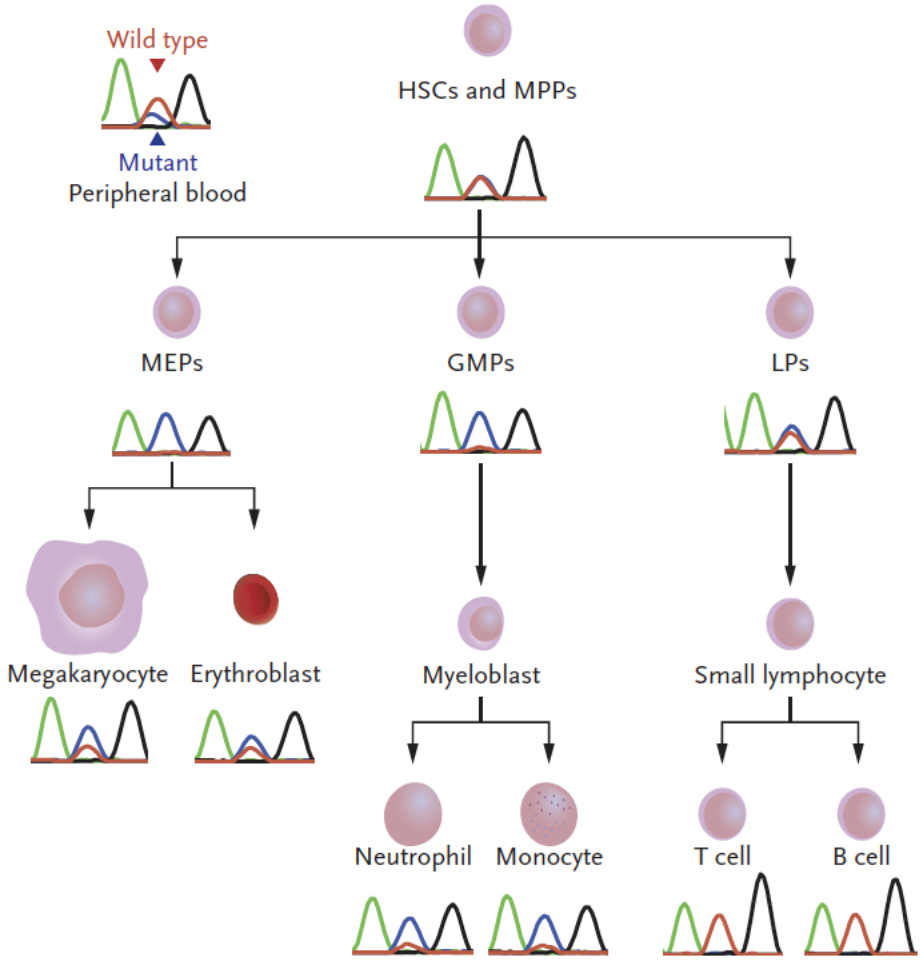
Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

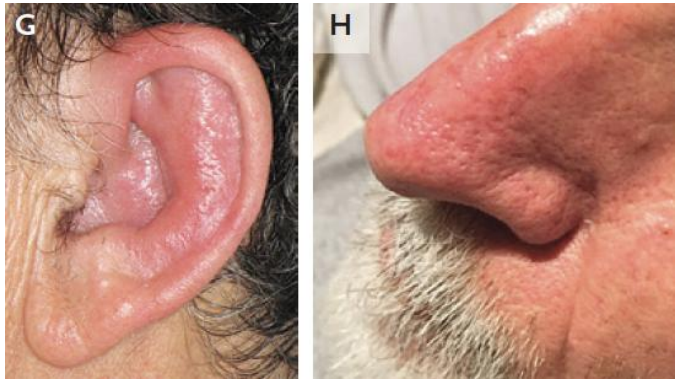
D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar,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



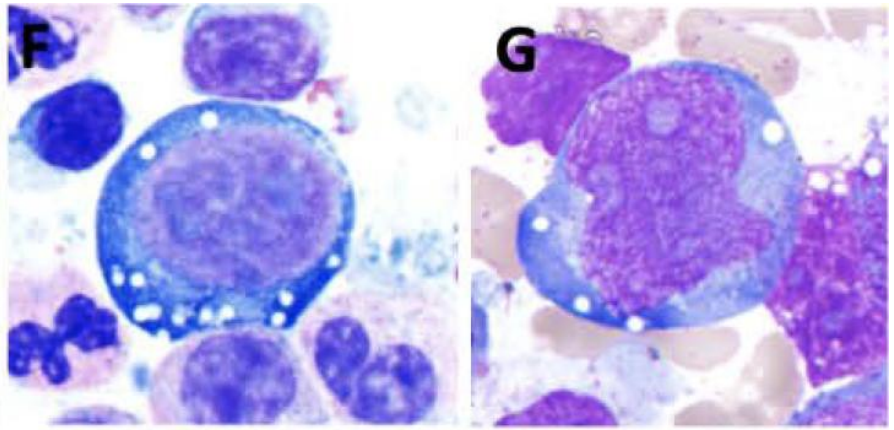
VEXAS (VACUOLES, E1 ENZYME, X-LINKED, AUTOINFLAMMATORY, SOMATIC)

Acquired HSC mutations in *UBA1* E1 in protein ubiquinylation





Rheumatologic: relapsing polychondritis, vasculitis, polyarteritis , Sweet syndrome, giant cell arteritis



Hematologic: cytopenias, MDS, MGUS, myeloma

Beck DB et al, N Engl J Med 2020; 383:2628

VEXAS IS NOT RARE

Estimated Prevalence and Clinical Manifestations of *UBA1* Variants Associated With VEXAS Syndrome in a Clinical Population

David B. Beck, MD, PhD; Dale L. Bodian, PhD; Vandan Shah, MD; Uyenlinh L. Mirshahi, PhD; Jung Kim, PhD; Yi Ding, MD, PhD; Samuel J. Magaziner, MPhil; Natasha T. Strande, PhD; Anna Cantor, MS; Jeremy S. Haley, MS; Adam Cook, MS; Wesley Hill; Alan L. Schwartz, MD, PhD; Peter C. Grayson, MD; Marcela A. Ferrada, MD; Daniel L. Kastner, MD, PhD; David J. Carey, PhD; Douglas R. Stewart, MD

JAMA 2023; 329:318

N = 163 096 (Geisinger MyCode Community Health Initiative; EHR; 1996-J2022)

Exome sequencing

11 individuals (9 men, 2 women) harbored likely somatic variants at known pathogenic UBA1 positions

Macrocytic anemia (hemoglobin: mean, 7.8 g/dL), concomitant thrombocytopenia .

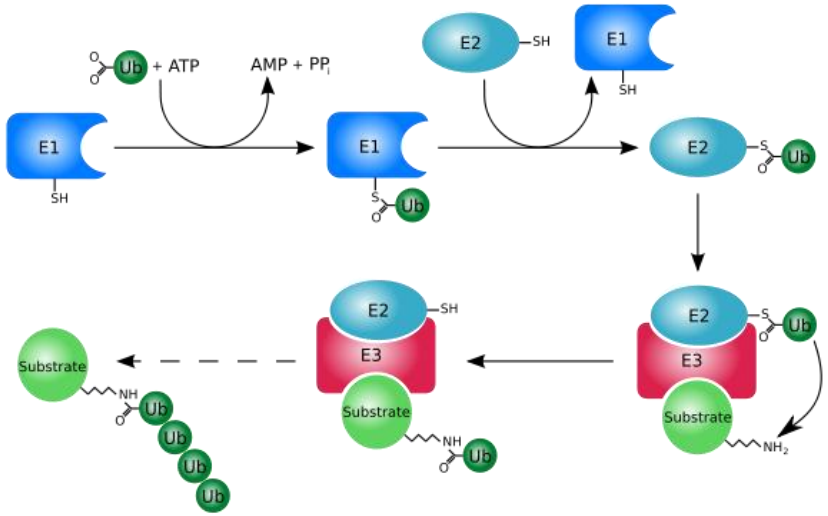
1 in 13 591 unrelated individuals (95% CI, 1:7775-1:23 758)

1 in 4269 men >50 years (95% CI, 1:2319-1:7859)

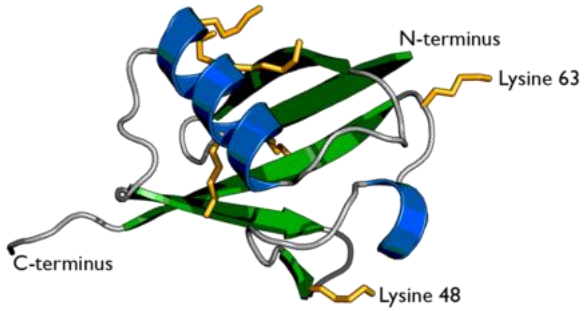
1 in 26 238 women older than 50 years (95% CI, 1:7196-1:147 669).

Ubiquitin-adenylate intermediate E1 binds both ATP and ubiquitin and catalyzes acyl-adenylation of C-terminus of ubiquitin.

UBA1 AND UBIQUTINYLATION



UBA1: catalyzes first step in ubiquitin conjugation (ubiquitination), to mark cellular proteins for degradation. UBA1 catalyzes the ATP-dependent adenylation of ubiquitin, forming a thiosester bond between the two. Participates in subsequent steps of ubiquination as a Ub carrier.

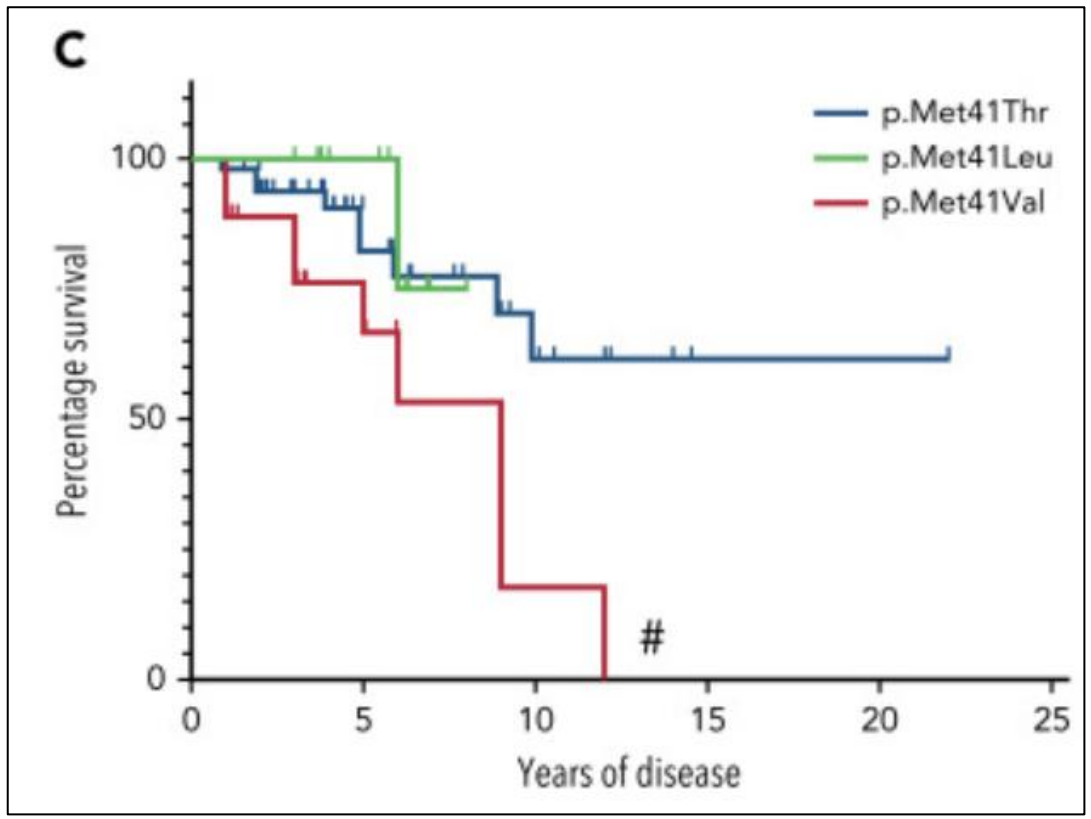


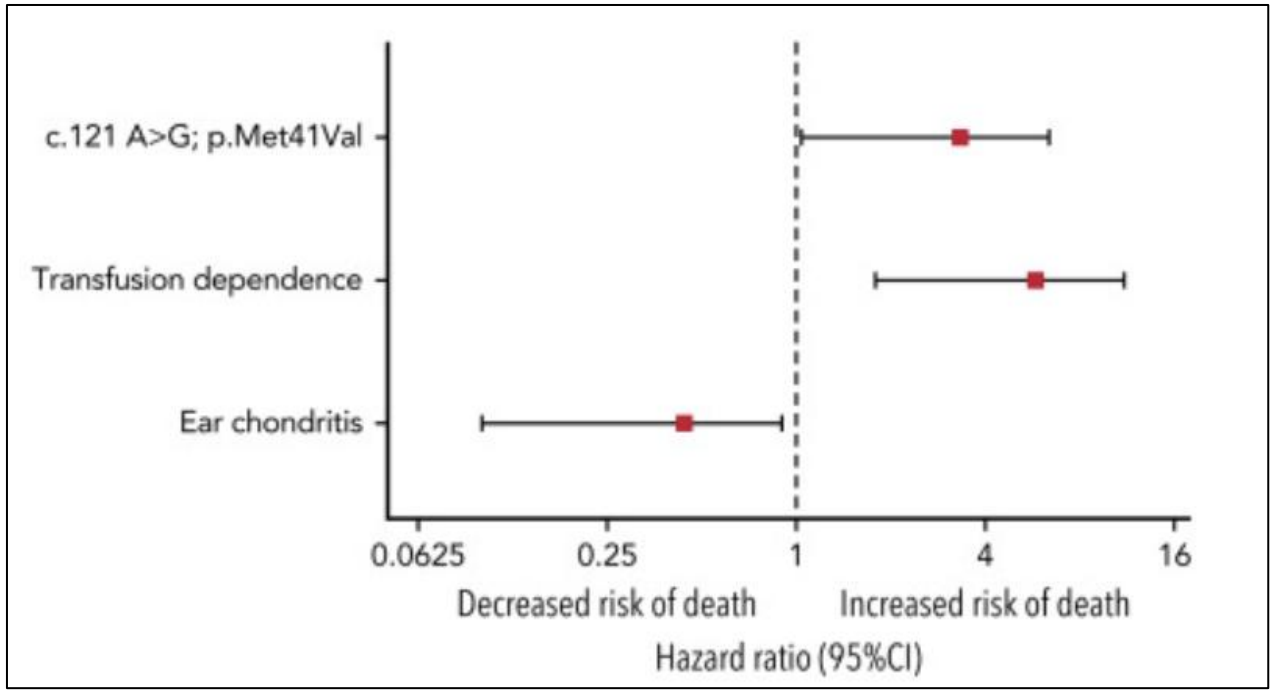
Ubiquitin: small (8.6 kdA), regulatory protein in most eukaryotes' tissues.

Ubiquitylation: marks proteins for proteasome degradation; alters protein localization; affects protein activity and interactions.

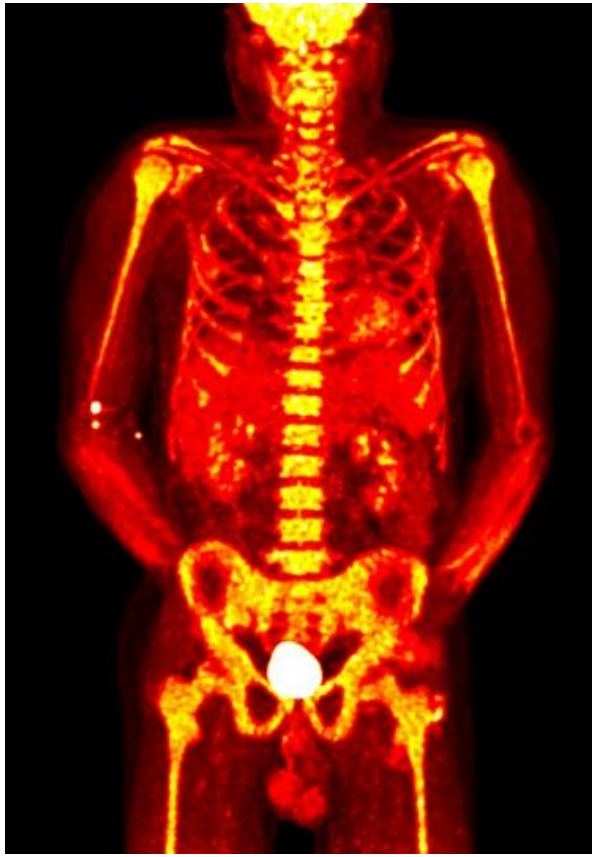
Ubiquitylation: activation (E1s), , conjugation (E2s),, and ligation (E3s) . Ubiquitin bound to lysine residues (isopeptide bond); cysteines (thioester bond); serine and threonine (ester bonds, N-terminal amino group (peptide bond).

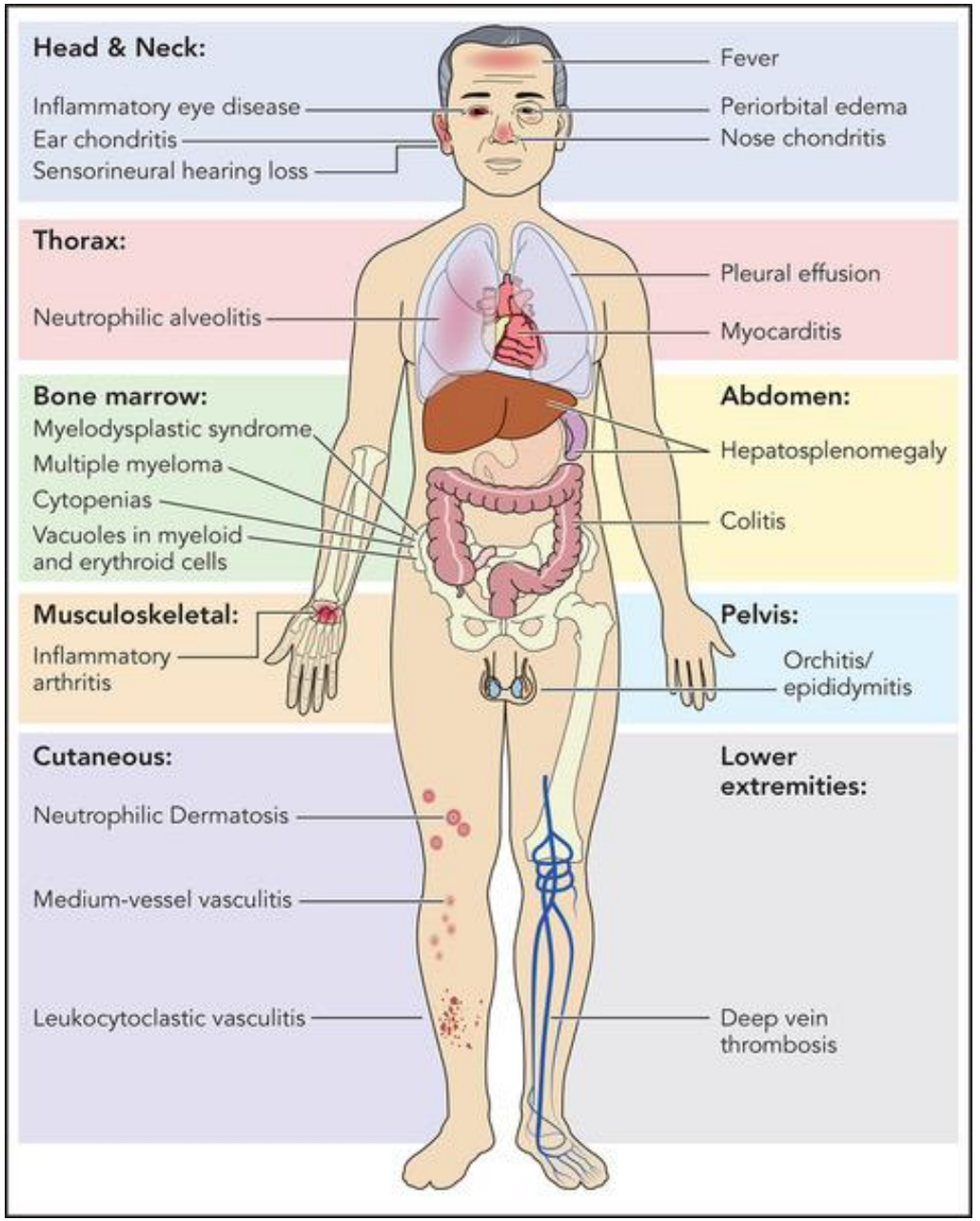
UBA1 GENOTYPE + CYTOPENIA ASSOCIATE WITH POOR PROGNOSIS





VEXAS: A MULTISYSTEM INFLAMMATORY SYNDROME





Grayson P, Patel B, Young NS, Blood 2021; 137:3591

VEXAS IN THE DIFFERENTIAL DIAGNOSIS OF RHEUMATOLOGIC DISEASE

Relapsing polychondritis

Sweet syndrome

“Vasculitis”

Polyarteritis nodosa

Rheumatoid arthritis

inflammatory arthritis

chondritis

vasculitis

inflammatory skin lesions

orbital inflammation

pulmonary infiltrates

Author	Sample Size	Const. Sx[a]	Inflammatory arthritis	Ear and/or Nose Chondritis	Vasculitis[b]	Non–vasculitic Inflammatory skin lesions[c]	VTE	Ocular inflammation[d]	Orbital and/or peri-orbital inflammation	Pulmona infiltrate
Beck et al.	25	25 (100)	10 (40)	16	11 (44)	12 (48)	11 (44)	7 (28)	4 (16)	18 (72)
Ferrada et al.	13	13 (100)	6 (46)	13 (100)	5 (38)	6 (48)	8 (62)	NR	4 (32)	10 (77)
Van der Made et al.	12	11 (92)	4 (33)	5 (42)	7 (58)	10 (83)	1 (8)	5 (42)	1 (8)	8 (67)
Bourbon et al.	11	10 (91)	3 (27)	5 (46)	7 (64)	5 (45)	4 (36)	5 (46)	NR	5 (46)
Poulter et al.	10	10 (100)	2 (20)	4 (40)	2 (20)	9 (90)	1 (10)	NR	1 (10)	2 (20)
Koster et al.	9	8 (88)	5 (55)	5 (55)	4 (44)	NR	4 (44)	4 (44)	0 (0)	0 (0)
Tsuchida et al.	8	6 (75)	3 (38)	8 (100)	NR	7 (88)	NR	3 (38)	NR	NR
Gurnari et al.	2	NR	1 (50)	0 (0)	0 (0)	2 (100)	2 (100)	NR	NR	NR
Staels et al.	2	2 (100)	1 (50)	2 (100)	1 (50)	2 (100)	2 (100)	2 (100)	NR	NR
Lee et al.	1	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)
Takahashi et al.	1	1 (100)	1 (100)	0 (100)	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)
Himmelmann and Brucker	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)
Sakuma et al.	1	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)
Lacombe et al.	1	0 (0)	1 (100)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Magnol et al	1	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (100)	1 (100)	0 (0)	0 (0)
Oganesyan et al.	1	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	(0)	0 (0)	1 (100)
Barba et al.	1	1 (100)	1 (100)	0 (0)	1 (100)	1 (100)	0 (100)	1 (100)	0 (100)	0 (0)
Huang et al.	1	NR	1 (100)	NR	NR	NR	NR	NR	NR	NR
Rieu et al.	1	NR	NR	NR	NR	1 (100)	NR	NR	NR	NR
Ross et al.	1	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Grey et al.	1	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)
Total, n (%)	102	94/100 (94)	41/95 (43)	63/102 (62)	42/94 (45)	61/94 (65)	38/94 (40)	29/77 (38)	12/79 (15)	48/81 (59)

Koster MJ, Warrington KJ, Sem Hematol 2021; 58:218

MAJOR HEMATOLOGIC FEATURES OF VEXAS

Anemia (multifactorial)

“MDS”

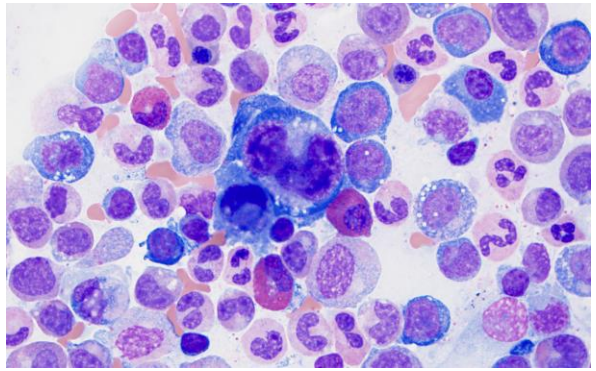
MGUS/smoldering myeloma/multiple myeloma

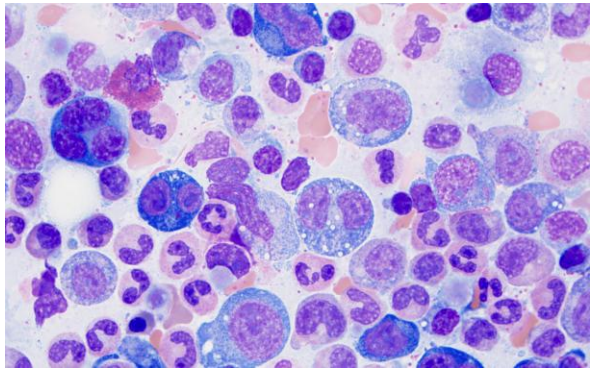
Venous thrombosis

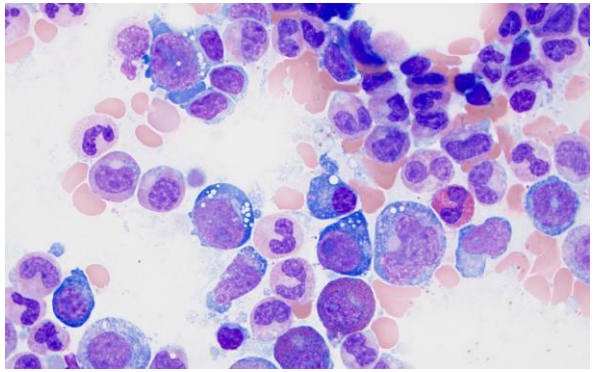
COINCIDENT DISEASES

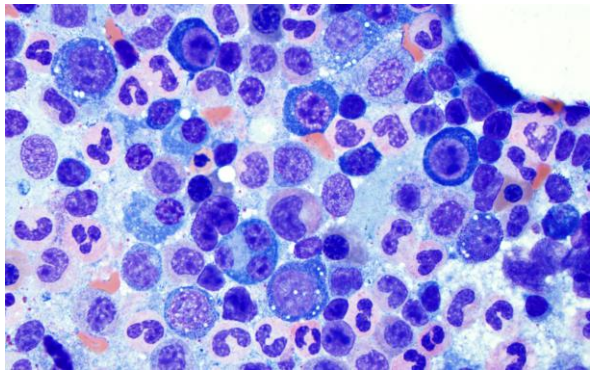
relapsing polychondritis
Sweet syndrome
vasculitides
unusual infections, especially pulmonary

HIGHLY VARIABLE MARROW MORPHOLOGY IN VEXAS



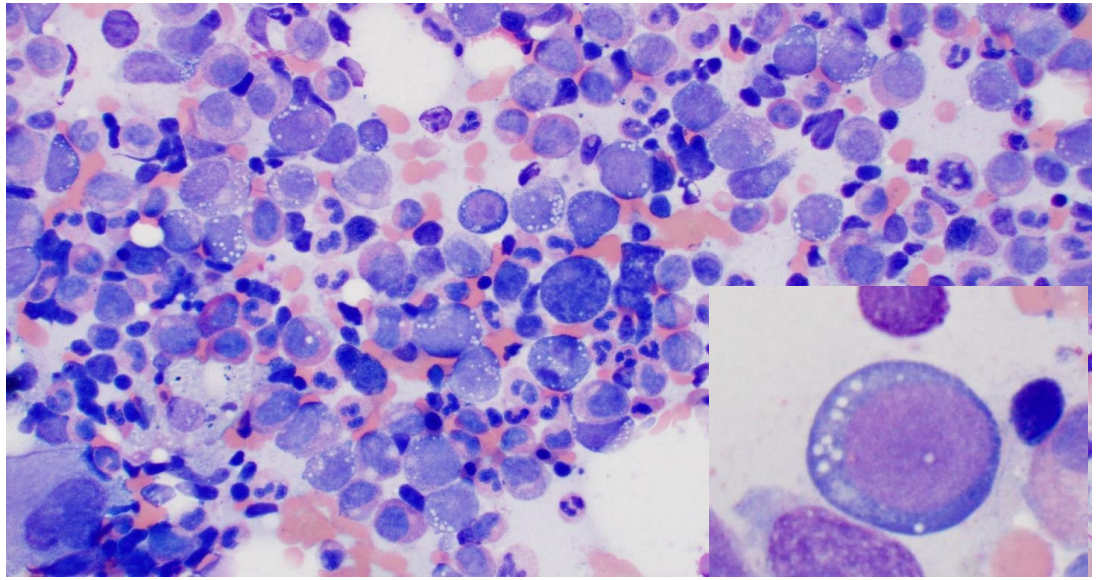


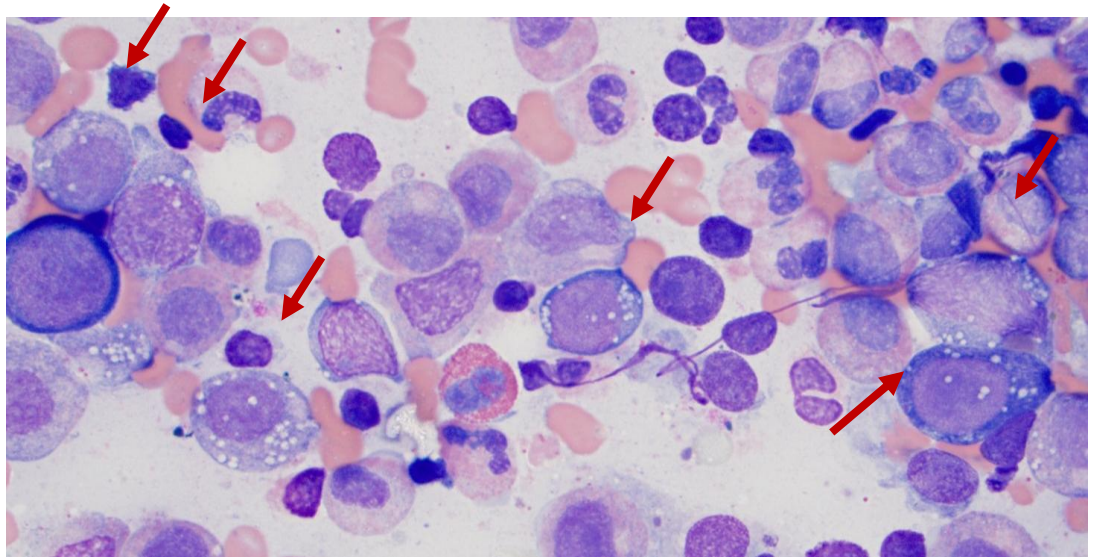




Frank MDS

Images courtesy of K Calvo, DLM, NIH





Vacuoles only

AUTOIMMUNITY IN MDS: HISTORICAL ASSOCIATION

IMMUNOLOGIC ABNORMALITIES IN MYELODYSPLASTIC SYNDROMES

Terry Hamblin, DM, FRCP, FRCPath

Hematol Oncol Clin North America 1992; 6:571

Maladies systémiques au cours des syndromes myélodysplasiques

M Hebbar[1], K Hebbar-Savéan[1], P Fenaux[2]

[1]*Service de médecine interne A,* [2]*service des maladies du sang, CHU de Lille, 1, place de Verdun, 59037 Lille Cedex, France*

(Reçu le 23 février 1995 ; accepté le 11 septembre 1995)

sont rares dans les SMD, le plus souvent purement biologiques, et sont l'apanage des leucémies myélomonocytaires chroniques. Les manifestations systémiques qui sont associées avec une fréquence significative aux SMD sont les arthrites séronégatives, les vascularites cutanées et la polychondrite atrophiante. Ces affections n'ont pas de *substratum* auto-immun évident. Environ 30% des polychondrites atrophiantes sont associées à un SMD. Inversement, 0,6% des SMD sont associés à une polychondrite. L'origine de cette association reste inconnue. Elle atteint

Rev Med Interne 1995; 16:897

Review > Int J Hematol. 1993 Dec;59(1):53-7.

A case of myelodysplastic syndrome progressing to acute myelocytic leukemia in which adult-onset Still's disease had occurred 6 years before

T Sugawara [1], T Tsukada, Y Wakita, Y Wake, K Kouyama, S Tamaki, M Tanigawa, E Iwasaki, C Ohta, S Kageyama, et al.

Case report

Relapsing polychondritis, smouldering non-secretory myeloma and early myelodysplastic syndrome in the same patient: three difficult diagnoses produce a life threatening illness

Rachel Hall *, Neil Hopkinson, Terry Hamblin

Departments of Rheumatology and Haematology, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW, UK

British Journal of Haematology, 1995, **91**, 403–408

Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: response to immunosuppressive therapy

Helen Enright, Harry S. Jacob, Gregory Vercellotti, Robert Howe, Michael Belzer and Wesley Miller

Department of Medicine, Division of Hematology, University of Minnesota Medical School, Minneapolis, Minnesota, U.S.A.

Autoimmune Phenomena in Patients with Myelodysplastic Syndromes

Helen Enright & Wesley Miller

Leuk Lymphoma 1997; 24:483

Rheumatology 2004;43:626–632
Advance Access publication 24 February 2004

Autoimmune phenomena in myelodysplastic syndromes: a 4-yr prospective study

S. Giannouli, M. Voulgarelis, E. Zintzaras[1], A. G. Tzioufas and H. M. Moutsopoulos

Research Article

Autoimmune Phenomena in Patients with Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

Muhammad Wasif Saif, Jon L. Hopkins & Steven D. Gore

Leuk Res 2000; 24:91

THROMBOSIS IN VEXAS

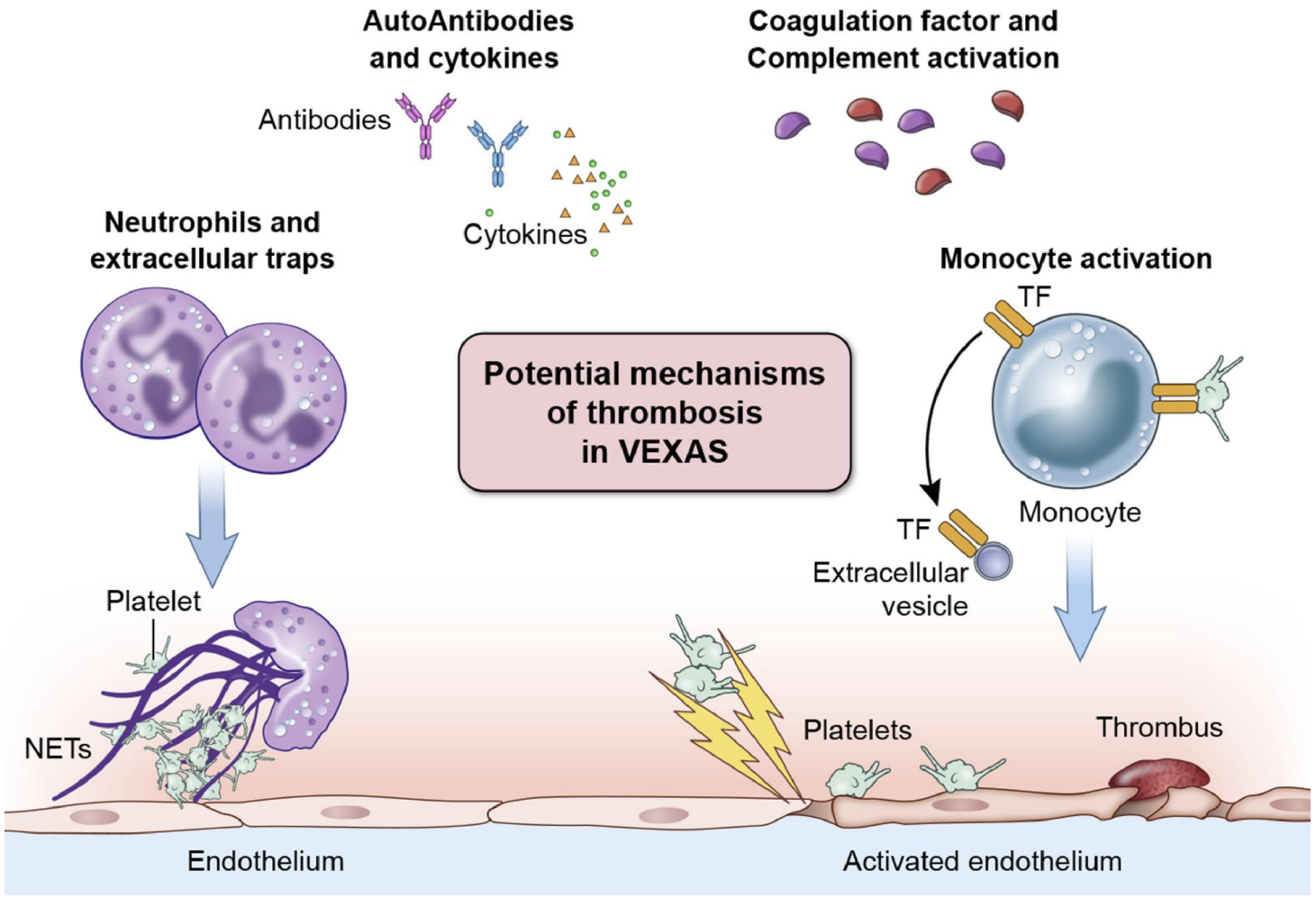
Nearly half of patients have thrombosis

Venous > arterial

Dx: recurrent, unprovoked DVT

Early in disease course (60% < 2 yrs)

High factor VIII, CRP, + LA → inflammation as the main driver



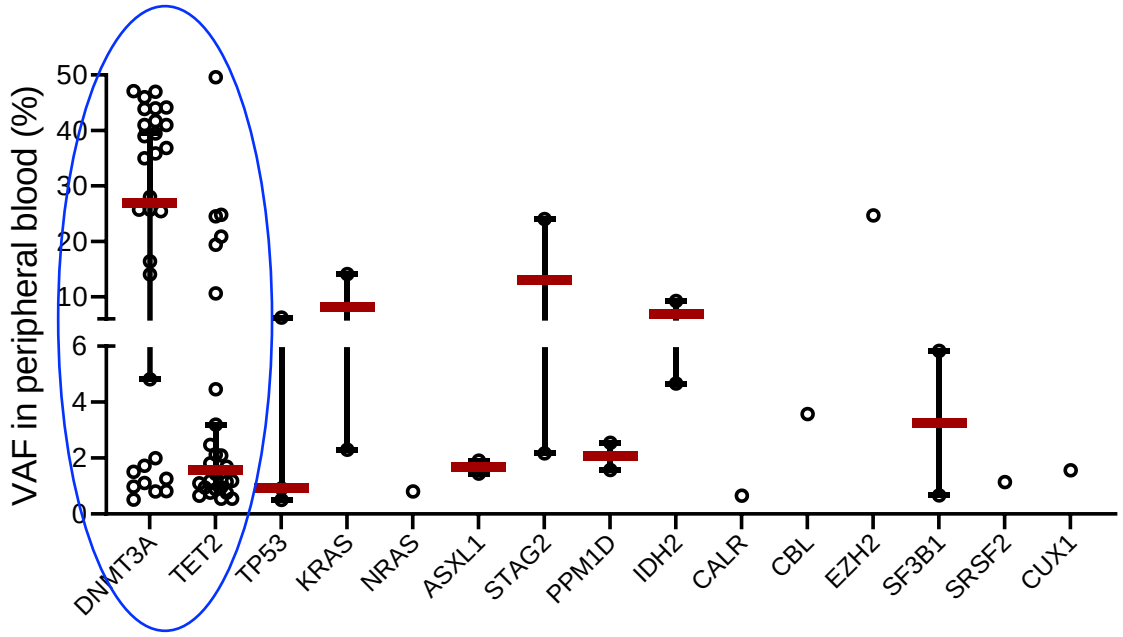
Groarke EM., Dulau-Florea AE., Kanthi Y. Semin Hematol.2021

Patel BA., Obiorah IE., Groarke EM. et al. Blood Adv. 2021

CHIP CLONES IN VEXAS

48/80 (60%) with typical CH mutations

1 (n=28; 35%)
≥2 (n=20; 23%)



Similar pattern in other vascultides

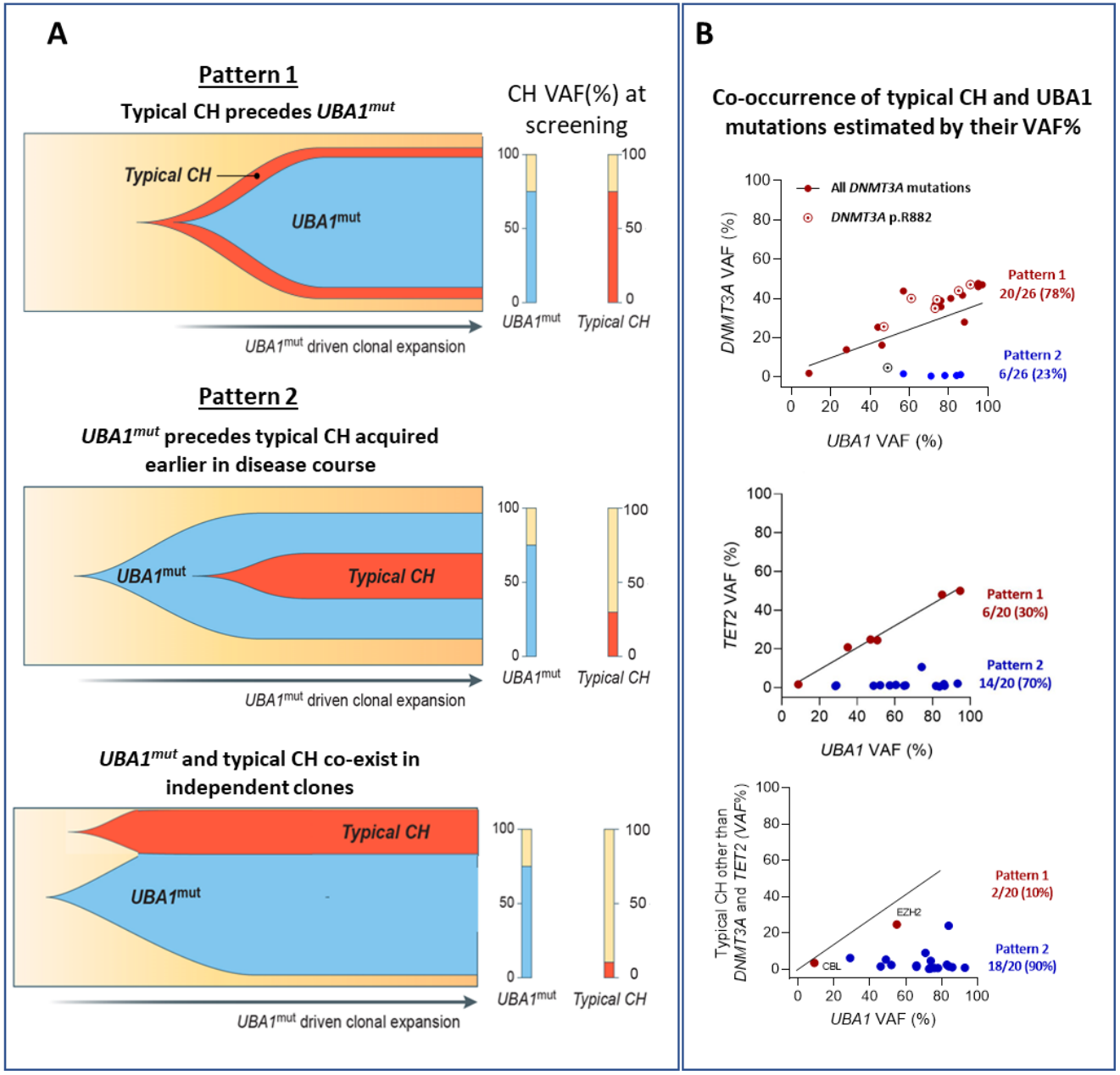
Patel BA., Gutierrez-Rodrigues F et al. Blood 2023; 142:244

CO-OCCURRING SOMATIC MUTATIONS IN VEXAS *UBA1* CLONE ALWAYS DOMINANT

Co-occurrence in 40% patients

CHIP clone *precedes* in half (pattern 1)
CHIP clone expands *after UBA1* clone in half (pattern 2)

UBA1 clone always dominant



Patel BA., Gutierrez-Rodrigues F et al. Blood 2023; 142:244

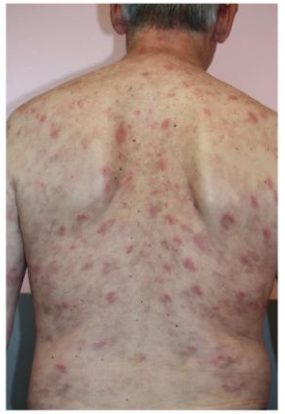
HEMATOPOIETIC STEM CELL TRANSPLANTATION IN VEXAS

CORRESPONDENCE

Check for updates

Allogeneic stem cell transplantation as a curative therapeutic approach for VEXAS syndrome: a case report

Loschi M et al, BMT 2022; 57:315



DOI: 10.1111/bjh.18488

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

LETTER TO THE EDITOR

Allogeneic haematopoietic stem cell transplantation for VEXAS syndrome: UK experience

Al-Hakim A et al, Br J Hematol 2022; 199;777

Mayo Clinic

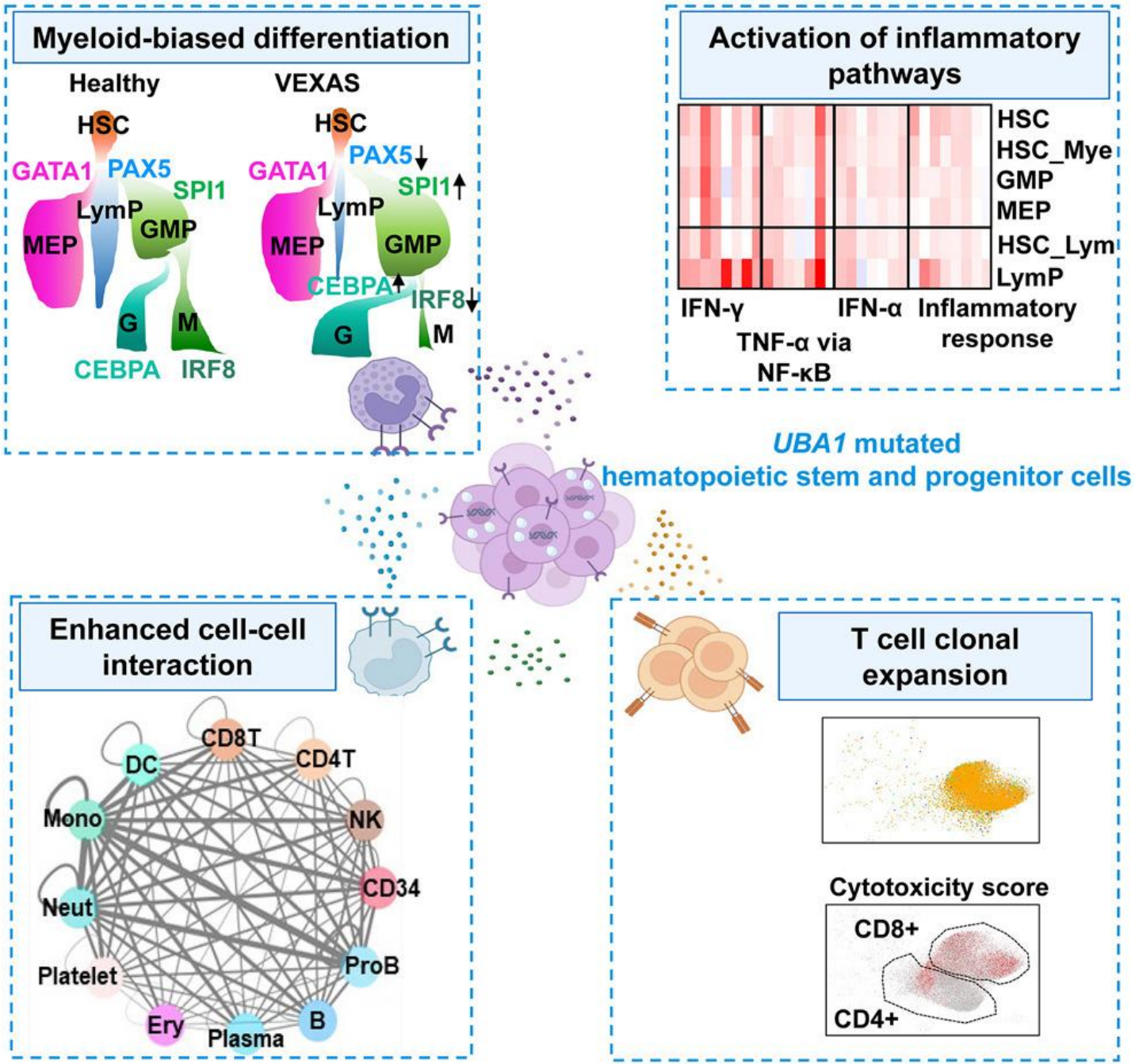
CORRESPONDENCE

AJH WILEY

Reduced intensity conditioning allogeneic hematopoietic stem cell transplantation in VEXAS syndrome: Data from a prospective series of patients

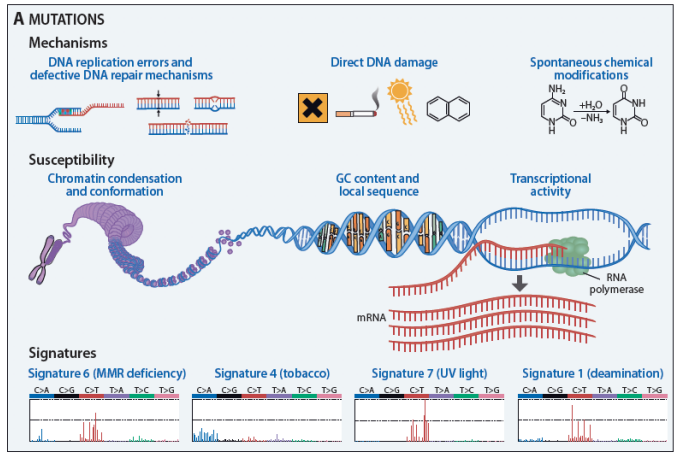
Mangaonkar AA et al, Am J Hematol 2023; 98E28

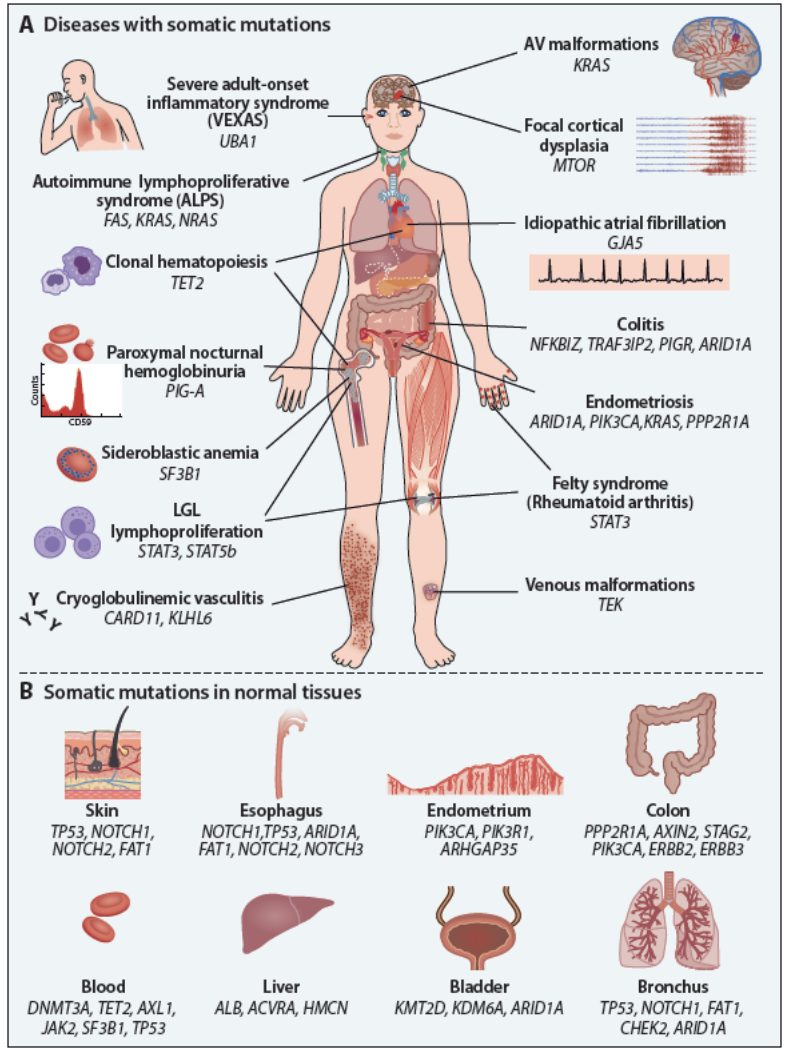
VEXAS ORIGINATES IN BM HSCS

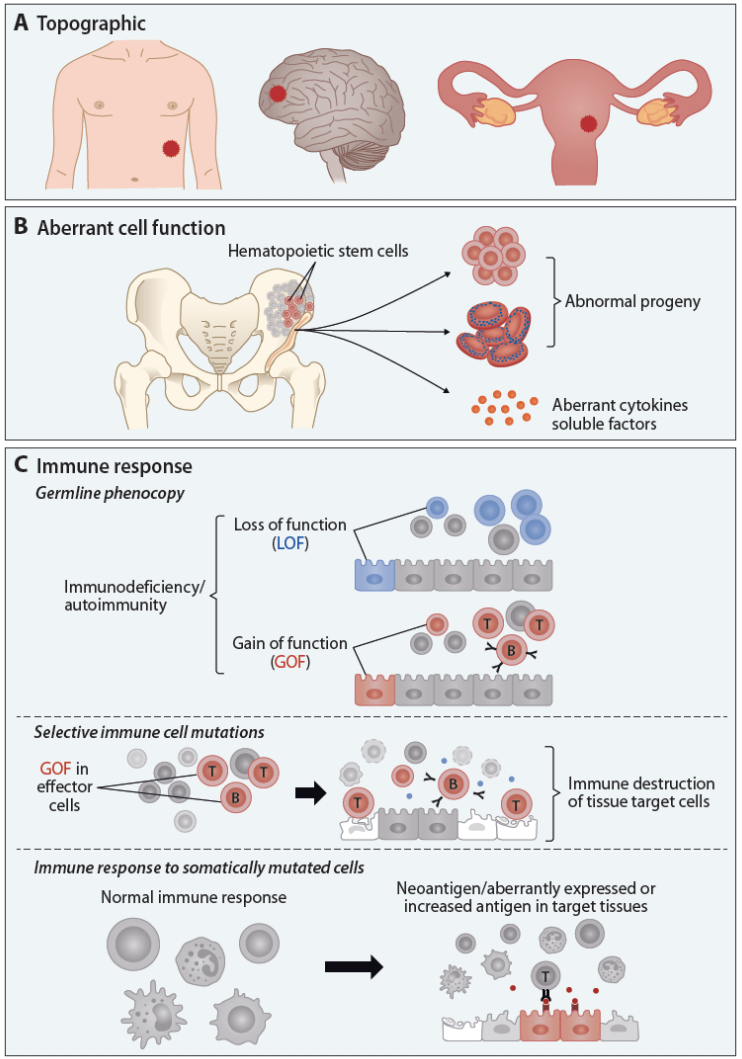


Wu Z et al, Cell Rep Med 2023; 4:101160

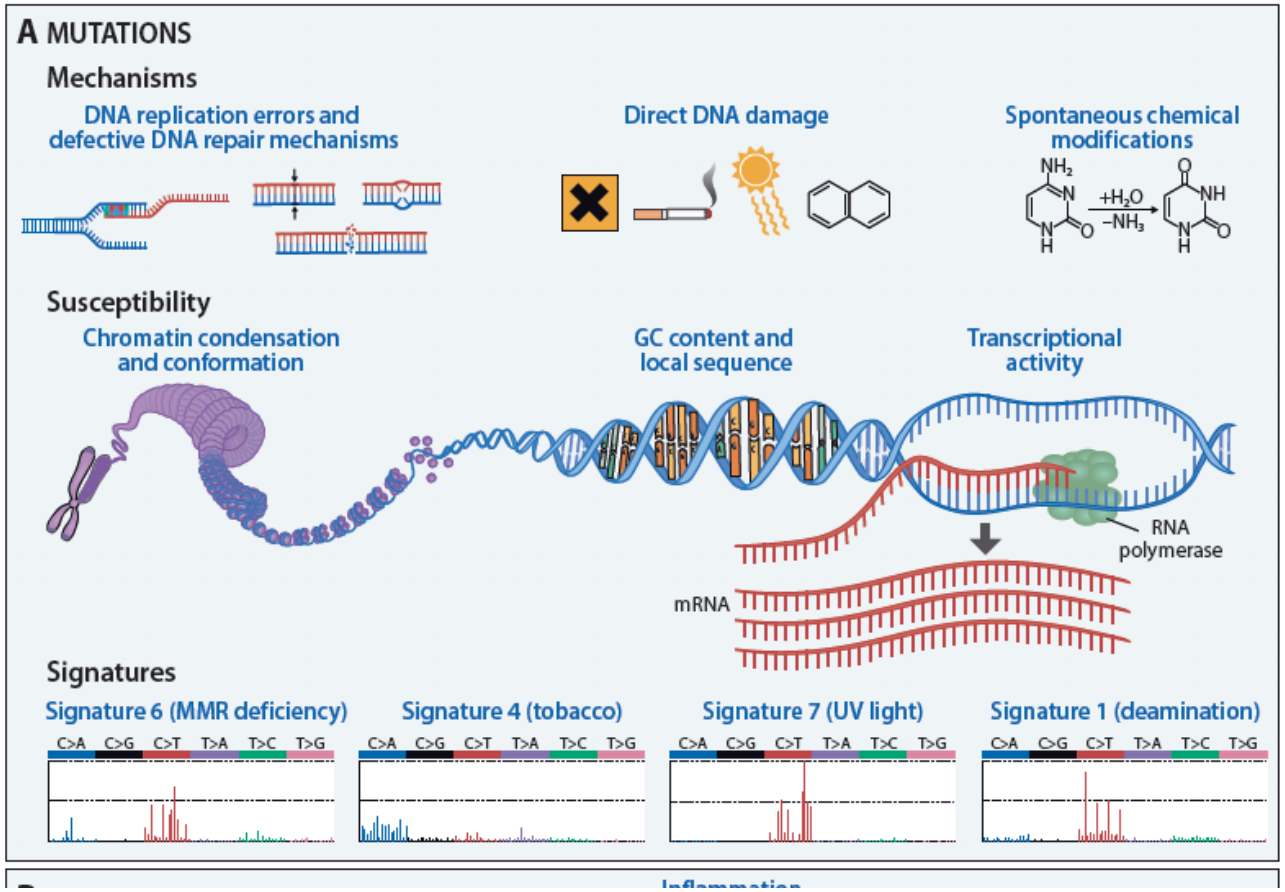
SOMATIC MUTATIONS IN “BENIGN” DISEASE







ORIGIN AND CHARACTERISTICS OF SOMATIC MUTATIONS



1-5 x 10^{-10}/base pair/cell division
3 x 10^{9} bp/genome

Somatic mutation rate>>germline rate

Mutations acquired *early,* post-zygotic/childhood organ growth

Variability among tissues/individuals/species
- multigenic
- telomere (*TERT)*
- repair mechanisms

Replication errors
- mismatched bases
- chromosome misalignment and breaks
- anomalous synthesis
- error prone DNA repair
- transposition
- homologous recombination

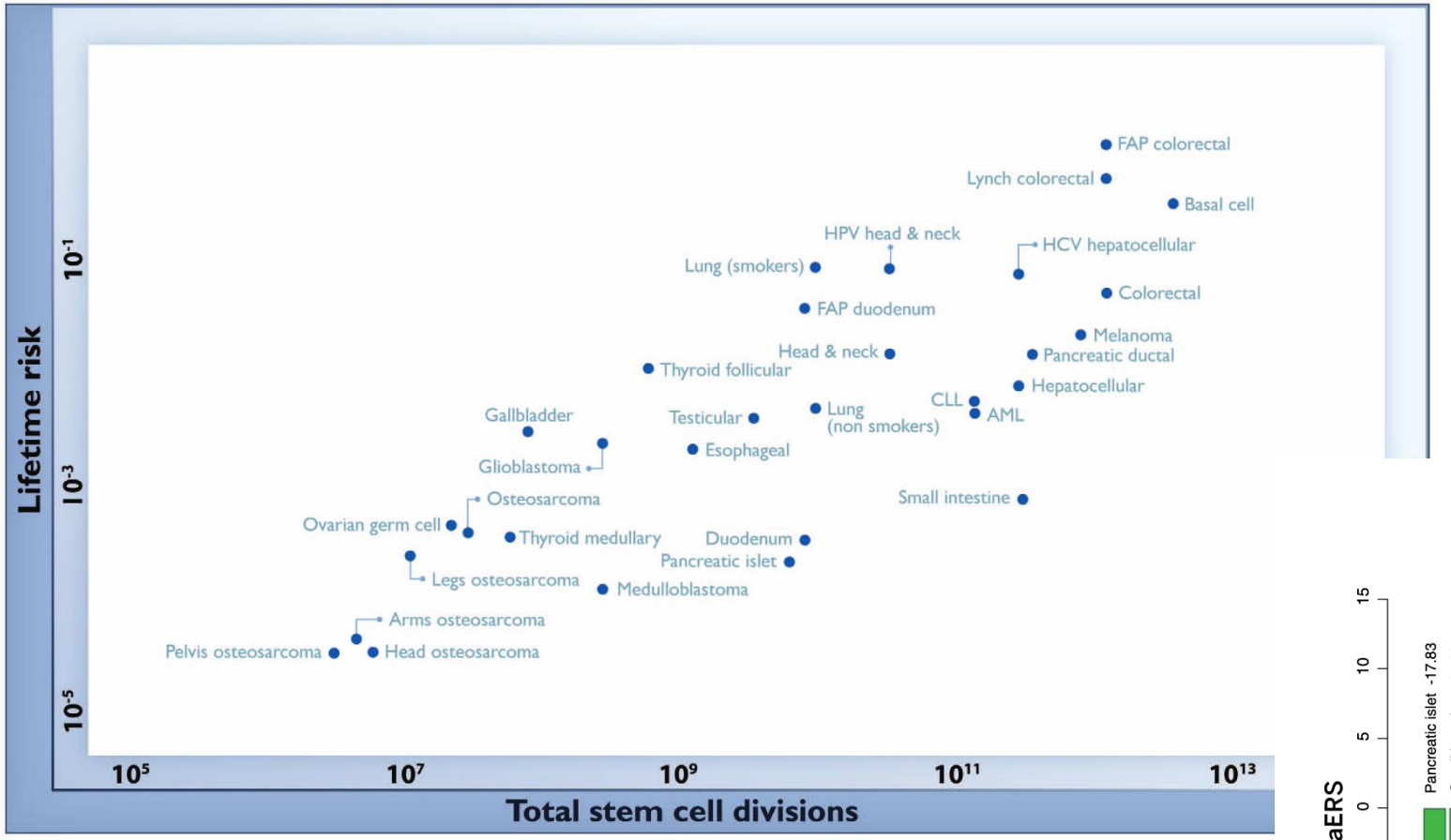
Endogenous factors
- cell metabolism products
- reactive oxygen and nitrogen species
- retroviruses/transposable elements

Environmental toxins

[Structural variants may be more common]

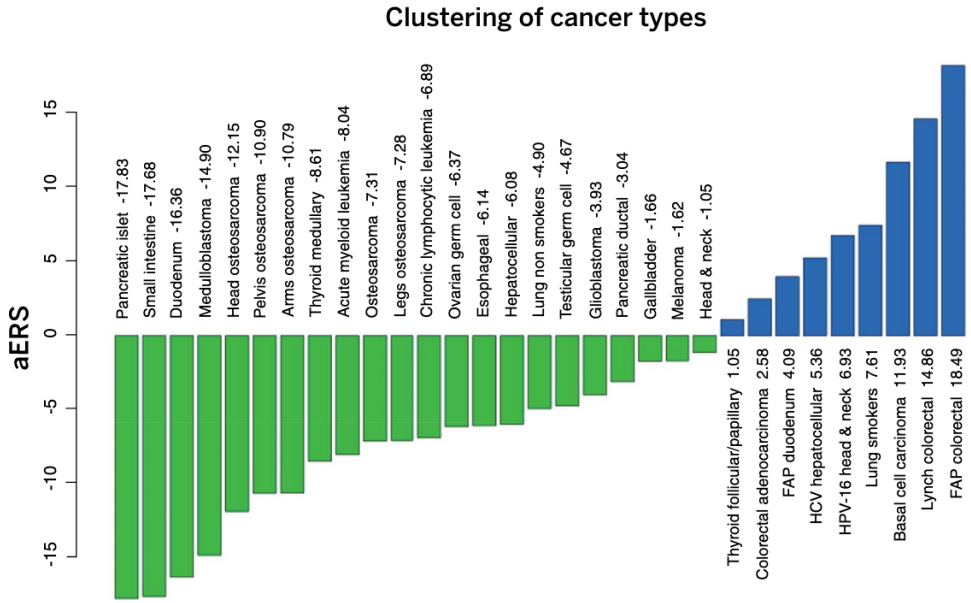
[Intronic, noncoding, regulatory sequences?]

CANCER SOMATIC MUTATIONS--MAINLY REPLICATION ERRORS



Lifetime risk of cancer α
mitoses in tissue stem cell

Replication errors (R) >2/3 risk



Tomasetti C, Vogelstein B, Science 2015; 347:78

ENVIRONMENTAL TOXINS AND SOMATIC MUTATIONS

Tobacco and bronchial epithelium (Yoshida K et al, Nature 2020; 578:266)

Current smokers: +1000-10,000 mutations/cell; distinct signatures; ↑driver gene mutations

Cirrhotic liver (Brunner SF et al, Nature 2019; 574:538)

↑SVs, mutation burden, driver mutations, exogenous signatures

Esophageal epithelium (Yokoyama A et al, Nature 2019; 565:312)

↑NOTCH1 mutated clones with smoking, alcohol (and aging, in normal tissue)

Sun-exposed skin (Martincorena I et al, Science 2015; 348:880)

UV-mutational signature (C>T), positive selection of “cancer genes” in normal individuals

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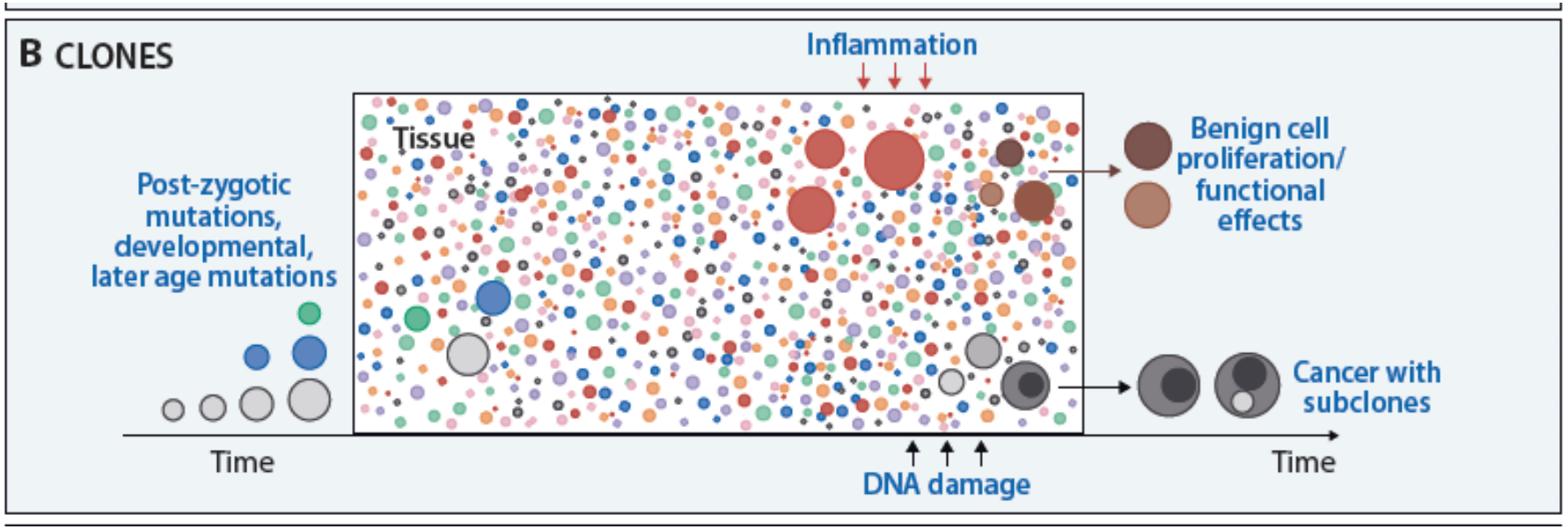
Many novel, yet-to-be annotated signatures!

CLONES IN TISSUES



Every tissue genetically “mosaic”

Cells accumulate mutations—100s-1000s/cell—at about 20-40 mutations/yr (deamination)

Almost all somatic mutations neutral—no functional effect

Deleterious mutations lead to cell elimination—senescence and apoptosis

Telomere/telomerase effects/genetic repair defects and BRCA1/epigenetic abnormalities

Positive selection of somatic clones (negative for organisms)

DARWIN FROM OUR PERSPECTIVE

Vast array of living examples

Extraordinary attention to detail

Emphasis on sexual transmission

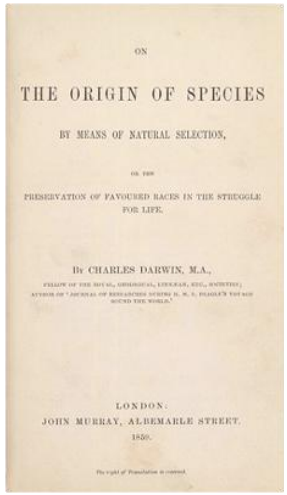
Focus on intermediate states

Influence of environments

Complexity of interactions

Temporal dynamism

Modesty in confronting ignorance


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

Heritability explained

No mechanism without genetics

Not medical, no pathophysiology

Life forces and a creator rather than statistics and population genetics

“We forget continually how large the world is.’

“Few of us know…what a million really means.”

“It is always advisable to perceive clearly our ignorance.”

NOT-SO-SIMPLE DARWINIAN EVOLUTION
MORE THAN "SELECTION BY THE ENVIRONMENT"

Information theory (Longo G, 2017)

transmission (DNA) vs instruction (genetic programs)

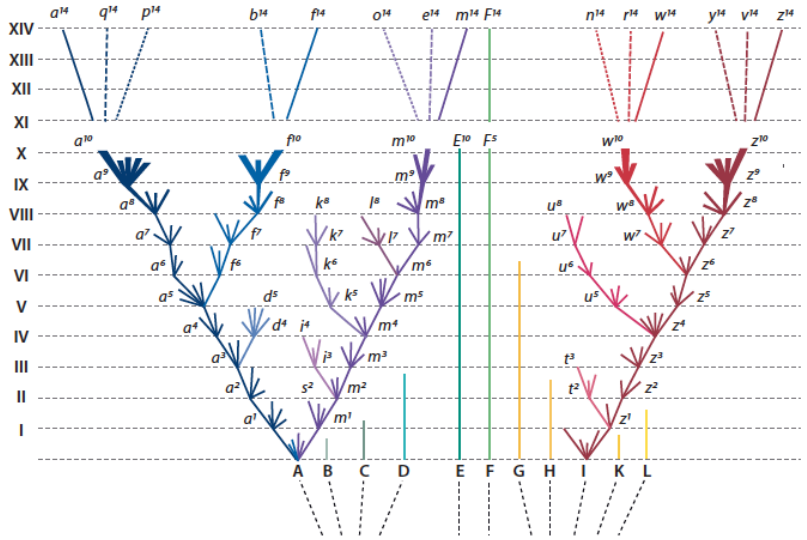
Stabilizing selection (Schmalhausen/Dobzhansky)

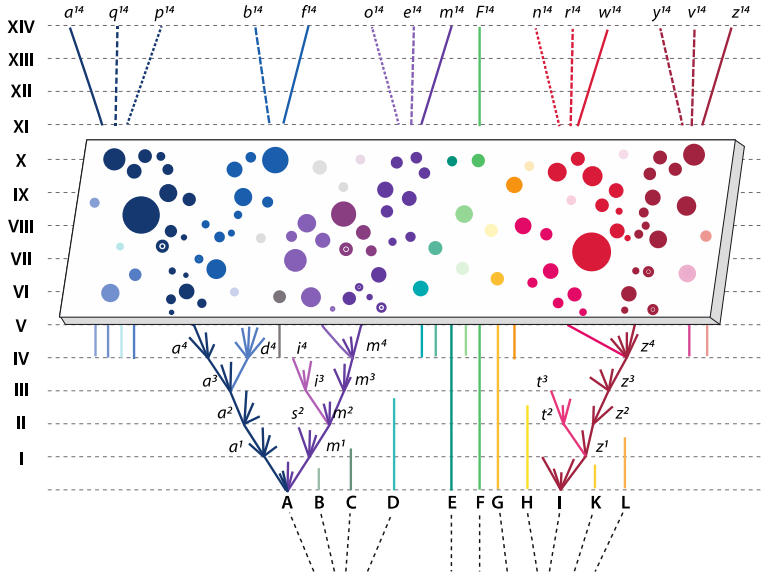
phenotypic plasticity (programmatic correlations)
robustness
self-regulation, compensatory networks, environment and epigenetics
regulation: "blueprint" vs "switchboard"
statistics: epigenetic landscape and developmental constraint (Waddington)
evolutionary opportunities: adjustment, multi-tasking, connection, interaction (Sharov)

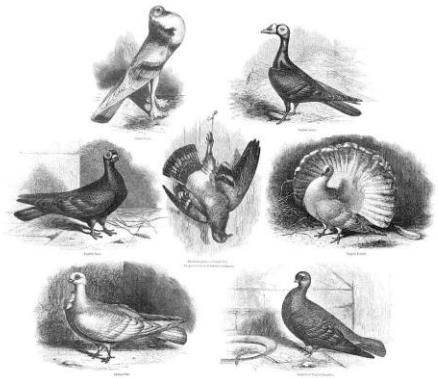
"Evolvabilty" (evolutionary potential) (Sharon AA, 2014)

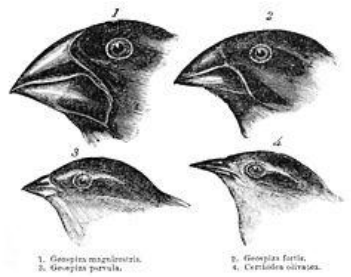
Multi-tasking as evolutionary rehearsal, basis of selection (programs, not genes)
Dedifferentiation: epigenetics = plasticity
Adaptability traits: low maintenance cost, long term effects, population effects
Connection and higher order regulation (allometry) vs modularity
"Baldwin effect": behavior reshapes fitness landscape
Exaption: hidden intermediates of selection

PROBLEM OF SPECIATION AND SOMATICALLY MUTATED CLONES

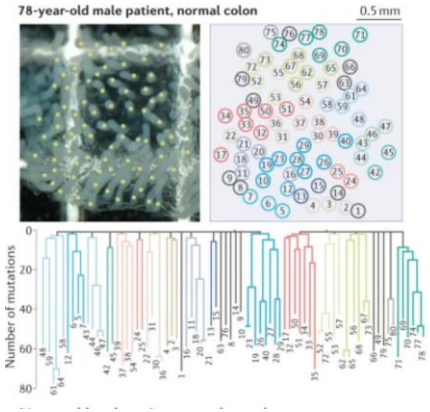






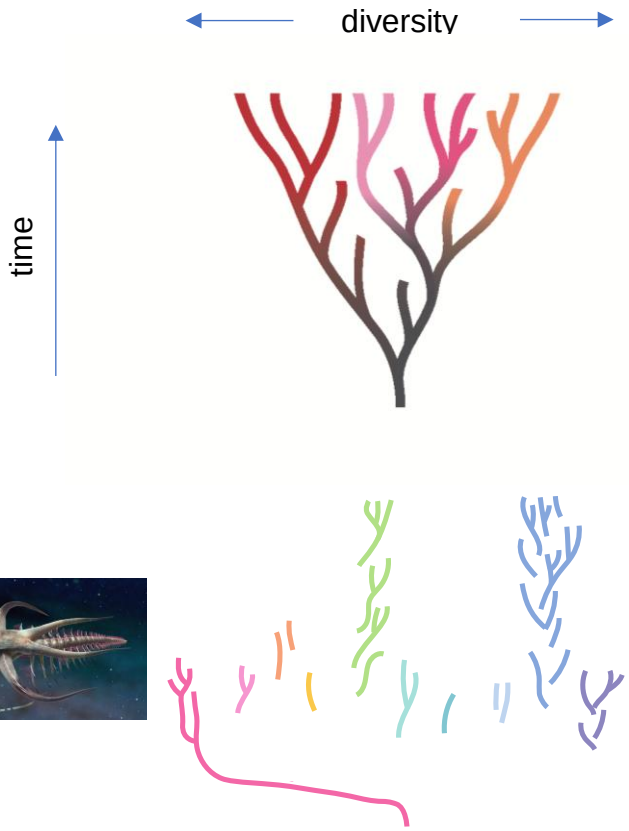


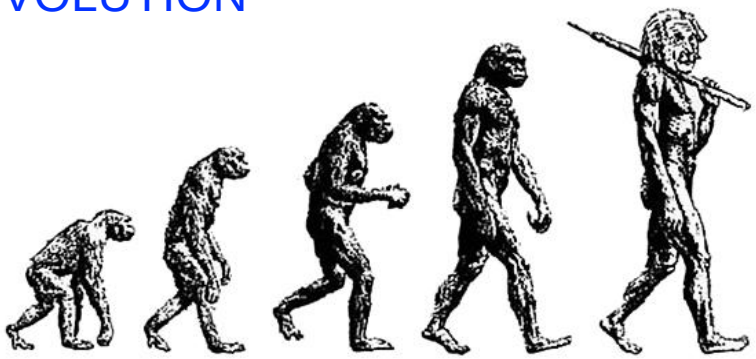
Varieties, variants, hybrids, quasi-species, species…

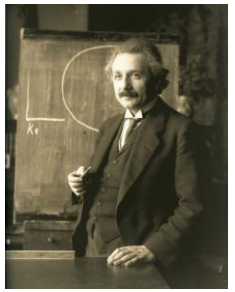


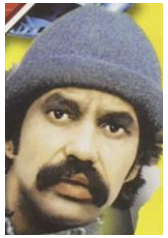
Cancer gene mutations in normal tissue (Kakiuchi N, Ogawa S, Nat Rev Cancer 2021; 21:239)

TWO VIEWS OF EVOLUTION





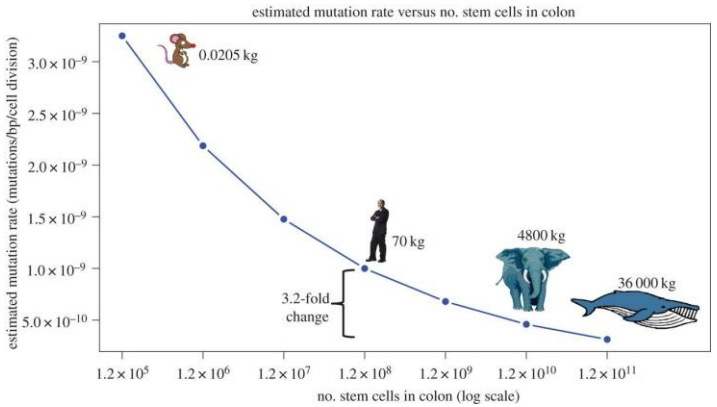




Selection's target: gene? organism? species?
Evolution's product: goals? exaptions?
Selection by "environment: intracellular to global?"
Dead ends in real time: extinction events? tempo and gaps?

After Gould SJ, Wonderful Life, 1989

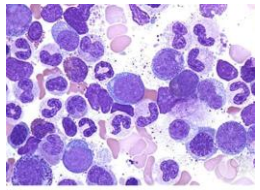
PARADOXES IN EVOLUTION: ORGANISM AND ORGAN



Peto's: Why do large, long-lived animals *not* have more cancer?

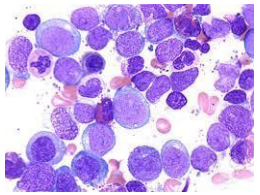
Dameshek's: Why does CML always lead to AML, ET and PV not?

CML

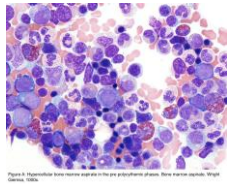


100%

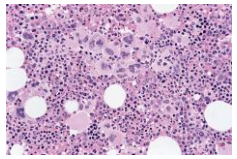
AML



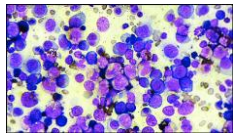
PV



ET



PNH

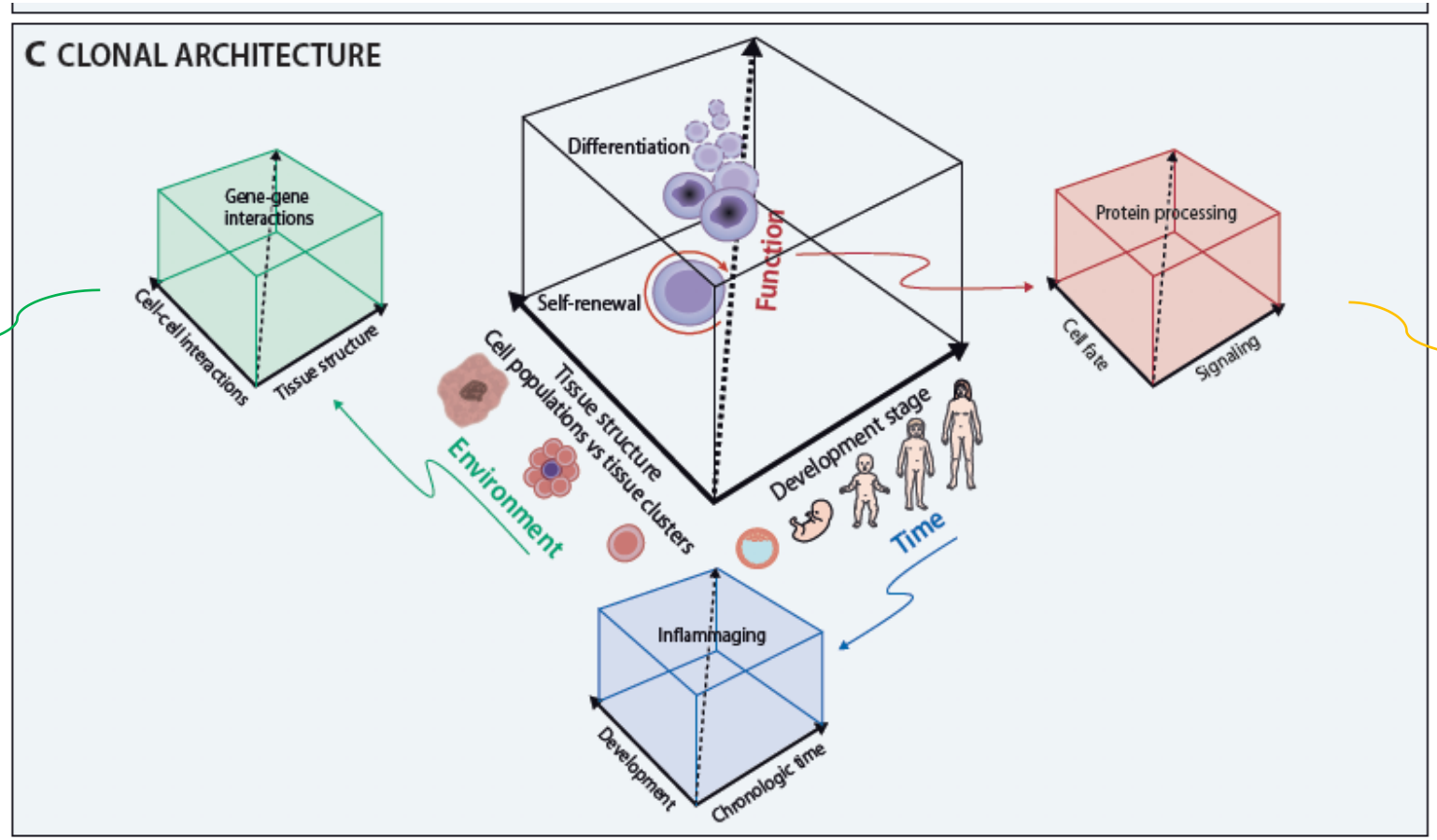


Infrequent transformation

COMPLEXITY OF CLONAL ARCHITECTURE

Cell-cell
stroma
ECM
hormones

Microenvironment
Microbiota
External environment



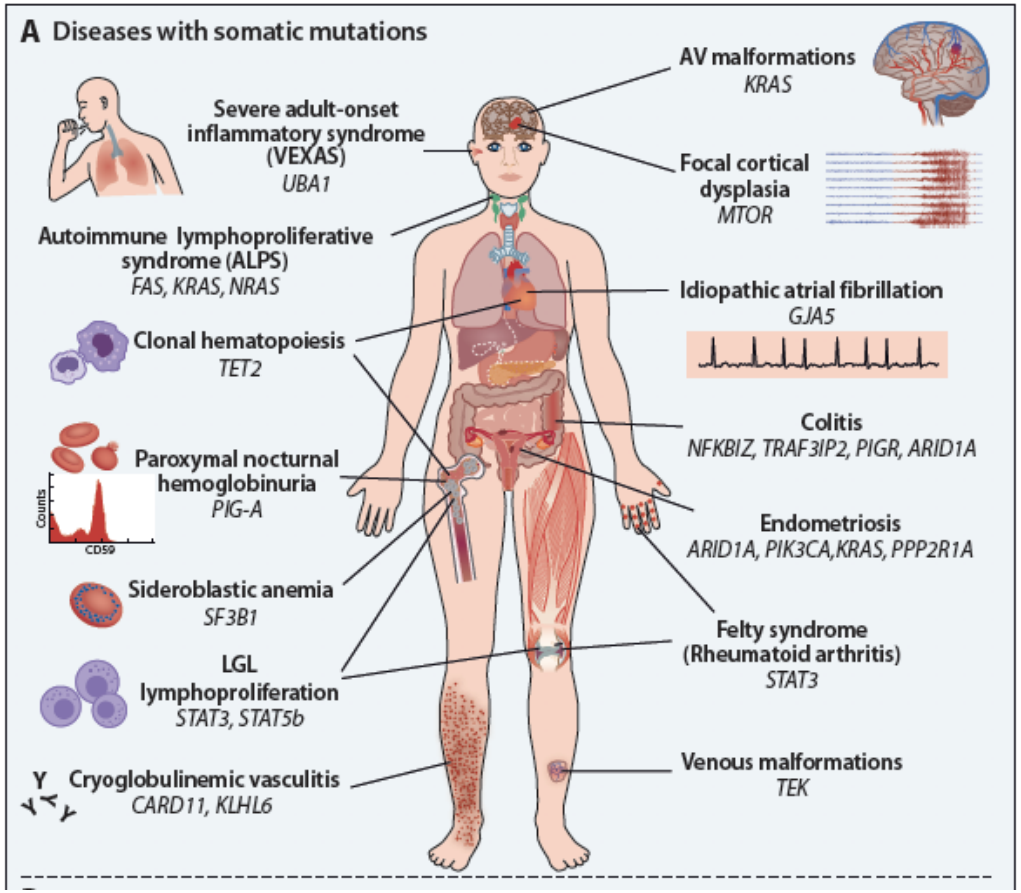
Processing
synthesis
degradation
stress responses

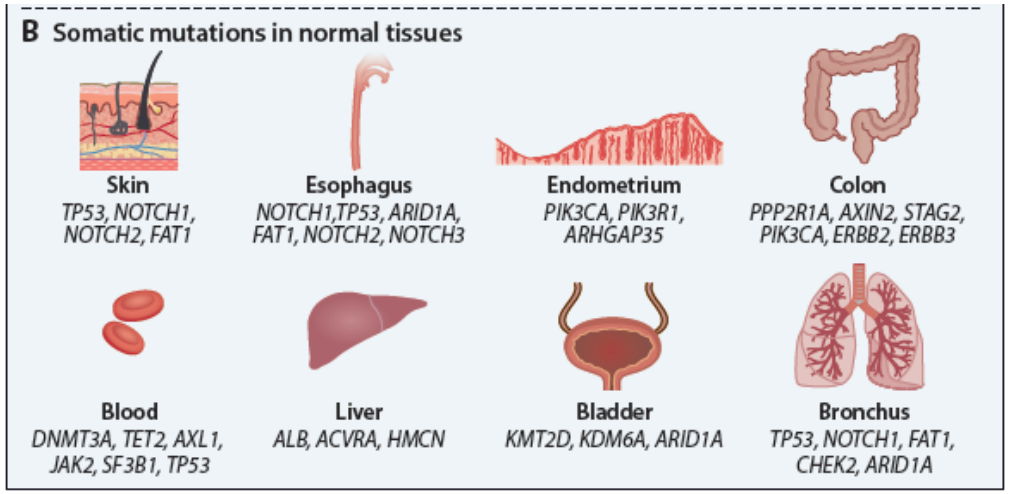
Proliferation
Viability
Apoptosis

Chronologic time
young/old
segmental time
exposure duration

Species lifespans
Germline genetics
Environmental influences

SOMATIC MUTATION DISEASES/SOMATIC MUTATION CLONES IN HEALTHY TISSUE





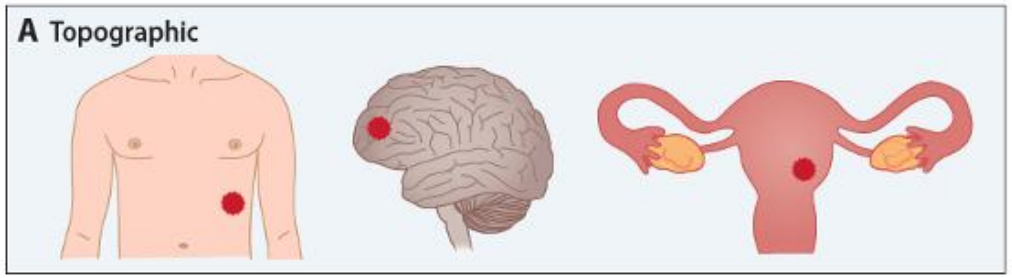
SOMATIC MUTATION DISEASES

Disease	Disease manifestation	Gene(s)	Mutated cell type	Effect of mutations	Freq of mutations	Reference
Topographic, local diseases and overgrowth syndromes						
AV malformations	Abnormal knot of blood vessels, predisposition to hemorrhagic stroke	*KRAS*	Endothelial cells	Increased activation of the MAPK–ERK signaling pathway	60% of cases	Nikolaev 2018
Venous malformations	Abnormal venous channels causing pain and organ obstruction	*TEK (TIE2)* *PIK3CA*	Endothelial cells	Chronic activation of AKT, dysregulation of angiogenesis	50-80% of sporadic cases	Limaye 2009, Soblet 2013, Limaye 2015, Natynki 2015
Focal Cortical dysplasia type IIb	Refractory epilepsy due to malformation of cerebral cortex	*MTOR*	Neuronal cells	Hyperactivation of MTOR pathway causing disruption of neuronal migration	15-40%	Nakashima 2015, D'Gama 2015, Lim 2015
Hemimegalence-phaly	Overgrowth of brain hemispheres, epilepsy	*PI3K* *AKT3* *MTOR*	Neuronal cells	Hyperactivation of PI3K-MTOR pathway	30%	Lee 2012
Sturge-Weber syndrome and port-wine stains	Congenital neurological and skin disorder, epilepsy, cutaneous capillary malformations	*GNAQ*	Post-zygotic cell	Activation of MAPK pathway	90%	Shirley 2013
Melorheostosis	Excess bone formation leading to functional impairment	*MAP2K1*	Post-zygotic cell	Activation of MEK1-ERK1/2 pathway	50%	Kang 2018
RHOA-related mosaic ectodermal dysplasia	Hypopigmentation, hypotrichosis, facial dysmorphism, acral and teeth anomalies	*RHOA*	Post-zygotic cell	Inactivating mutation, cytoskeletal alterations in cells	Diagnosed by genetic finding	Vabres 2019
Proteus syndrome	Overgrowth of brain, connective tissue, and skin	*AKT1*	Post-zygotic cell	Activation of the PI3K–AKT pathway	90%	Lindhurst 2011
Progressive overgrowth of fibrous and adipose tissue and bone	Segmental progressive overgrowth of fibroadipose tissue with skeletal overgrowth	*PIK3CA*	Post-zygotic cell	Activation of PI3K signaling pathway	Diagnosed by genetic finding	Lindhurst 2012
Idiopathic atrial fibrillation	Rapid cardiac arrhythmia without underlying cause	*GJA5*	Myocytes	Abnormal intracellular transport of connexin and gap-junction formation	20%	Gollob 2006
Endometriosis	Ectopic endometrial lesions causing dysmenorrhea, pelvic pain, and infertility	Multiple cancer driver genes	Epithelial cells	Loss of function mutation in *ARID1A*, activating *KRAS* mutation	80%	Anglesio 2017
Phenocopies of germline disease						
ALPS	Lymphadenopathy, splenomegaly, autoimmunity	*FAS*	HSC	Impaired FAS-induced apoptosis	>30% in sporadic ALPS cases	Holzelova 2004, Dowdell 2010
RALD	Lymphadenopathy, splenomegaly, autoimmunity	*NRAS* *KRAS*	HSC	Increased RAF/MEK/ERK signaling causing impaired apoptosis	Diagnosed by genetic finding	Oliveira 2007, Tagaki 2011, Niemela 2011
CAPS	Systemic autoinflammatory disorder (fever, urticaria-like rash, arthralgia, myalgia)	*NLRP3*	HSC/HPC	Enhanced activation of the NLRP3-inflammasome	Common in late-onset disease	Saito 2005
Sporadic NF1/NF2	A tumor predisposition syndrome with café-au-lait spots, dermal neurofibromas and neurological symptoms	*NF1* *JJAZ1*	Post-zygotic cell	Microdeletions of tumor suppressor NF1 gene area covering also flanking genes such as *JJAZ1*	40%	Kehrer-Sawatzski 2004
Alport syndrome	Kidney disease, hearing loss, eye abnormalities	*COL4A5* and other associated genes	Post-zygotic cell	Defect in type IV collagen	Diagnosed by genetic finding	Plant 2000
HIES	Primary immune deficiency syndrome, increased serum IgE	*STAT3*	Post-zygotic cell	Impaired STAT3 function due to loss-of-function mutation	Diagnosed by genetic finding	Hsu 2013
INFLTR8	Inflammation, neutropenia, bone marrow failure, lymphoproliferation	*TLR8*	Post-zygotic cell	Gain-of-function TLR8 alteration leading to T-cell activation	Diagnosed by genetic finding	Aluri 2021
Hematopoietic stem cell and other hematologic diseases						
PNH	Hemolytic anemia due to destruction of red blood cells, thrombosis	*PIG-A*	HSC	Absence of GPI anchors on cell surface due to loss of PIGA enzyme	100%	Takeda 1993
Sideroblastic anemia	Anemia, ring sideroblasts in BM	*SF3B1*	HSC	Aberrant spliceosome function	60-90%	Papaemmanuil 2011
ATMDS	Severe anemia due to alpha-thalassemia, high HbH levels and myelodysplastic changes	*ATRX*	HPC	Down-regulation of α-globin gene expression due to inactivating mutations	Diagnosed by genetic finding	Gibbons 2003, Steensma 2014
Cardiovascular diseases associated with CHIP	Clonal expansion and abnormal inflammatory reactivity of myeloid cells	*TET2*	HSC	Proliferation advantage for myeloid precursor cells, abnormal cytokine production	NA	Jaiswal 2014, Jaiswall 2017, Fuster 2017, Sano 2018, Wang 2020
Histiocytic disorders (Langerhans histiocytosis, Erdheim-Chester disease)	Accumulation of histiocytes in the tissues, local and systemic inflammation	*BRAF,* *MAP2K1* other MAPK pathway genes	HSC	Constitutive activation of MEK-ERK pathway	90%	Badalian-Very 2010, Haroche 2012, Brown 2014, Chakraborty 2014
VEXAS	Systemic autoinflammatory disorder (fever, cytopenia, vasculitis, dysplastic bone marrow)	*UBA1*	HSC	Decreased ubiquitylation due to loss of cytoplasmic isoform of UBA1	Diagnosed by genetic finding	Beck 2020
Schnitzler Syndrome	Urticarial-like rash, IgM paraprotein	*MYD88*	HSC	Increased NF-kB and JAK-STAT signaling	30%	Pathak 2019
Autoimmune and other immunological diseases						
LGL lymphoproliferation	Lymphoproliferation, autoimmunity	*STAT3* *STAT5B*	Mature T or NK cell	Increased JAK-STAT signaling, resistance to apoptosis	30-50%	Koskela 2012, Jerez 2012, Rajala 2013, Andersson 2016
Felty syndrome	Rheumatoid arthritis, splenomegaly, neutropenia	*STAT3*	Mature CD8+ T cell	Increased JAK-STAT signaling, resistance to apoptosis	50%	Savola 2018
AA and hypoplastic myelodysplastic syndrome	Immune destruction of BM by cytotoxic T cells	*STAT3* other MAPK genes	Mature CD8+ T cell	Increased JAK-STAT signaling, resistance to apoptosis	10%	Jerez 2013, Lundgren 2021
PRCA	Red cell aplasia, anemia	*STAT3*	Mature CD8+ T cell	Increased JAK-STAT signaling, resistance to apoptosis	40%	Qiu 2013, Ishida 2014, Kawakami 2018
cGVHD	Aberrant clonal cytotoxic T cell expansions	*MTOR*	Mature T cell	Increased MTOR signaling, increased cytotoxicity	2%	Kim 2020
Multiple sclerosis	Clonal expansions of T cells	*STAT3* and other individual genes	Mature CD8+ T cell	Increased JAK-STAT signaling	NA	Valori 2017, Van Horebeek 2019
Sjogren's syndrome with cryoglobulinemic vasculitis	Vasculitis (purpura) due to pathological insoluble autoantigen-antibody aggregates	Lymphoma driver genes *(CARD11K LHL6)*	Memory B cells	Dysregulation of NF-kB signaling, cell cycle, and antibody mutation (clonal evasion of B cells)	NA	Singh 2020
Colitis	Intestine inflammation	*NFKBIZ,* other IL17 pathway genes	Epithelial cells	Aberrant IL17 signaling (resistance to proapoptotic response)	30%	Kakiuchi 2020, Nanki 2020, Olafsson 2020
Liver cirrhosis	Liver dysfunction due to fibrosis	*PKD1* *PPARGC1B* *KMT2D* *ARID1A*	Hepatocyte	Increased hepatocyte fitness	10% in individual genes, most patients had mutations	Zhu 2019, Brunner 2019

PROVISIONAL CATEGORIES

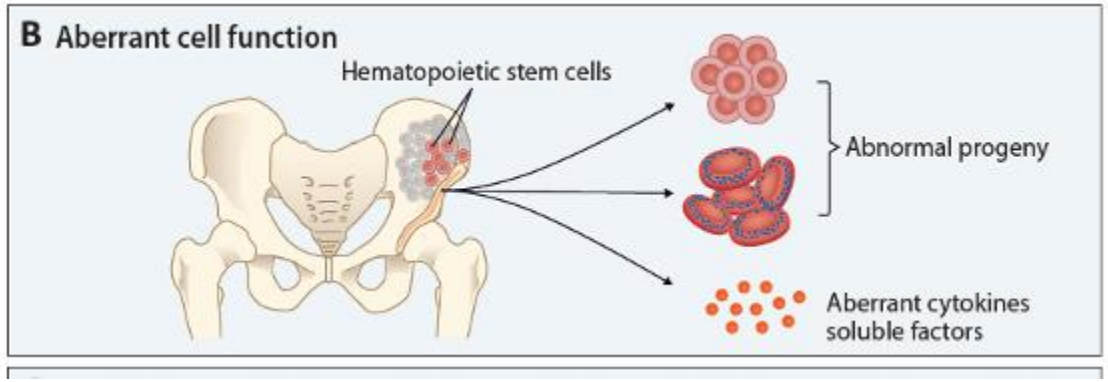
TOPOGRAPHIC
PHENOCOPIES
HSC AND STEM CELL ORIGIN
IMMUNE/AUTOIMMUNE

TOPOGRAPHIC SOMATIC MUTATION DISEASE



Brain (intractable epilepsy)
Skin (nevus)
Vasculature (A-V malformations/cavernoma)
Uterus (endometriosis)

HSC SOMATIC MUTATION DISEASE



PNH

VEXAS

SF3B1 sideroblastic anemia

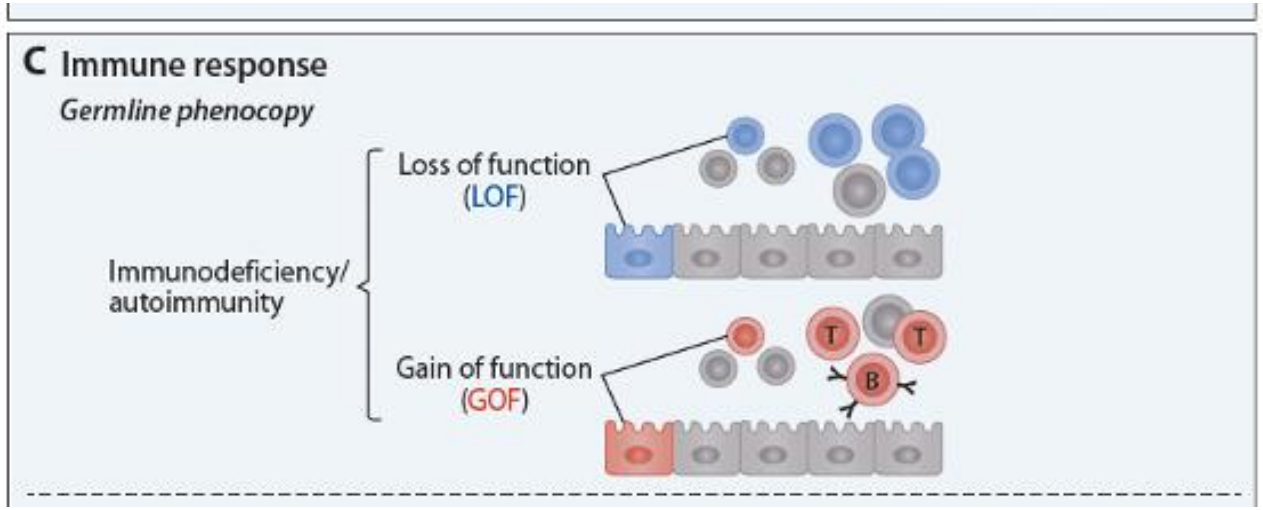
TET2 ASCVD (CHIP/ARCH)

Histiocytoses

Alpha-thalassemia-MDS

MPN’s (PV and ET?)

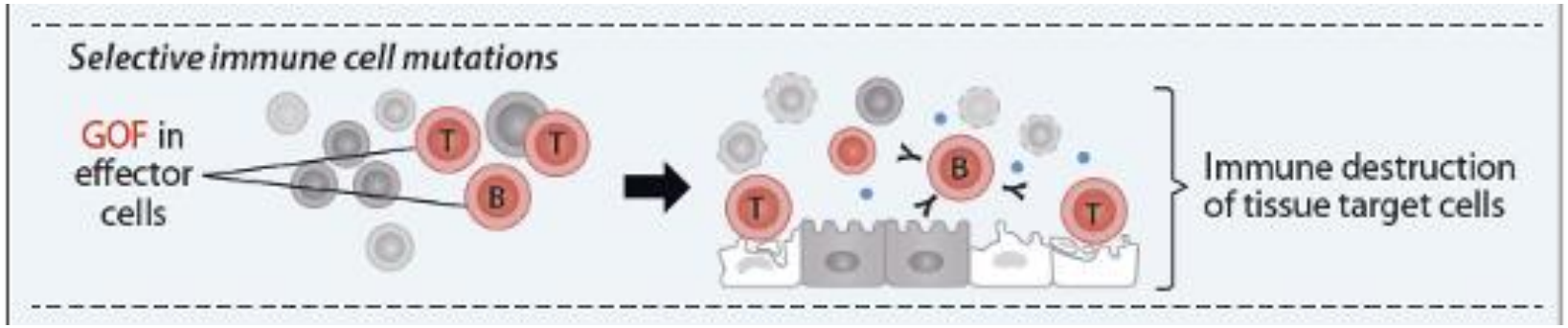
SOMATIC MUTATION DISEASES OF THE IMMUNE SYSTEM
(I) GERMLINE PHENOCOPIES (MOSAICS)



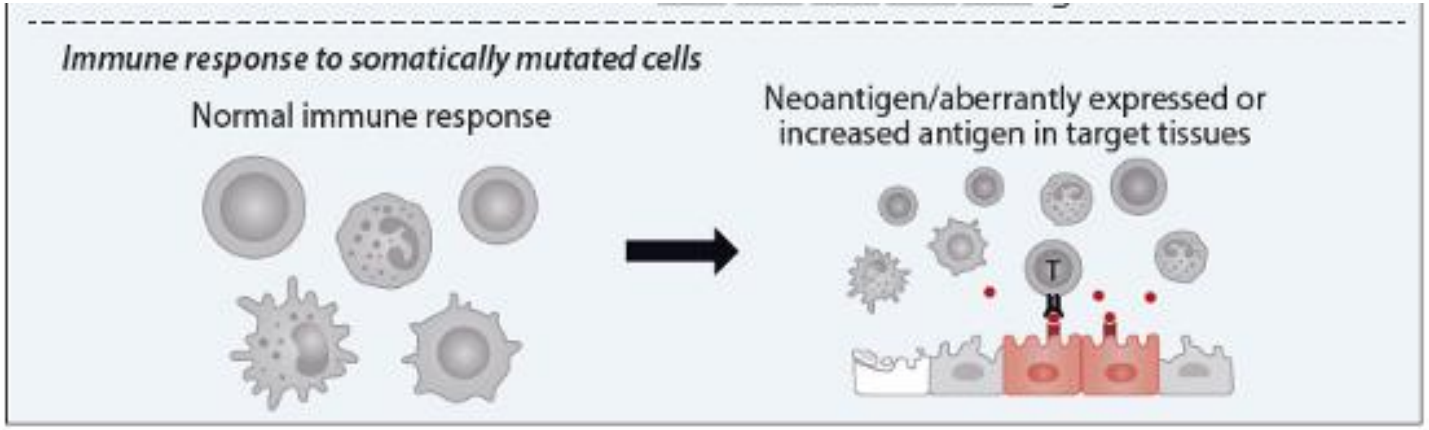
ALPS and *many* immunodeficiency/hyperinflammatory syndromes

SOMATIC MUTATION DISEASES OF THE IMMUNE SYSTEM

(II) SELECTIVE GAIN- OR LOSS-OF-FUNCTION



(III) NEO- AND ABERRANT ANTIGENS

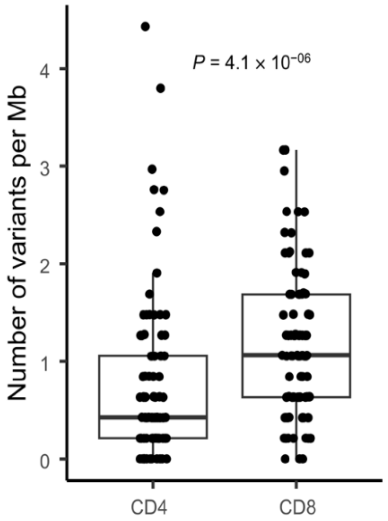


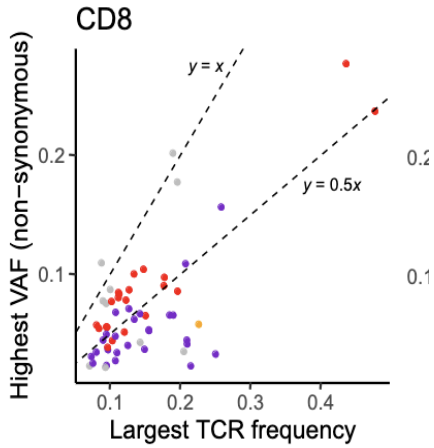
LGL, PRCA, AA

Hypo/low risk MDS

Autoimmune disease in general?

SOMATIC MUTATIONS IN LYMPHOCYTES ACRPSS AUTOIMMUNE HEMATOLOLGIC DISEASES





Somatic mutations associate with clonal expansion of CD8$^+$ T cells

Sofie Lundgren[1,2*], Mikko Myllymäki[1,2†], Timo Järvinen[1,2,3†], Mikko A. I. Keränen[1,2,4], Jason Theodoropoulos[1,2], Johannes Smolander[1,2], Daehong Kim[1,2], Urpu Salmenniemi[4,5], Gunilla Walldin[6], Paula Savola[1,2,7], Tiina Kelkka[1,2], Hanna Rajala[1,2,4], Eva Hellström-Lindberg[6], Maija Itälä-Remes[5], Matti Kankainen[1,2,3], Satu Mustjoki[1,2,8*]

Sci Adv 2024

N= 90 pts with hematologic/immunologic disease
NSV in **CD8**, not CD4 T cells; correlate with clonality VAF
Mutation signature: **endogenous** clock, MMR
Healthy donors: **CD8 clones, but no increase in mutations**
Mutations in **functional pathways**: activation, co-stimulation, MAPK, ERK1; IL7/negative regulation of cell growth

SOMATIC MUTATIONS AND CHROMOSOME ABERRATIONS IN SINGLE NEURONS
SCHIZOPHRENIA AND AUTISM

Analysis of somatic mutations in 131 human brains reveals aging-associated hypermutability

Taejeong Bae[1]†, Liana Fasching[2]†, Yifan Wang[1]†, Joo Heon Shin[3,4]†, Milovan Suvakov[1], Yeongjun Jang[1], Scott Norton[2], Caroline Dias[5,6]‡, Jessica Mariani[2], Alexandre Jourdon[2], Feinan Wu[2] Arijit Panda[1], Reenal Pattni[7], Yasmine Chahine[5,6], Rebecca Yeh[5,6], Rosalinda C. Roberts[8], Anita Huttner[9], Joel E. Kleinman[3,10], Thomas M. Hyde[3,4,10], Richard E. Straub[3], Christopher A. Walsh[5,6], Brain Somatic Mosaicism Network§, Alexander E. Urban[7], James F. Leckman[2], Daniel R. Weinberger[3,4,10,11,12]*, Flora M. Vaccarino[2,13]*, Alexej Abyzov[1]*

Science 2022

Mapping recurrent mosaic copy number variation in human neurons

Received: 3 March 2023

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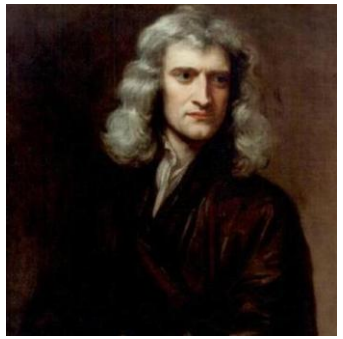
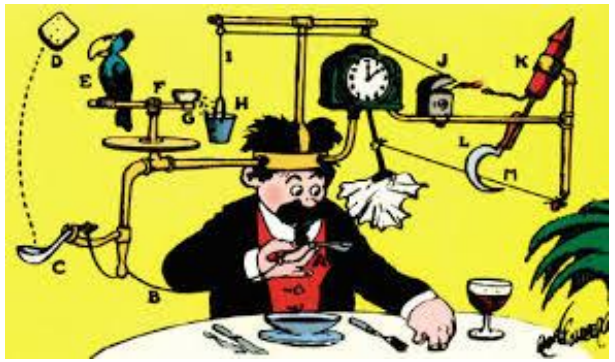
Published online: 17 May 2024

Chen Sun[1,23], Kunal Kathuria[2,23], Sarah B. Emery[3], ByungJun Kim[1], Ian E. Burbulis[4,5], Joo Heon Shin[2], Brain Somatic Mosaicism Network*, Daniel R. Weinberger[2,6,7], John V. Moran[3,8], Jeffrey M. Kidd[1,3], Ryan E. Mills[1,3] ✉ & Michael J. McConnell[2] ✉

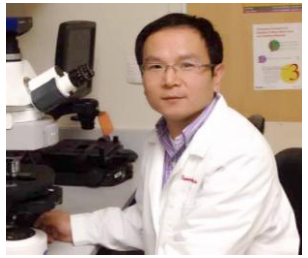
Nat Comm 2024

MECHANICS VS SYSTEMS





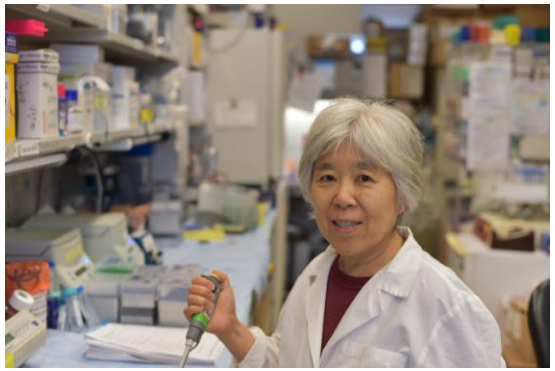
STAFF SCIENTISTS AND LONG-TERM COLLABORATORS



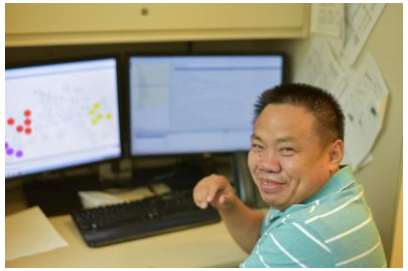
Xingmin Feng

Colin Wu

Jichun Chen



Sachiko Kajigaya



Shouguo Gao

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Ivana Darden
Tatiana Machado
Jen Lotter

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Shouguo Gao
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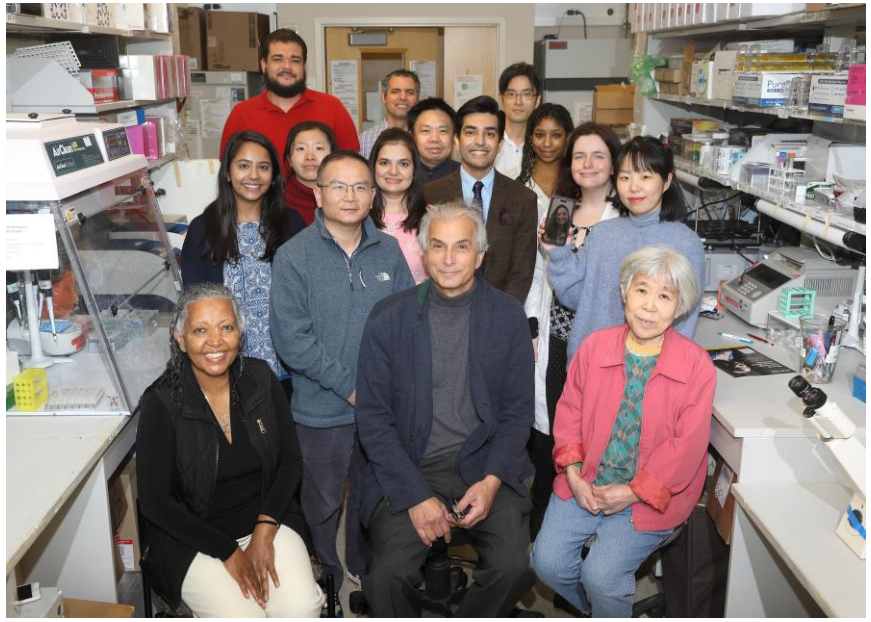
Lemlem Alelu



MY EXCEPTIONAL AND SUCCESSFUL FELLOWS!

1980s
Pedro Gascon
Nicholas Zoumbos
Leonary Bielory
Eric Raefsky
Gary Kurtzman
Keiya Ozawa
Bruce Baranski
Leonidas Platanias
Sachiko Kajigaya
Eileen Leonard
Shinji Nakao
Hiroyuki Fujii

1990s
Hideo Ema
Stephen Rosenfeld
Norbert Frickhofen
Kohji Yoshimoto
Satoshi Shimomura
Jorge Antunez de Mayolo
Antonia Nistico
Tomako Saikawa
Prokopis Katevas
Koichi Miyamura
Giorgio Gallinella
Mikio Momoeda
Jonathan Hibbs
Richard Little
Kevin Brown
Hiroaki Mizukami
Carmine Selleri
Masako Kawase
Daniel Dunn
Tadatsugu Sato
Shinichi Muramatsu
Nobuhisa Iwata
Shoichi Nagakura
Jaroslaw Maciejewski

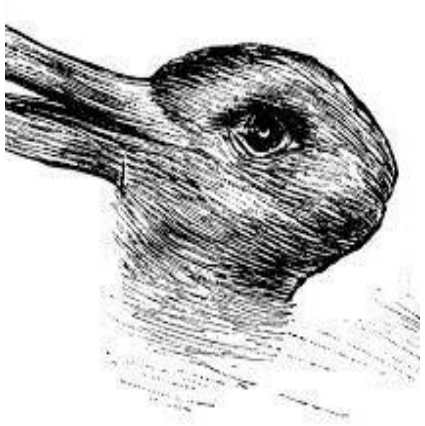
2000s
Hoon Kook
Akira Miyazato
Antonio Risitano
Hiroki Yamaguchi
Myung-Geun Shin
Guibin Chen
Yoji Ogasawara
Weihua Zeng
Claudia Filippone
Yunfeng Cheng
Elena Solomou
Georgios Amexis
Yong-Gang Yao
Yong Tang
Stephanie Omokaro
Zhihong Wan
Tomoiku Takaku
Valeria Visconte
Regis Peffault De La Tour
Rodrigo Calado
Philip Scheinberg

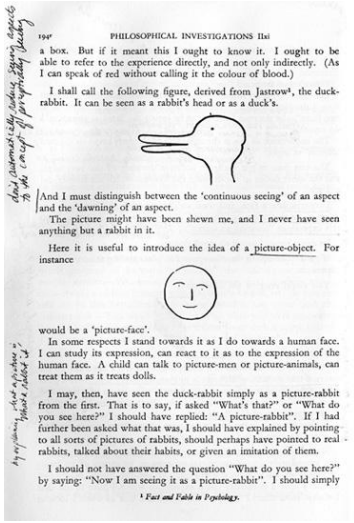
2010s
Kazuya Sato
Yasutaka Ueda
Bogdan Dumitriu
Kohei Hosokawa
Wanling Sun
James Cooper
Xin Zhao
Danielle Townsley
Valentina Giudice
Rebecca Ortolano
Bhavisha Patel
Fernanda Rodrigues
Zhijie Wu
Yoshitaka Zaimoku
Emma Groarke
Ruba Shaloub

2020s
Naoki Watanabe
Roma Rajput
Hiroke Mizumaki
Ashvind Prabahran
Jibran Durrani
Joshua Glass
Nicholas Lee
Rui Miao

REFRAMING—RENAMING (?)--MDS AND CHIP

Ludwig Wittgenstein





194 PHILOSOPHICAL INVESTIGATIONS IIxi

a box. But if it meant this I ought to know it. I ought to be able to refer to the experience directly, and not only indirectly. (As I can speak of red without calling it the colour of blood.)

I shall call the following figure, derived from Jastrow[1], the duck-rabbit. It can be seen as a rabbit's head or as a duck's.

And I must distinguish between the 'continuous seeing' of an aspect and the 'dawning' of an aspect.

The picture might have been shewn me, and I never have seen anything but a rabbit in it.

Here it is useful to introduce the idea of a picture-object. For instance

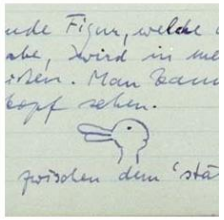
would be a 'picture-face'.

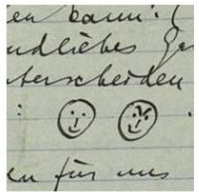
In some respects I stand towards it as I do towards a human face. I can study its expression, can react to it as to the expression of the human face. A child can talk to picture-men or picture-animals, can treat them as it treats dolls.

I may, then, have seen the duck-rabbit simply as a picture-rabbit from the first. That is to say, if asked "What's that?" or "What do you see here?" I should have replied: "A picture-rabbit". If I had further been asked what that was, I should have explained by pointing to all sorts of pictures of rabbits, should perhaps have pointed to real rabbits, talked about their habits, or given an imitation of them.

I should not have answered the question "What do you see here?" by saying: "Now I am seeing it as a picture-rabbit". I should simply

[1] *Fact and Fable in Psychology.*





To generalize is to be an idiot. To particularize is the alone merit of distinction.

William Blake

Keine neue Weld ohne neue Sprache. (No new world without new language.)

Ingeborg Bachmann

REFRAMING MDS AND CHIP

Confusion in MDS and now CHIP clinics

- “inevitability” of leukemia, competing classification schemes, inconsistencies

Historical misconceptions and category errors

- MDS: reliance on histology; CHIP: simple (simplistic?) sequencing
- Definitions of “leukemia” and meaning of “risk” (ontogeny: essence/attributes)

Statistics

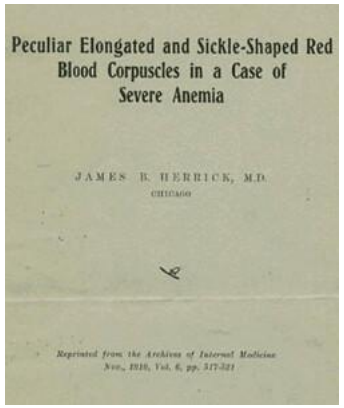
- Unbiased associations vs plausible causal inference models

More perspicuous nosologies (than histopathology)?

- Somatic mutation etiology
- Mechanism/pathopysiology and/or system similarities
- End organ specific effects

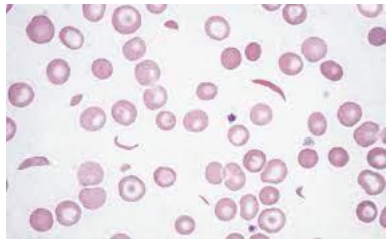
DISEASES: “SOCIAL CONSTRUCTION” AND LANGUAGE

SCD


Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia

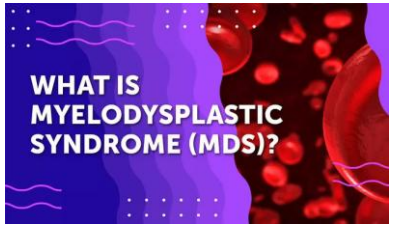
JAMES B. HERRICK, M.D.
CHICAGO

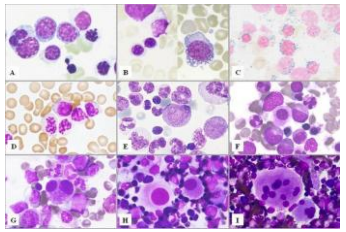
Reprinted from the Archives of Internal Medicine
Nov., 1910, Vol. 6, pp. 517-521

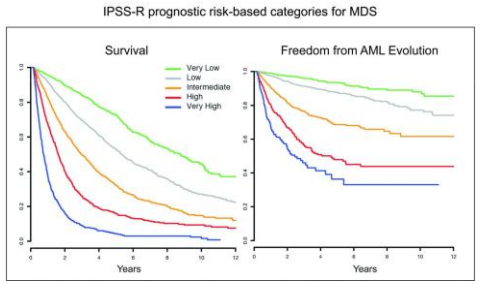


Blood smear
Anemia
Vaso-occlusion
Red cell dysfunction
Globin modification
Gene
Modifiers
Etc.

MDS







Morphologic characteristics?
Leukemia risk--or existence?
Marrow failure syndrome
Distinct syndromes (PNH, VEXAS, sideroblastic anemia, 5q-)
Somatic mutation diseases?

OTHER DISEASES

VEXAS (acronym *and* label)
~~Fifth disease~~ Parvovirus infection
“PNH” ~~PIGA mutation~~
[collagen vascular diseases]
[schizophrenia, hysteria, fugue epidemic]
[chronic fatigue]
[Downs]

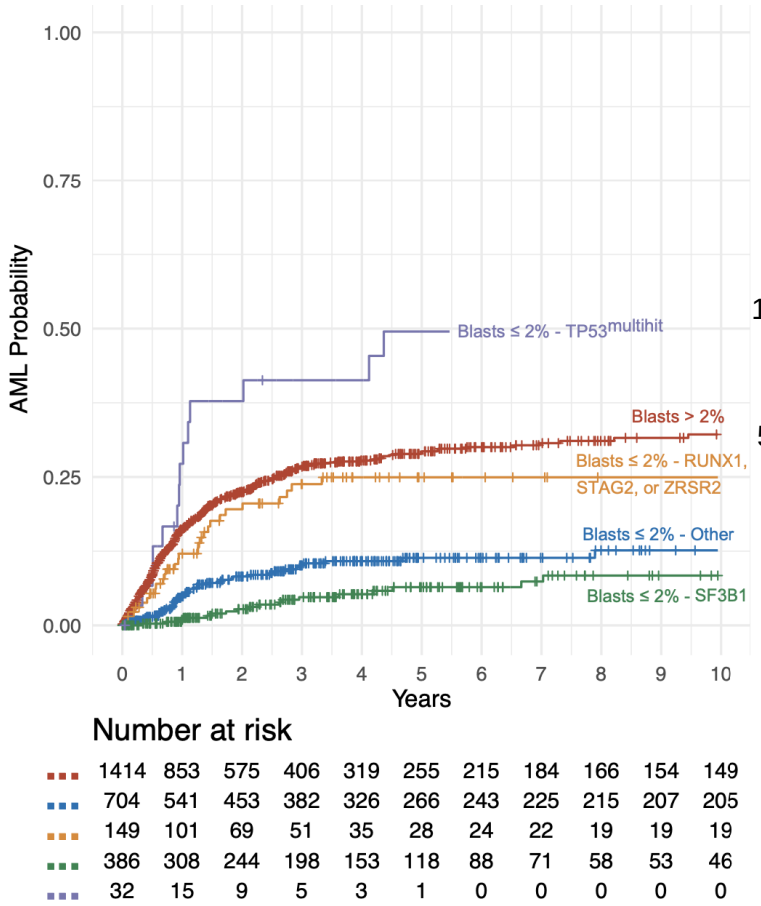
NAMING: NO RULES!

Etiology
Pathophysiology
End organ pathology
Eponym
Geography

REFRAMING MDS AND CHIP

MDS

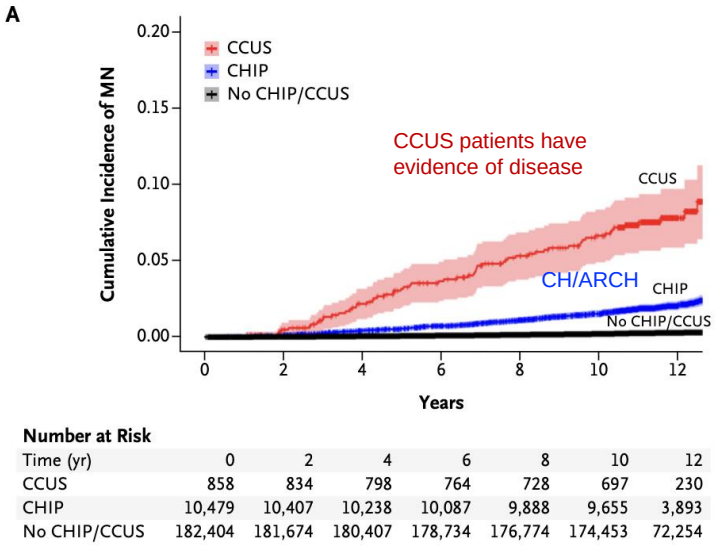
CHIP



1%

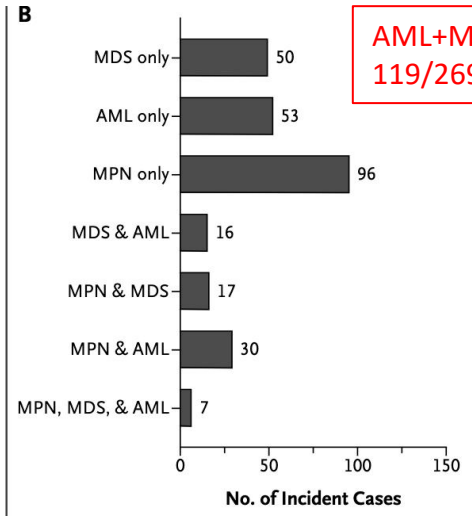
53% mostly blasts

41%

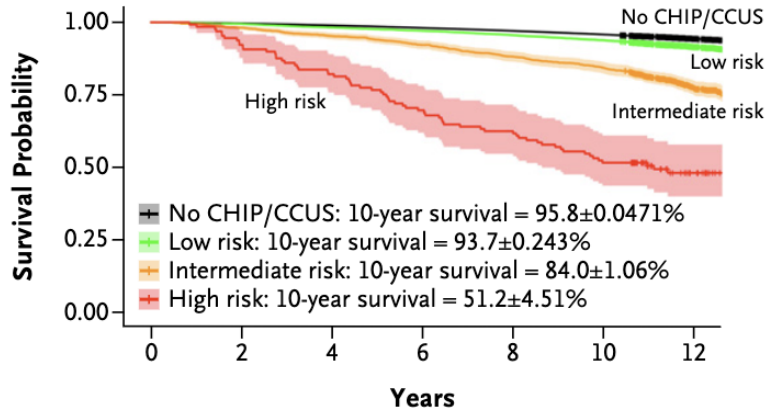


Number at Risk

Time (yr)	0	2	4	6	8	10	12
CCUS	858	834	798	764	728	697	230
CHIP	10,479	10,407	10,238	10,087	9,888	9,655	3,893
No CHIP/CCUS	182,404	181,674	180,407	178,734	176,774	174,453	72,254



AML+MDS = 119/269 = <50%

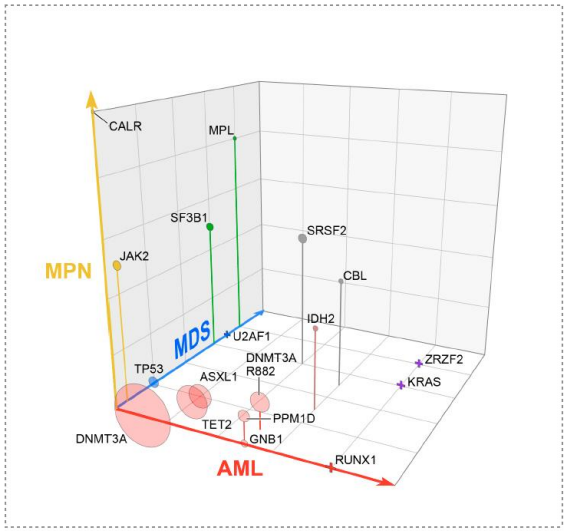


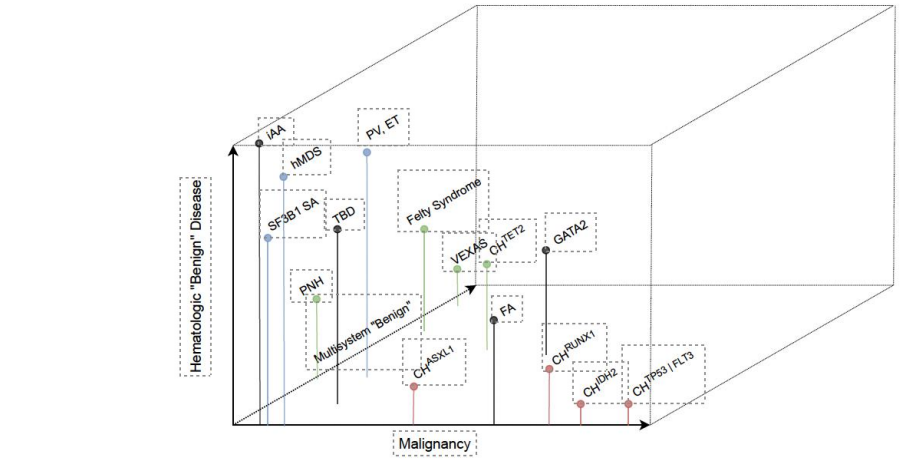
Number at Risk

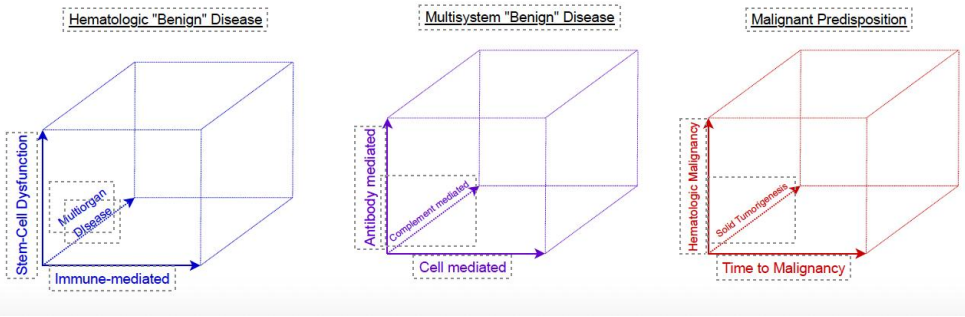
Time (yr)	0	2	4	6	8	10	12
High risk	123	113	101	86	76	63	25
Int. risk	1,196	1,176	1,141	1,101	1,051	1,005	354
Low risk	10,018	9,963	9,830	9,717	9,567	9,386	3,793
No CHIP/CCUS	182,406	181,706	180,486	178,864	76,967	174,688	72,376

High risk = 123/12,656 = 1%

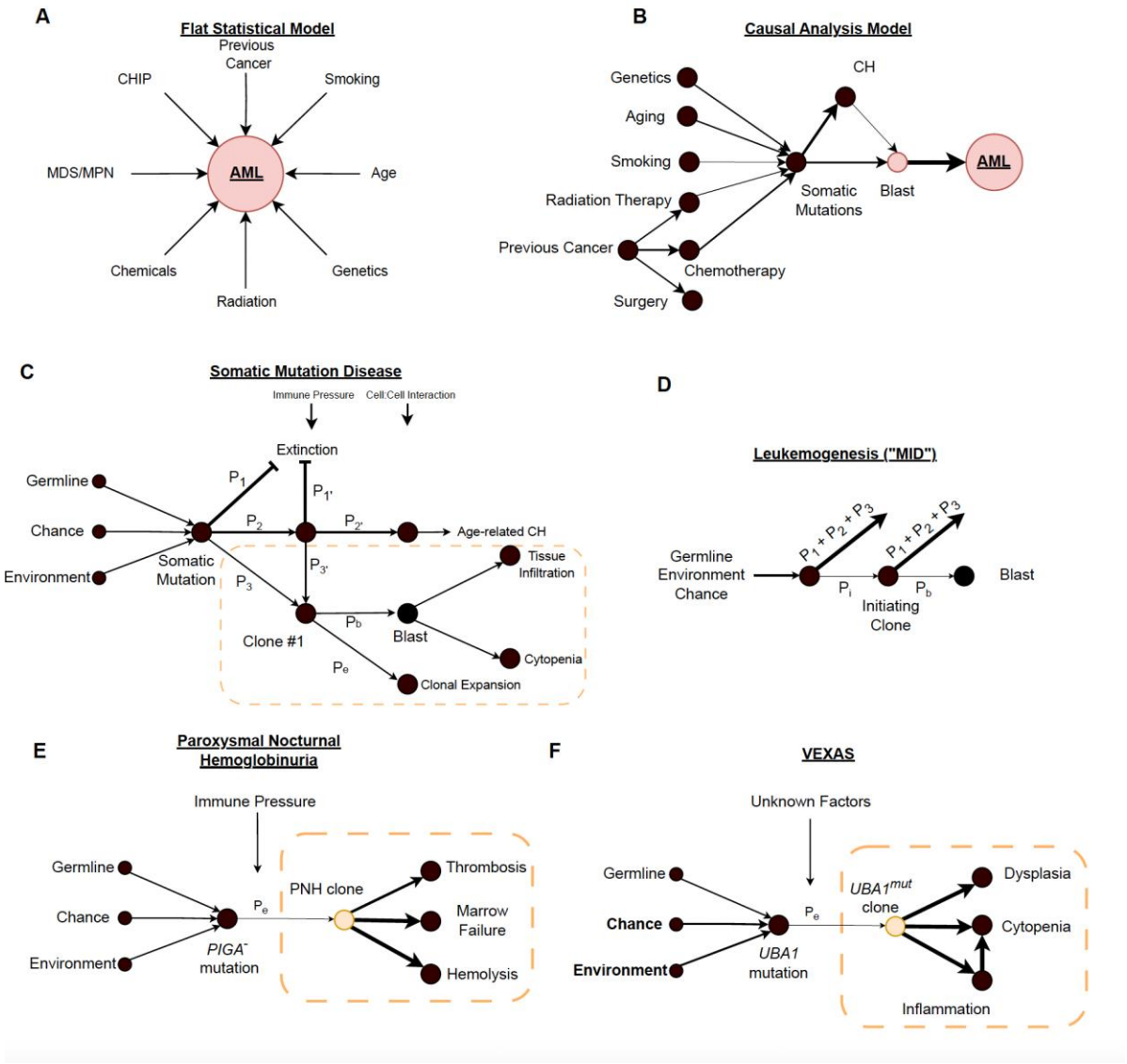
SOMATIC MUTATIONS AND MALIGNANT AND “BENIGN” SOMATIC MUTATIONS AND CLONES







PLAUSIBLE INFERENCE AND SOMATIC MUTATIONS/CLONES



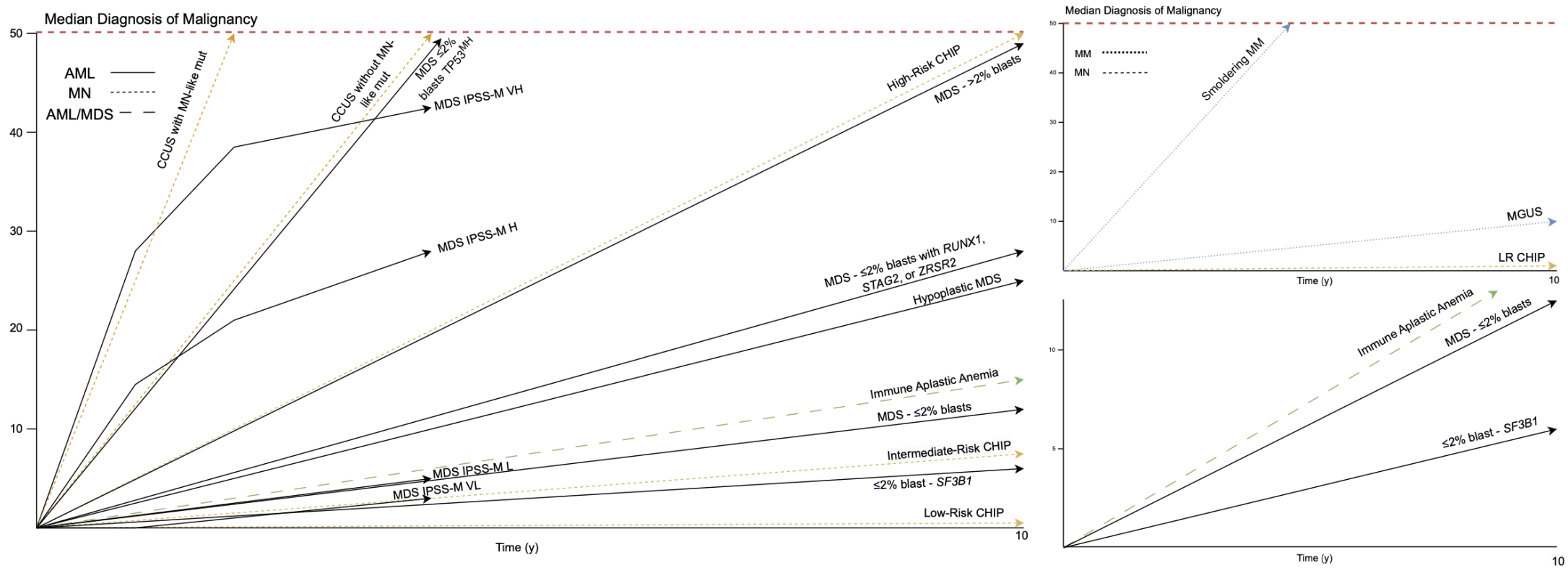
What is cause and what is consequence?
(essence/attribute)

How to define disease?
(clinical features, pathology, genomics)

When does disease begin?
(MID)

Can we quantify clonal evolution?
(assign meaningful p's)

HIGHLY VARIABLE DYNAMICS OF MALIGNANT DEVELOPMENT



ALTERNATIVE NOSOLOGIES

A. Shrink the **pie charts—**rename recognizable diseases

MDS: Remove distinct subclasses : early AML, TP53, SF3B1 anemia, VEXAS

(remainder yet to be defined)

CHIP: Remove early AML (1%) and TET2-opathy; (remainder aging-related and insignificant)

B. Create **sets**

Leukemia partially overlapping Bone Marrow Failure, with subsets

C. Hierarchy from etiology

Somatic mutations (malignant/benign)

Function(proliferation, differentiation, altered regulation, etc.)

Tissue (HSC, GI, brain, etc.)