1

Disclosure Statement

- I have nothing to disclose

2

First VEXAS Case…

2011
HCQ
MTX
MMF
AZA
High doses of prednisone
CYC
2013
Anakinra skin reaction
High doses of prednisone
2017
Worsening fevers
Pulmonary infiltrates
Disseminated mycobact. chelonea
2020
Death

Ongoing inflammation

Progressive bone marrow failure
Macrocytic anemia, thrombocytopenia
Ongoing inflammatory sx
Multiple infections

Worsening Anemia-Thrombocytopenia
Frequent blood transfusion-Platelet transfusions
Ongoing inflammatory sx
Multiple hospitalizations

Fever
Orchitis
Skin nodules
Face swelling
DVT
Ear chondritis

Evaluation at NIH UDP
Observed GC taper
CRP + flare
Dermal arteritis

Worsening Macrocytic Anemia
Requiring blood transfusions

Atypical Polyarteritis Nodosa

Marrow: Hypercellular, myeloid predominance, negative genomic studies for MDS

Diagnosis - ???

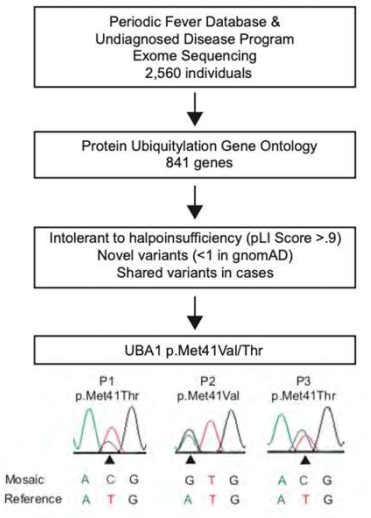
Two more cases over the next three years…

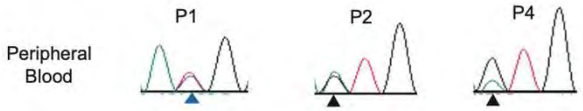
3

Genotype-first discovery…

4

Somatic Mutations in a Single Residue of UBA1 are Associated with a Severe Adult-Onset Autoinflammatory Disease

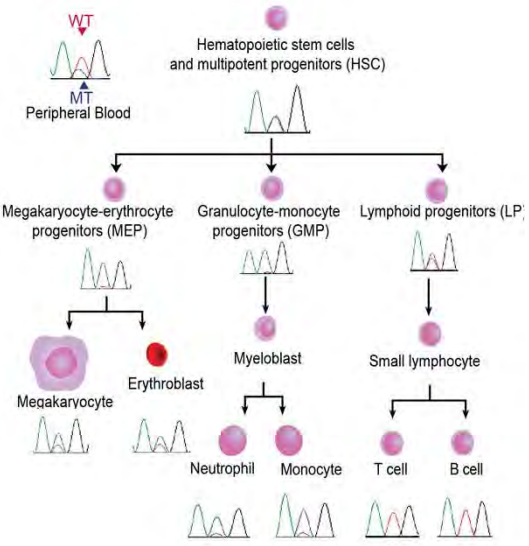


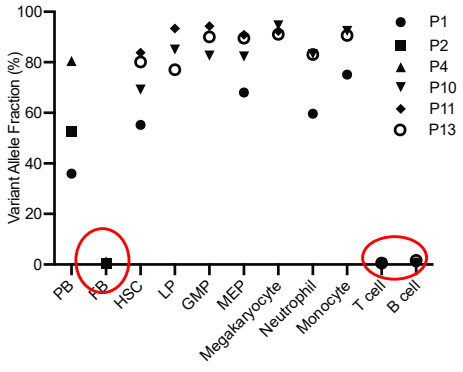


Beck et al NEJM 2020

5

Somatic Mutations are Myeloid Restricted

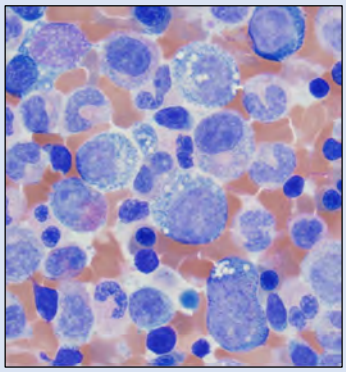




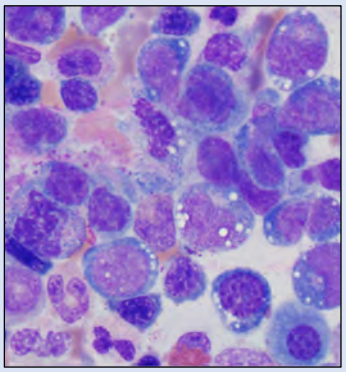
Beck et al., *NEJM 2020*

6

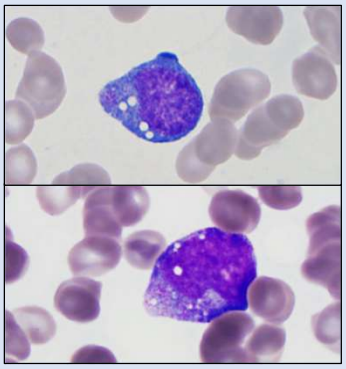
Bone Marrow Vacuoles in VEXAS Syndrome



P1- 54 y/o male
Bone Marrow



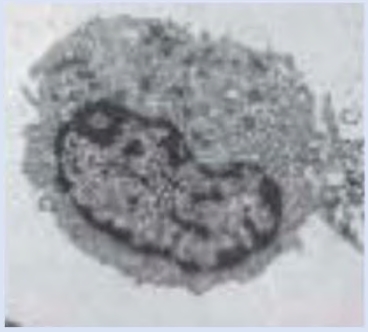
P2- 61 y/o male
Bone Marrow

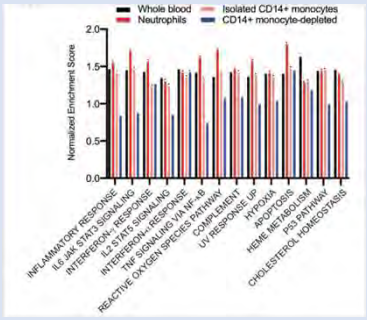


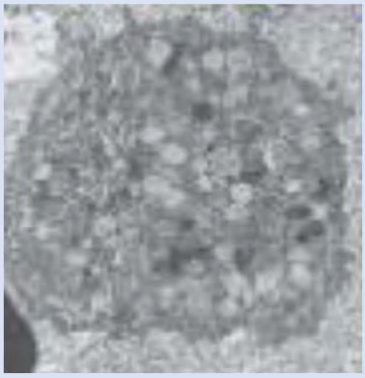
P3- 74 y/o male
Bone Marrow

Dr. Kathy Calvo

7





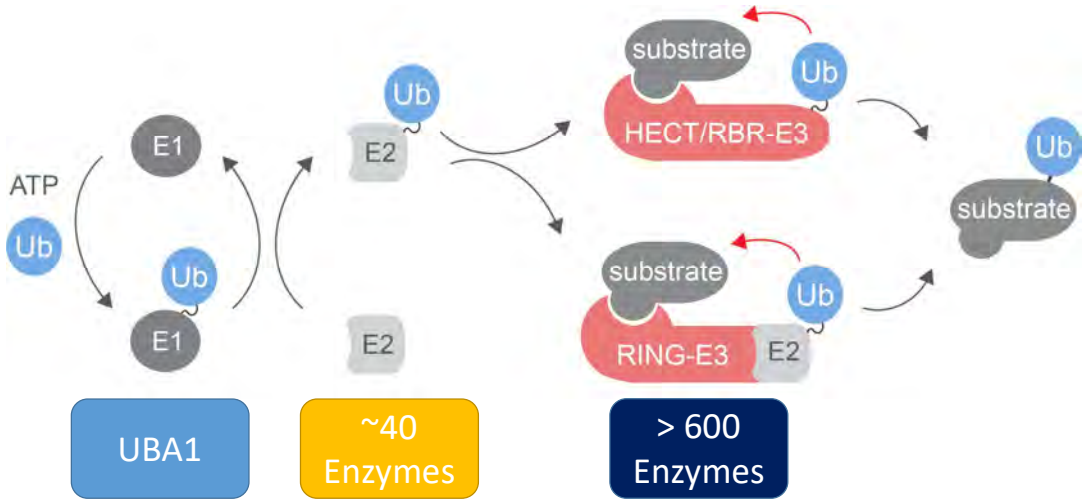


Mechanism of Inflammation

Beck et al., *NEJM 2020*

8

Ubiquitylation and Disease



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V acuoles

E 1 enzyme

X - linked

A utoinflammatory

S omatic

Beck et al., *NEJM 2020*

10

How to spot the disease…

11

Demographics of VEXAS

Age at Disease onset median (range)	64 (45-80)
Sex n(%)	
Male	25 (100)
Race n(%)	
White	25 (100)
Diagnosis n(%)	
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)

n=25

Beck et al., *NEJM 2020*

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Chondritis of ear and nose

Images from the NIH Cohort

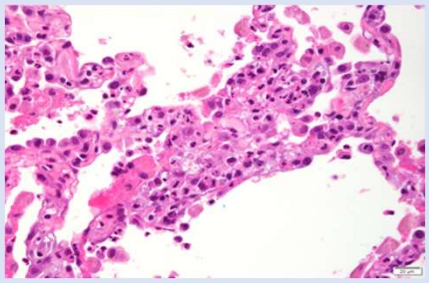
13

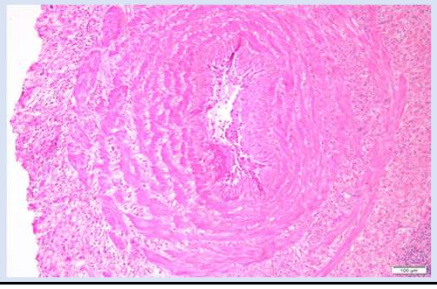
Skin Manifestations

Images from the NIH Cohort

14

Pulmonary Involvement

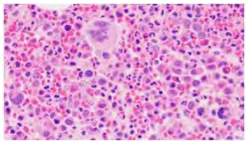




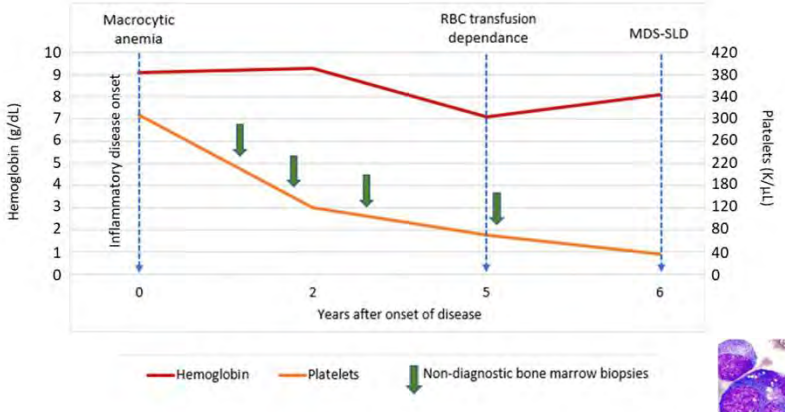
Images from the NIH Cohort

15

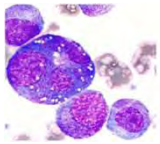
Natural History of VEXAS Syndrome



Hypercellular marrow



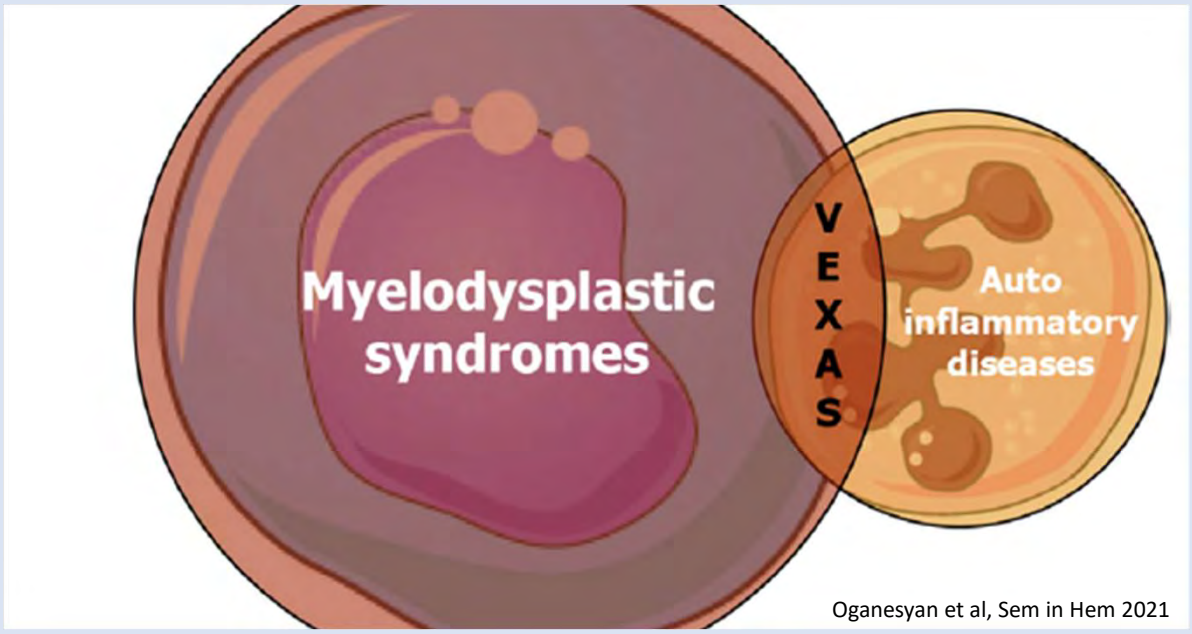
Disease progression to MDS



Abnormal myeloid cells

Oblorah et al., *Blood Adv, 2021*

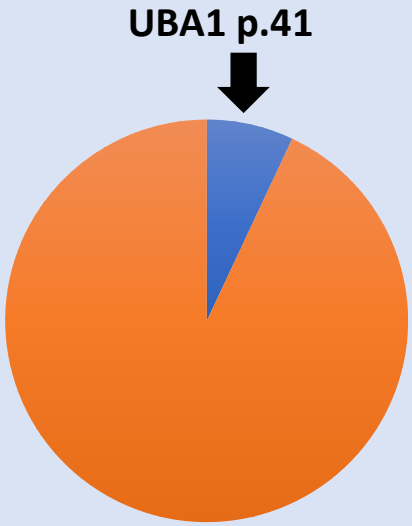
16



Oganesyan et al, Sem in Hem 2021

17

8% of Relapsing Polychondritis is VEXAS



NIH RP Cohort

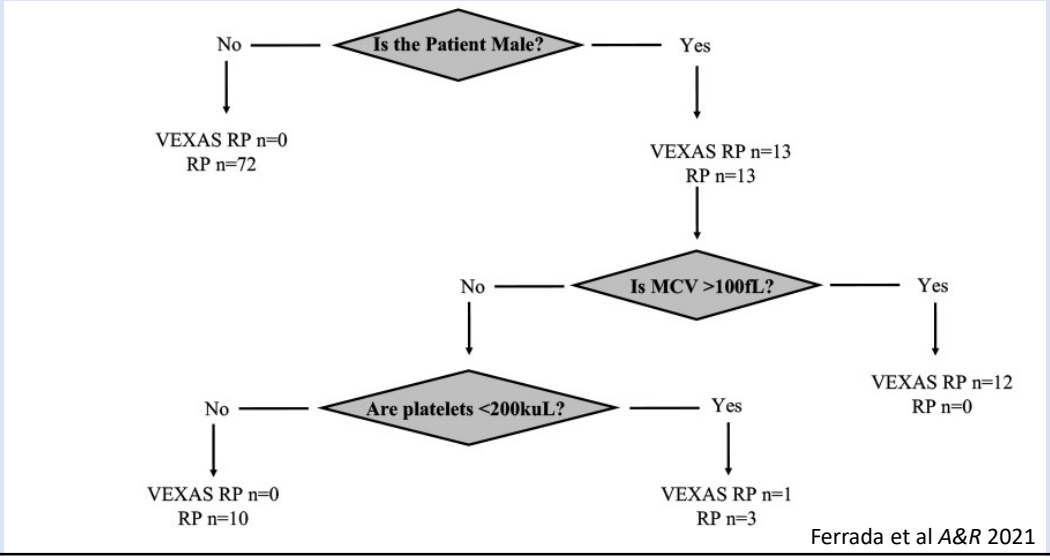
n= 92

Ferrada et al A&R 2021

18

Simple Clinical Algorithm with 97% Accuracy

In a patient with ear or nose chondritis…



Ferrada et al *A&R* 2021

19

Elevated MCV in an adult patient with severe inflammation involving skin, cartilage, or lungs should trigger genetic testing for VEXAS syndrome

20

VEXAS Syndrome

Prevalence Estimates

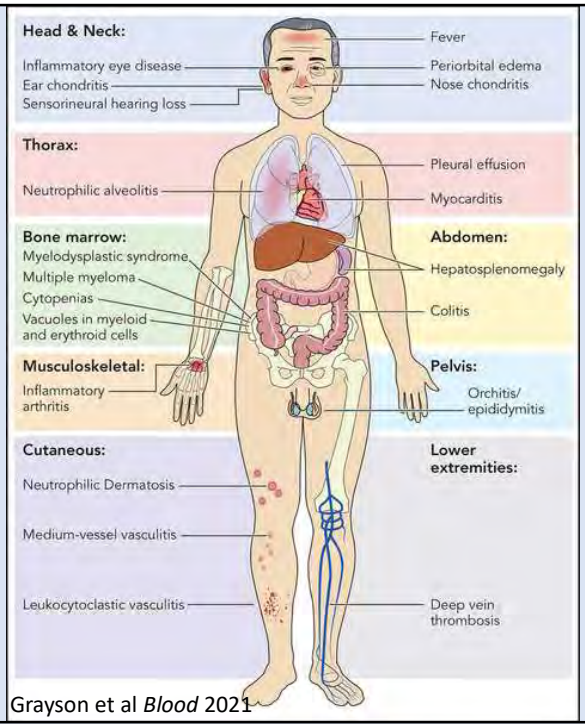
1 in 14,000

1 in 4000 men > 50 years

Genomic ascertainment for *UBA1* variants and VEXAS syndrome: a population-based study

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

doi: https://doi.org/10.1101/2022.07.27.22277962



Grayson et al *Blood* 2021

21

Expanding the spectrum of **VEXAS syndrome**: association with acute-onset CIDP.
Bert-Marc
J Neurol
A case
lympho
Kao RL,
Furth
large
Georg
Ardoi
Zhao
Vinzic
Bourg
Chasse
Lobbes H
Faucher E
Fenaux P,
MINHEM
Br J Derm
PMID: 34632574

VEXAS IS THE NEW GREAT MIMIC IN MEDICINE

polychondritis, venous thromboembolism and macrocytic anaemia.
Lee SMS, Fan BE, Lim JH, Goh LL, Lee JSS, Koh LW.
Rheumatology (Oxford). 2021 Sep 1;60(9):e304-e306. doi: 10.1093/rheumatology/keab200.
PMID: 33630036 No abstract available.

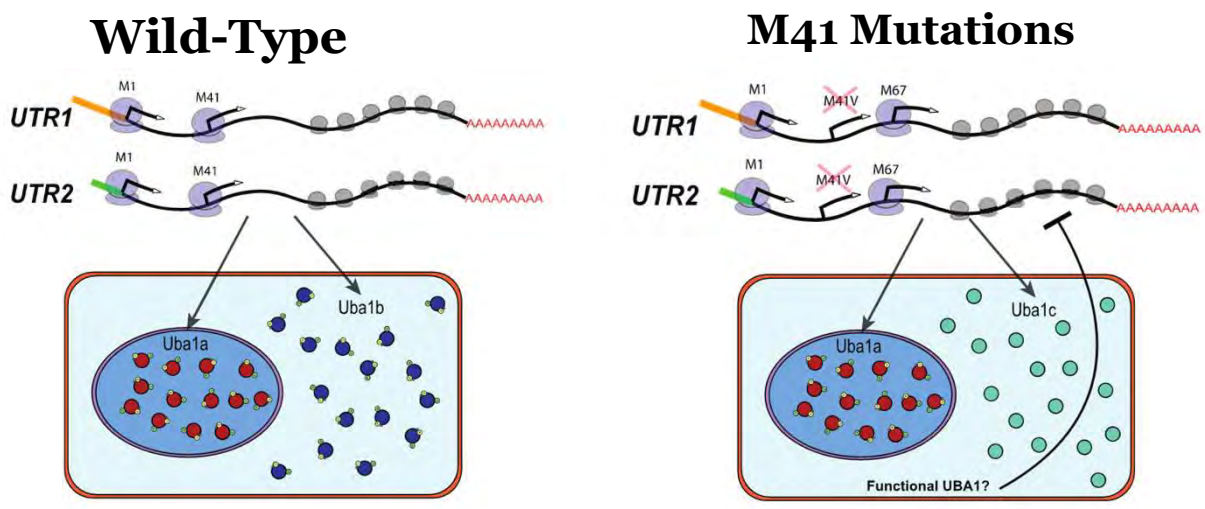
VEXAS syndrome with **systemic lupus erythematosus**: expanding the spectrum of associated conditions.
Sharma **Behçet's** disease with a somatic UBA1 variant:Expanding spectrum of Arthritis autoinflammatory phenotypes of **VEXAS syndrome**.
PMID: 3
Matsumoto H, Asano T, Tsuchida N, Maeda A, Yoshida S, Yokose K, Fujita Y, Temmoku J, Matsuoka N, Yashiro-Furuya M, Sato S, Irie K, Norikawa N, Yamamoto T, Endo M, Fukuchi K, Ohkawara H, Ikezoe T, Uchiyama Y, Kirino Y, Matsumoto N, Watanabe H, Migita K.
Clin Immunol. 2022 May;238:108996. doi: 10.1016/j.clim.2022.108996. Epub 2022 Apr 7.
PMID: 35398520 No abstract available.

22

Pathogenetic mechanism of disease…

23

Mutational Hotspot at Codon 41



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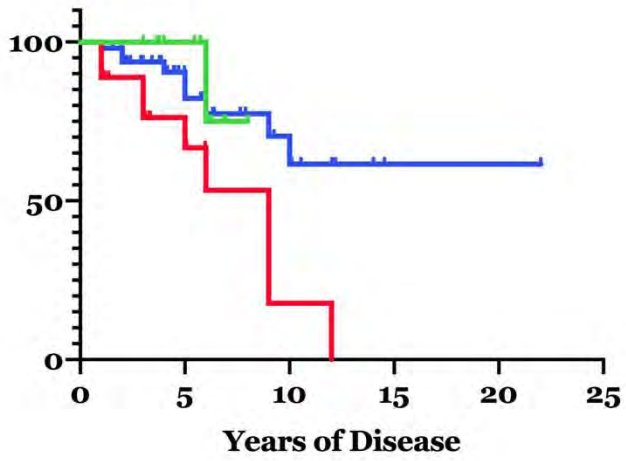
Molecular data has prognostic value



Ferrada et al., *Blood* 2022

25

Treatment Strategies

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Goals of Medical Therapy

- **Control inflammation**
  - *Steroids remain foundation of treatment*
  - Tocilizumab
  - JAKinibs – ruxolitinib
  - IL-1 antagonists – anakinra injection site reactions
  - Conventional DMARDs
- **Eradicate the clone**
  - Hypomethylating agents – azacitidine
- **Prevent complications**
  - Prophylaxis
  - Anticoagulation

27

Bone Marrow Transplant – Curative?

EXCEPTIONAL CASE REPORT | FEBRUARY 4, 2022

Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: a 2-center experience

Ava Diarra, Nicolas Duployez, Elise Fournier, Claude Preudhomme, Valérie Coiteux, Leonardo Magro, Bruno Quesnel, Maël Heiblig, Pierre Sujobert, Fiorenza Barraco, Marie Balsat, Quentin Scanvion, Eric Hachulla, David Launay, Ibrahim Yakoub-Agha, Louis Terriou, on behalf of the French VEXAS study group

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Implications for rheumatology…

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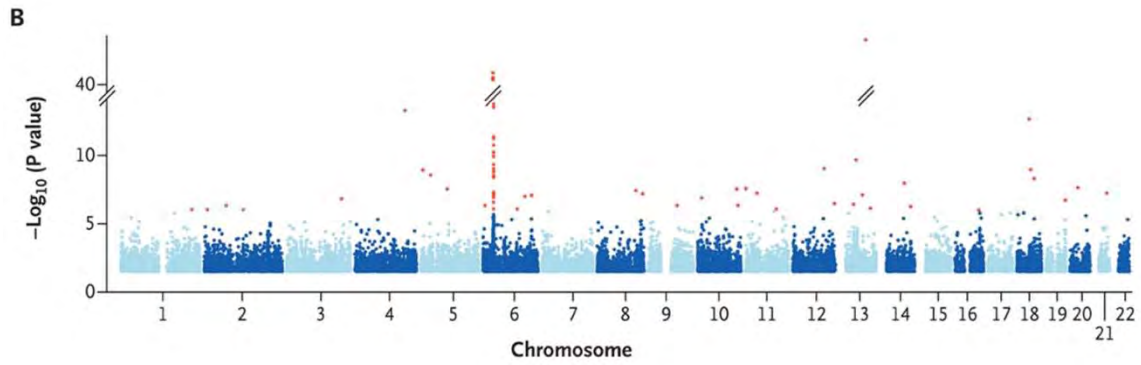
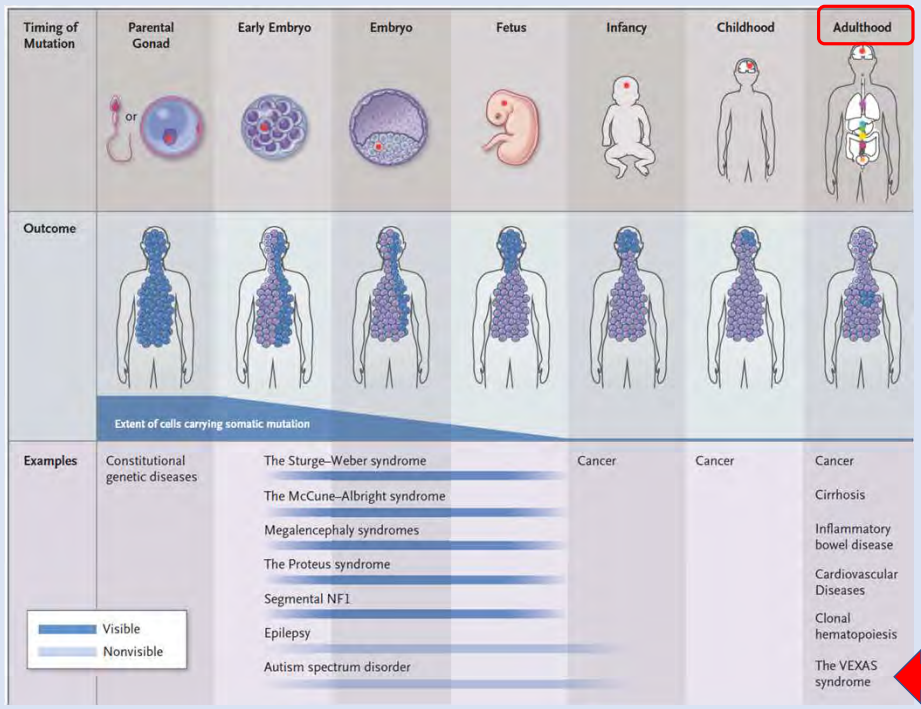
Genetics - GWAS



Lyon et al, *NEJM, 2012*

30



Somatic Mutations

Levy-Lahad and King NEJM 2020

31

Genome is unstable

- Every cell in our body mutates at least once every week or two
  - Rate varies by tissue (lowest in blood and highest in colon)
- Intrinsic (aging) and extrinsic (environmental) factors
  - Inflammation both a driver and consequence of somatic mutations
- Somatic mutations in rheumatologic diseases
  - Causal in subsets of patients
  - Sustain disease in other subsets of patients
  - Contribute to disease-associated events

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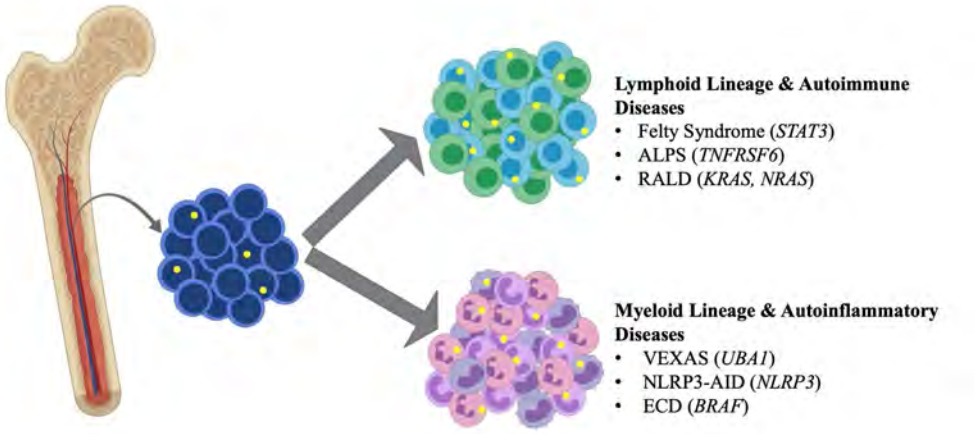
Myeloid and Lymphoid Mutations



Sikora et al., *Rheumatology, 2022*

33

Conclusions

- VEXAS is an overlap disease with severe inflammation and bone marrow failure
  - Caused by acquired mutations in UBA1 in bone marrow stem cells
  - Elevated MCV is a key clue to spot this disease!
- VEXAS syndrome is a prototype for new disease paradigm
  - Somatic mutations in blood and solid organs may underlie adult-onset rheumatologic diseases
- **Genetics can dynamically contribute to autoimmunity**
  - **Expand thinking beyond the germline!!**

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Acknowledgements

- **NIAMS Vasculitis Translational Research Program**
  - Marcela Ferrada, Kaitlin Quinn, Elaine Novakovich, Wendy Goodspeed
  - Kristina Wells, Yiming Luo, Emily Rose
- **Team VEXAS**
  - David Beck, Keith Sikora, Amanda Ombrello, Kaplan Lab, Colbert Lab, Bhavisha Patel, Emma Groake, Neal Young, Kathy Calvo, Helen Lachmann, Sanisa Savic, Achim Warner, Dan Kastner

peter.grayson@nih.gov @petercgrayson

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