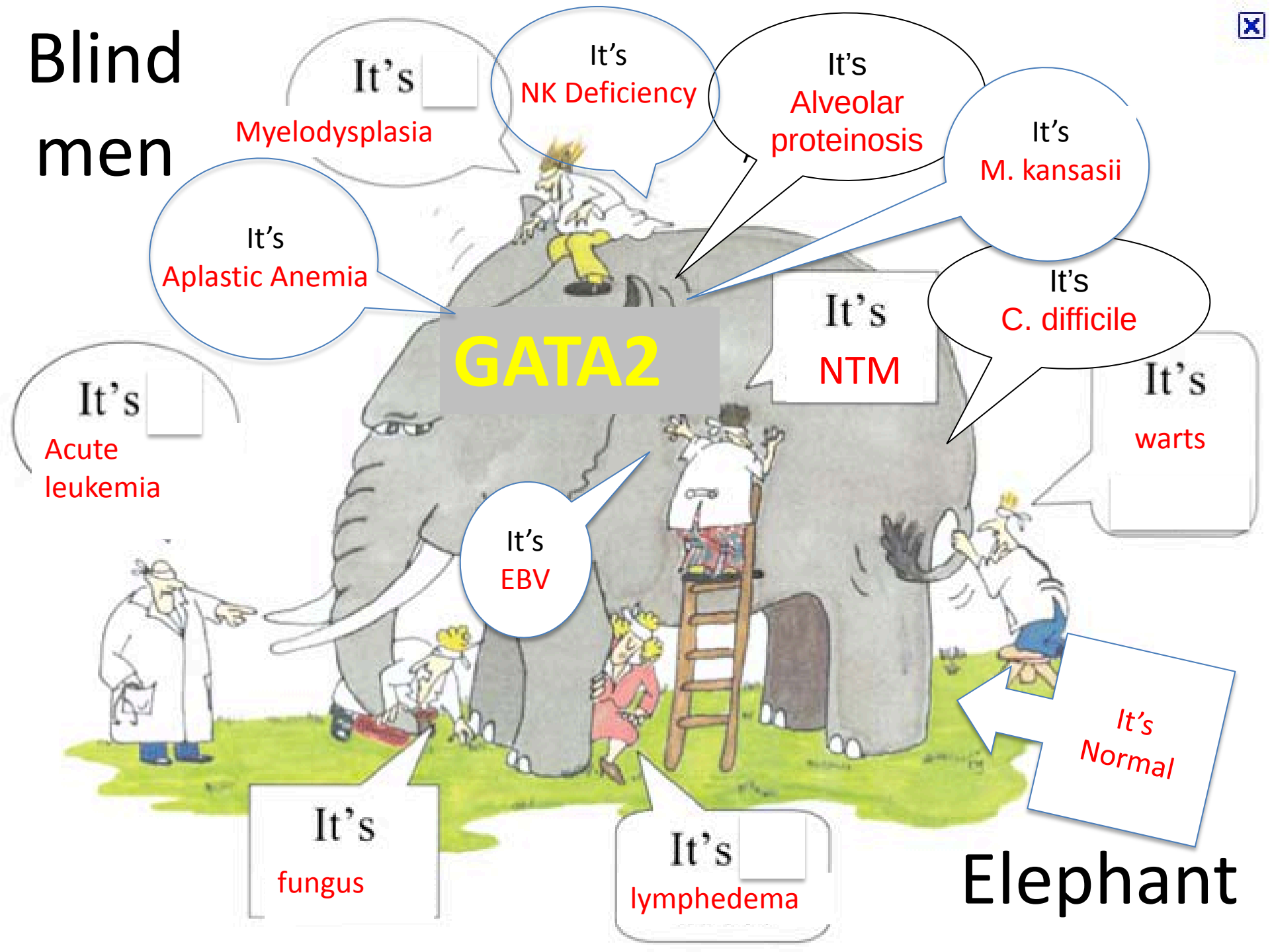
GATA2 Deficiency: The Ὀδυσσεύς of Immunodeficiency

Steven M. Holland, MD
Laboratory of Clinical Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
smh@nih.gov


Blind men
It's Myelodysplasia
It's NK Deficiency
It's Alveolar proteinosis
It's M. kansasii
It's Aplastic Anemia
GATA2
It's NTM
It's C. difficile
It's Acute leukemia
It's warts
It's EBV
It's Normal
It's fungus
It's lymphedema
Elephant

MEDICAL INTELLIGENCE

SEVERE HERPESVIRUS INFECTIONS IN AN ADOLESCENT WITHOUT NATURAL KILLER CELLS

CHRISTINE A. BIRON, PH.D., KEVIN S. BYRON, AND JOHN L. SULLIVAN, M.D.

NEJM 1989;320:1731

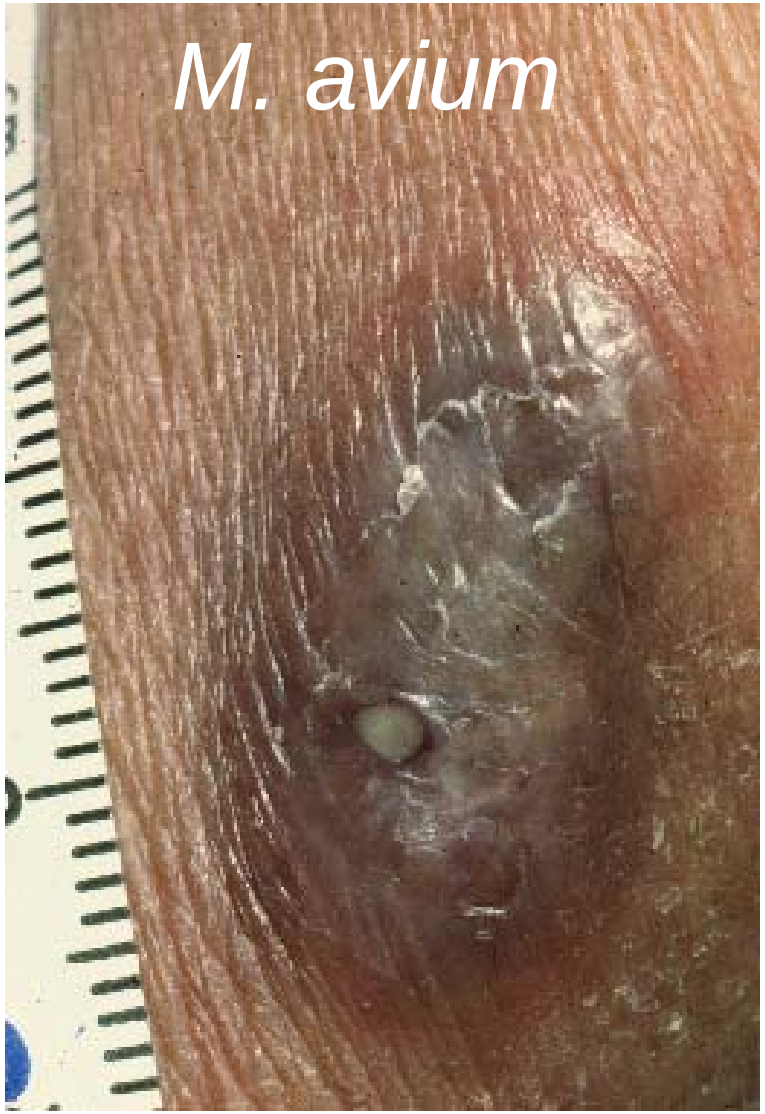
Case Report

A 13-year-old girl presented in February 1984 at the University of Massachusetts Medical Center with a life-threatening varicella virus infection. Her body was covered by chicken pox lesions, and there was clinical and radiologic evidence of varicella pneumonia; she was treated with intravenous acyclovir (500 mg per square meter of body-surface area every eight hours). The patient's medical history was notable for recurrent otitis media with perforations since infancy and recurrent leukopenia, with white-cell counts ranging between 2.0 and 7.2×10^9 per liter. There was no family history of immune deficiency.

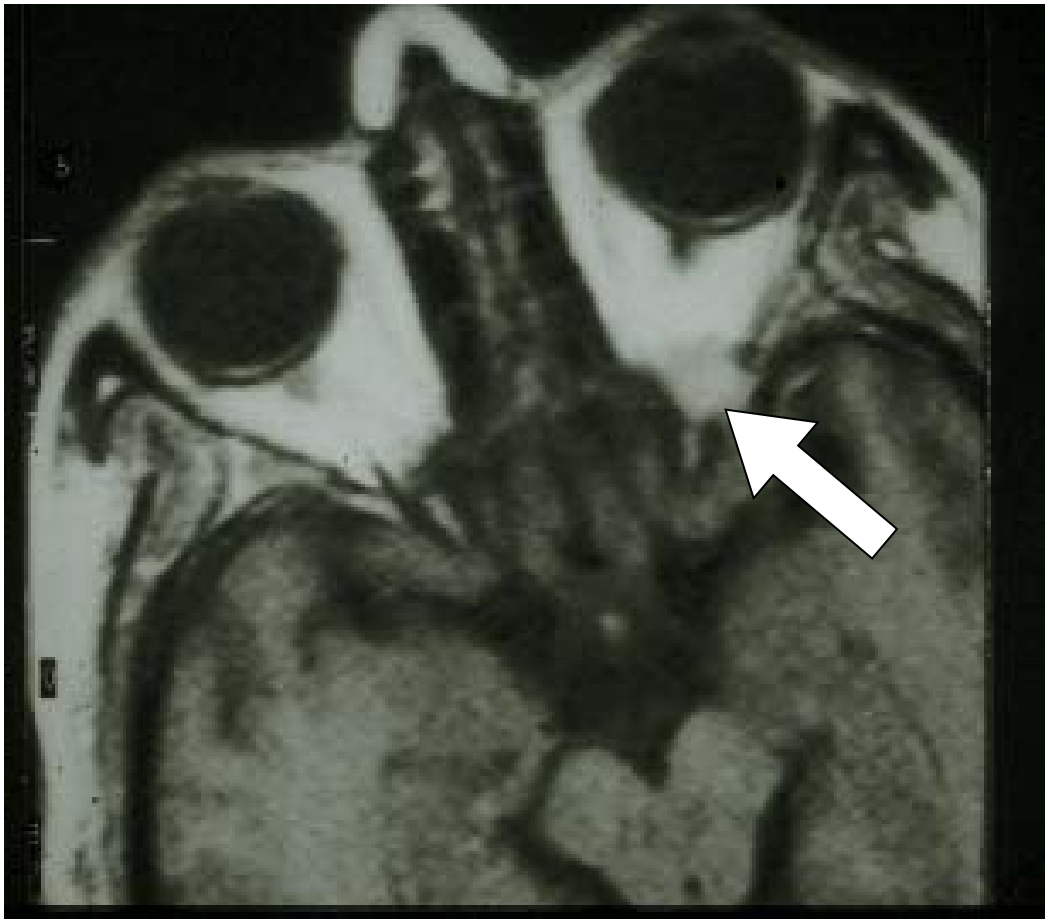
Subsequently died while waiting for bone marrow transplant.

NEJM 1989;320:1731

1992: 41 yo Woman Refractory MAC Infection



EBV+ Smooth Muscle Tumor

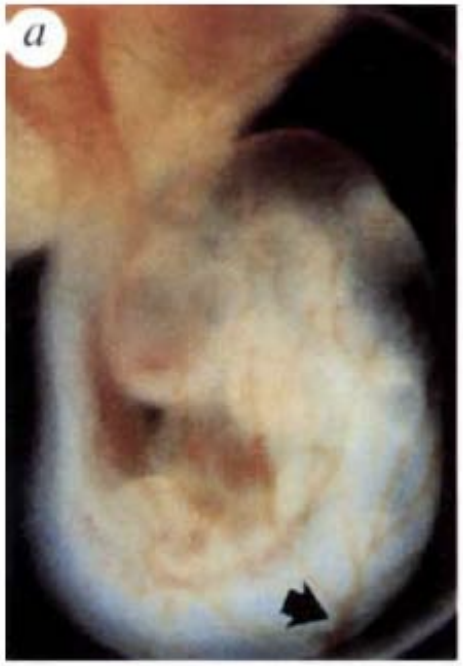


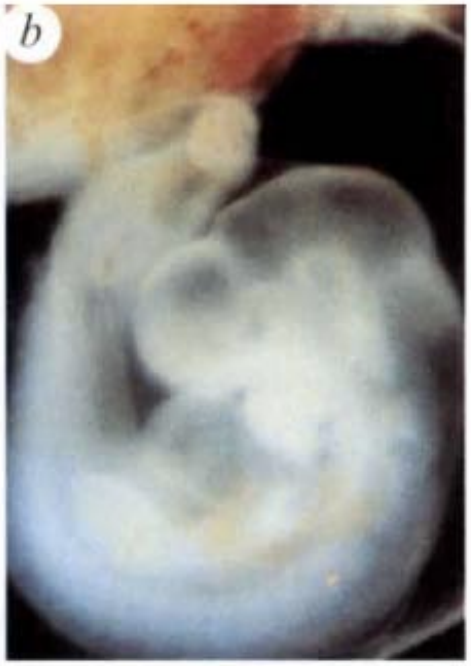
Gata2$^{-/-}$ die d10.5

An early haematopoietic defect in mice lacking the transcription factor GATA-2

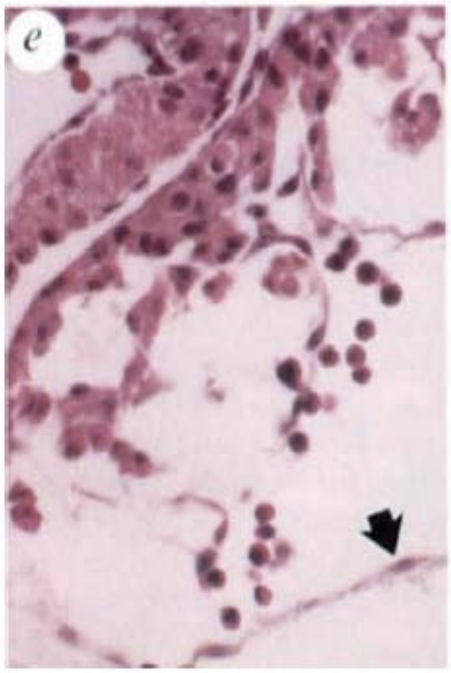
Fong-Ying Tsai[*†], Gordon Keller[‡], Frank C. Kuo[§], Mitchell Weiss[*], Jianzhou Chen[‖], Margery Rosenblatt[*], Frederick W. Alt[†‖] & Stuart H. Orkin[*†¶]

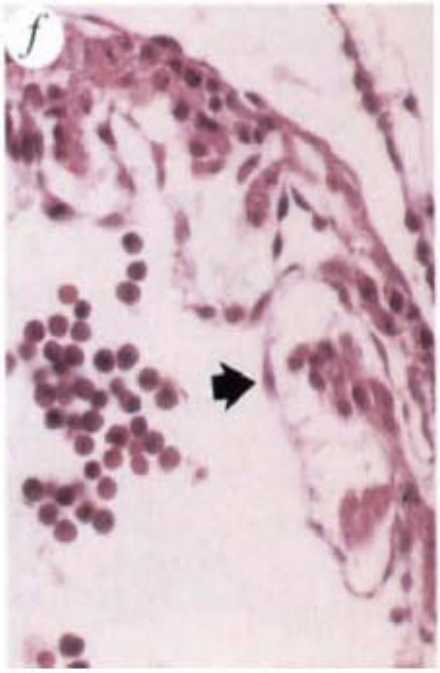
E 9.5





Heart





Nature 371:221, 1994

Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia

*Donald C. Vinh,[1] *Smita Y. Patel,[1] Gulbu Uzel,[1] Victoria L. Anderson,[1] Alexandra F. Freeman,[1,2] Kenneth N. Olivier,[1] Christine Spalding,[1] Stephen Hughes,[3] Stefania Pittaluga,[4] Mark Raffeld,[4] Lynn R. Sorbara,[5] Houda Z. Elloumi,[1] Douglas B. Kuhns,[6] Maria L. Turner,[7] Edward W. Cowen,[7] Danielle Fink,[6] Debra Long-Priel,[6] Amy P. Hsu,[1] Li Ding,[1] Michelle L. Paulson,[1] Adeline R. Whitney,[8] Elizabeth P. Sampaio,[1] David M. Frucht,[9] Frank R. DeLeo,[8] and Steven M. Holland[1]

MonoMAC Syndrome

Mycobacterial infection	78%
HPV infection	78%
MDS/leukemia	50%
Fungal infection	28%
Pulmonary alveolar proteinosis	38%
E. nodusum/panniculitis	33%
Death during study	28%

2010

BLOOD, 25 FEBRUARY 2010 • VOLUME 115, NUMBER 8

blood

Prepublished online June 13, 2011;
doi:10.1182/blood-2011-05-356352

Mutations in *GATA2* are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome

Amy P. Hsu, Elizabeth P. Sampaio, Javed Khan, Katherine R. Calvo, Jacob E. Lemieux, Smita Y. Patel, David M. Frucht, Donald C. Vinh, Roger D. Auth, Alexandra F. Freeman, Kenneth N. Olivier, Gulbu Uzel, Christa S. Zerbe, Christine Spalding, Stefania Pittaluga, Mark Raffeld, Douglas B. Kuhns, Li Ding, Michelle L. Paulson, Beatriz E. Marciano, Juan C. Gea-Banacloche, Jordan S. Orange, Jennifer Cuellar-Rodriguez, Dennis D. Hickstein and Steven M. Holland

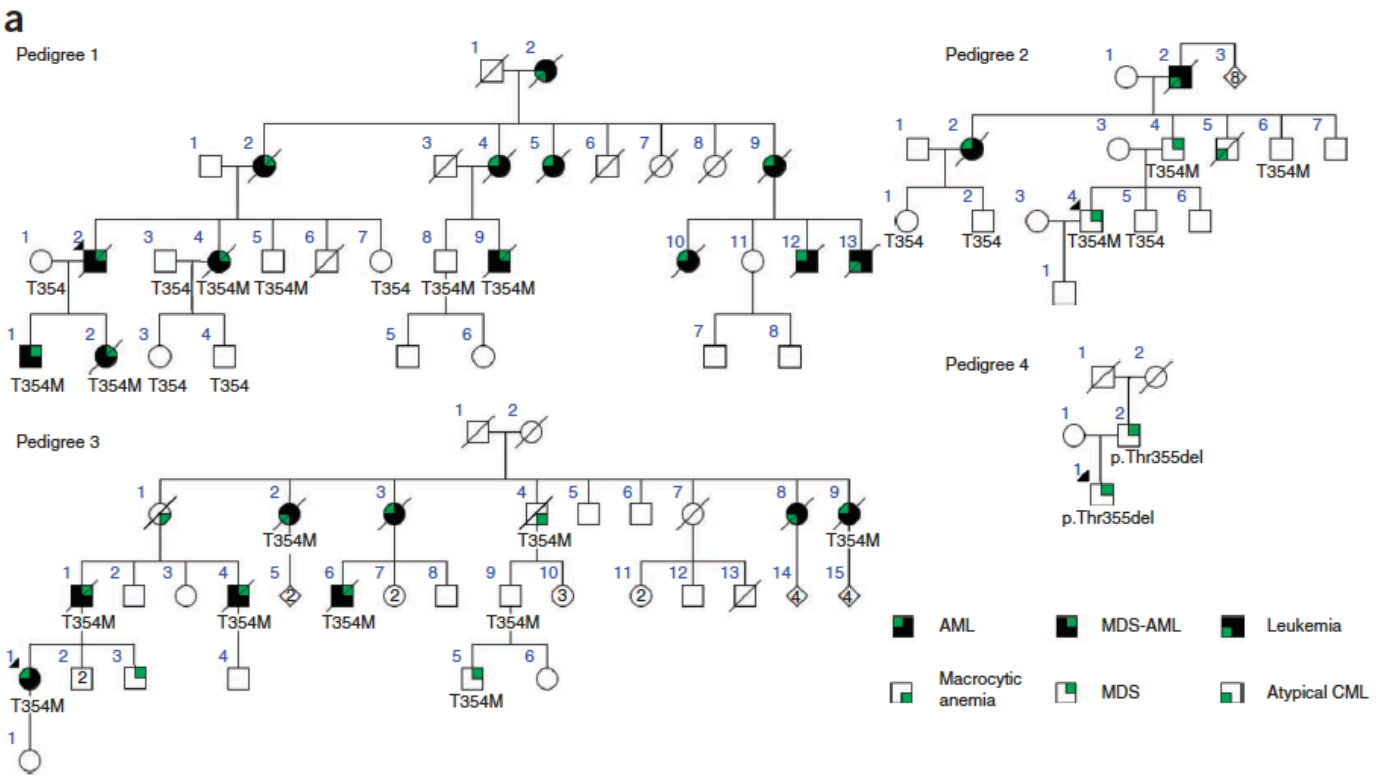
19 years: NIH

nature genetics

"out of the blue" familial leukemia

Heritable *GATA2* mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia

Christopher N Hahn[1,2], Chan-Eng Chong[1,2,14], Catherine L Carmichael[3,14], Ella J Wilkins[3,13], Peter J Brautigan[1], Xiao-Chun Li[1], Milena Babic[1], Ming Lin[1], Amandine Carmagnac[3], Young K Lee[1], Chung H Kok[4,5], Lucia Gagliardi[1], Kathryn L Friend[6], Paul G Ekert[7], Carolyn M Butcher[4,5], Anna L Brown[5], Ian D Lewis[2,5], L Bik To[2,5], Andrew E Timms[8], Jan Storek[9], Sarah Moore[1], Meryl Altree[10], Robert Escher[3,13], Peter G Bardy[5], Graeme K Suthers[10,11], Richard J D'Andrea[2,4,5,15], Marshall S Horwitz[8] & Hamish S Scott[1–3,12,15]

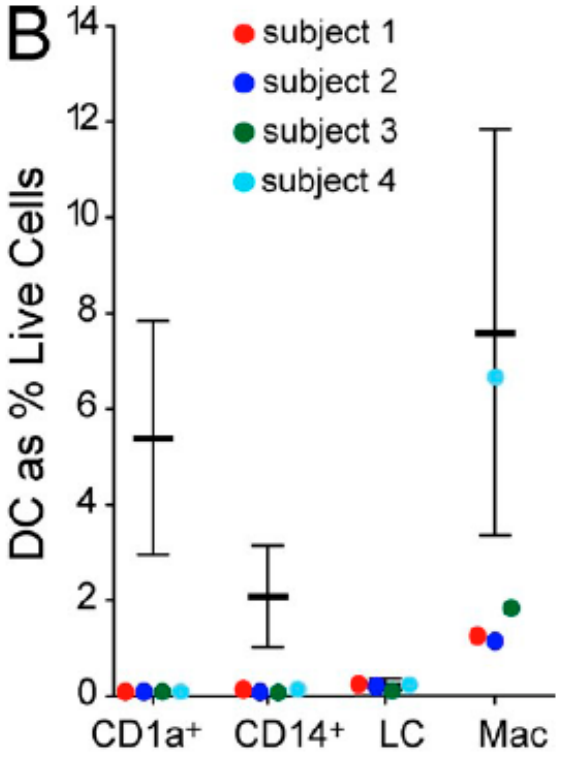


Sept 2011

Published January 17, 2011

JEM

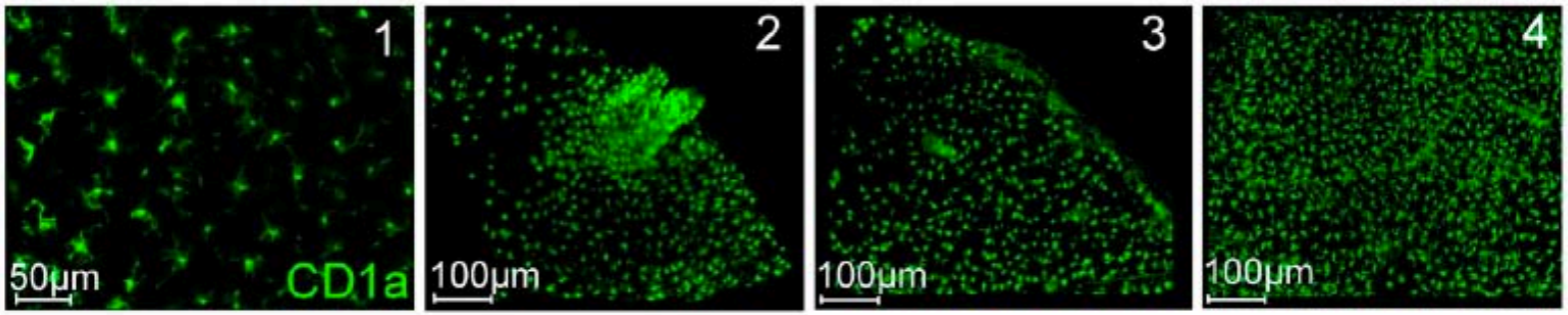
Brief Definitive Report

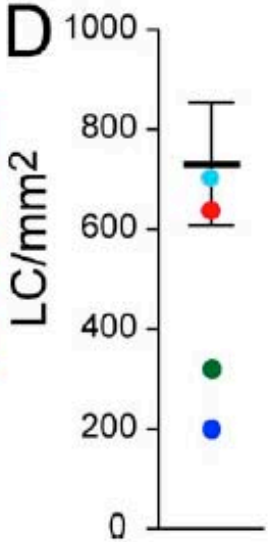


The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency

Venetia Bigley,[1] Muzlifah Haniffa,[1] Sergei Doulatov,[2] Xiao-Nong Wang,[1] Rachel Dickinson,[1] Naomi McGovern,[1] Laura Jardine,[1] Sarah Pagan,[1] Ian Dimmick,[1] Ignatius Chua,[3] Jonathan Wallis,[4] Jim Lordan,[4] Cliff Morgan,[5] Dinakantha S. Kumararatne,[6] Rainer Doffinger,[6] Mirjam van der Burg,[7] Jacques van Dongen,[7] Andrew Cant,[4] John E. Dick,[2] Sophie Hambleton,[1] and Matthew Collin[1]

DCML





J. Exp. Med. 208:227-234, 2011

nature genetics

Mutations in *GATA2* cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome)

Pia Ostergaard[1,13], Michael A Simpson[2,13], Fiona C Connell[3], Colin G Steward[4], Glen Brice[5], Wesley J Woollard[2], Dimitra Dafou[2], Tatjana Kilo[6], Sarah Smithson[7], Peter Lunt[7], Victoria A Murday[8], Shirley Hodgson[5], Russell Keenan[9], Daniela T Pilz[10], Ines Martinez-Corral[11], Taija Makinen[11], Peter S Mortimer[12], Steve Jeffery[1], Richard C Trembath[2] & Sahar Mansour[5]

4 September 2011; doi:10.1038/ng.923

MEDICAL INTELLIGENCE

GATA2 c.1025_1026insGCCG p.A342GfsX41

SEVERE HERPESVIRUS INFECTIONS IN AN ADOLESCENT WITHOUT NATURAL KILLER CELLS

CHRISTINE A. BIRON, PH.D., KEVIN S. BYRON, AND JOHN L. SULLIVAN, M.D.

NEJM 1989;320:1731

GATA2 Deficiency

5 names, one disease

MonoMAC

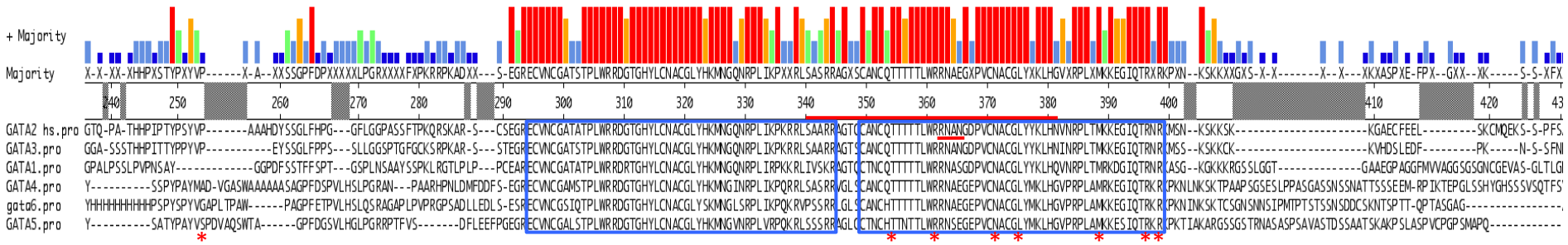
DCML

Emberger syndrome

Familial MDS/AML

Classical NK cell Deficiency

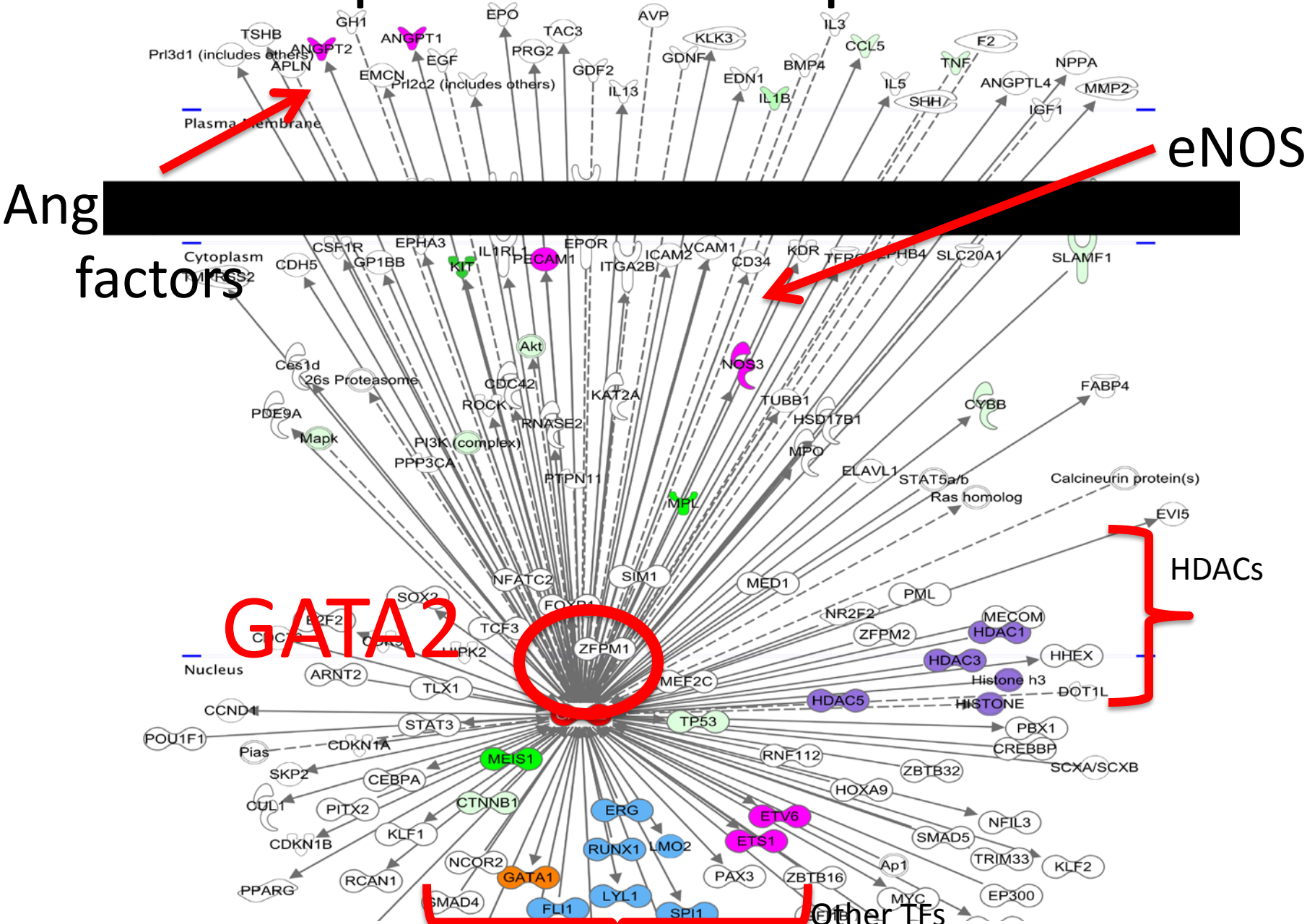
Homo sapiens GATA proteins



ZF1 ZF2

GATA1	Xp11.23	anemia with thrombocytopenia; DBA
GATA2	3q21.3	MonoMAC, DCML, Emberger, MDS/AML
GATA3	10p14	HDR (hypopara, deafness, renal)
GATA4	8p23.1	atrial and ventricular defects, TOF
GATA5	20q13.33	expressed in heart and urinary tract
GATA6	18q11.2	PACHD (pancreatic agenesis and congenital heart disease)

Hematopoietic Transcription Factor

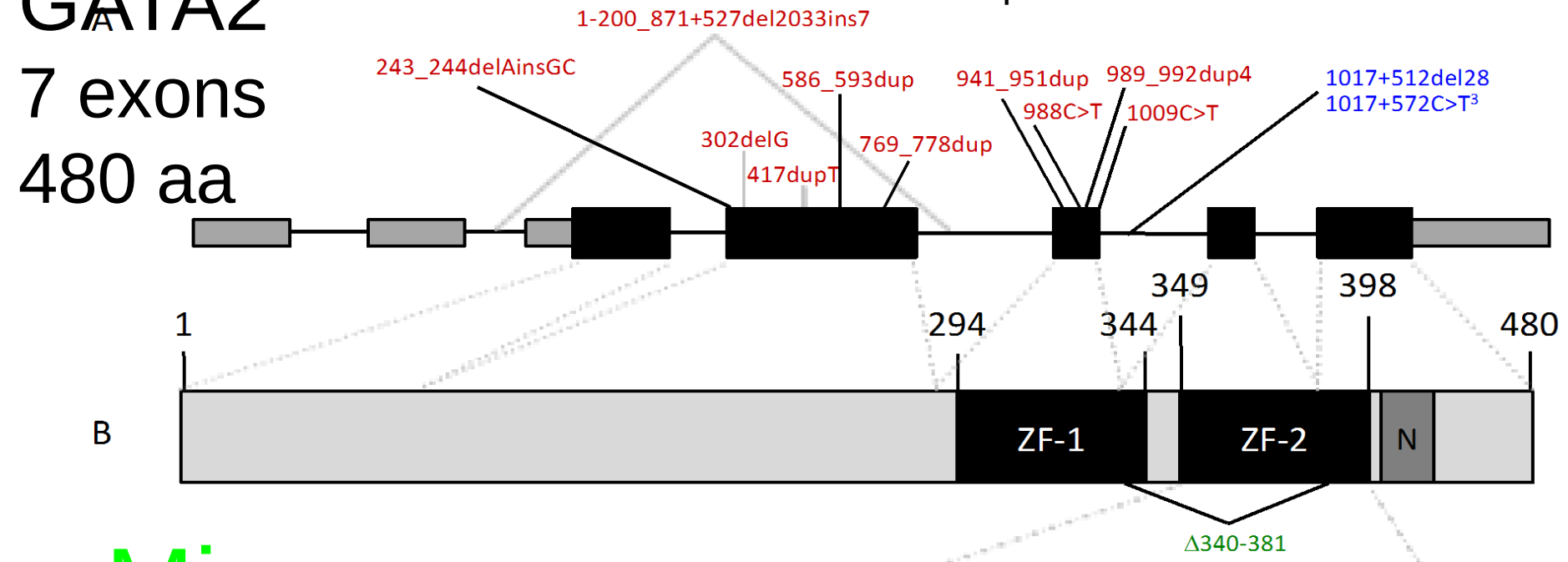


Human Disease is Heterozygous

GATA2

7 exons

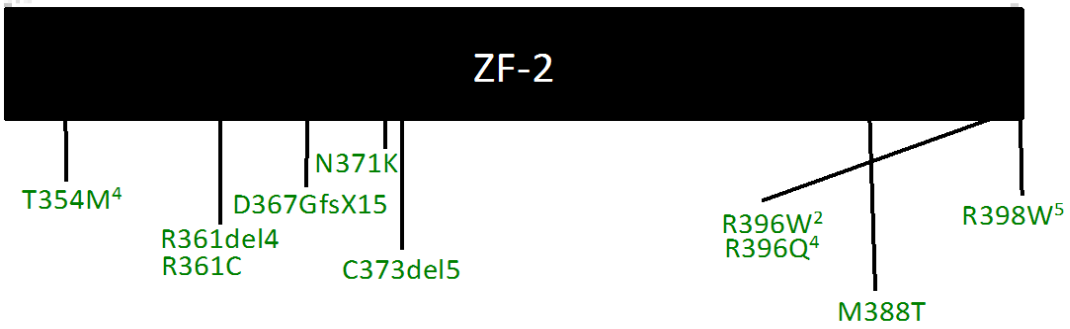
480 aa



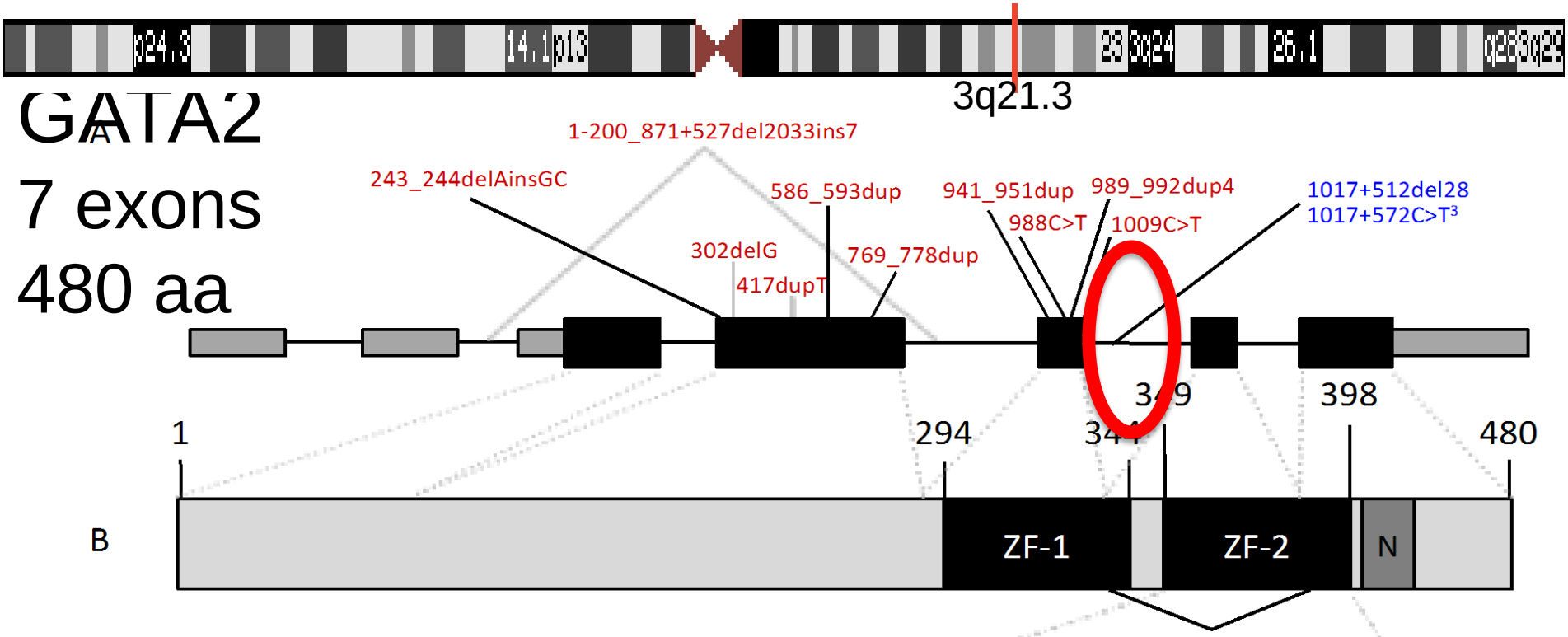
Missense

Nonsense

Intronic



Uniallelic (only one allele expressed)

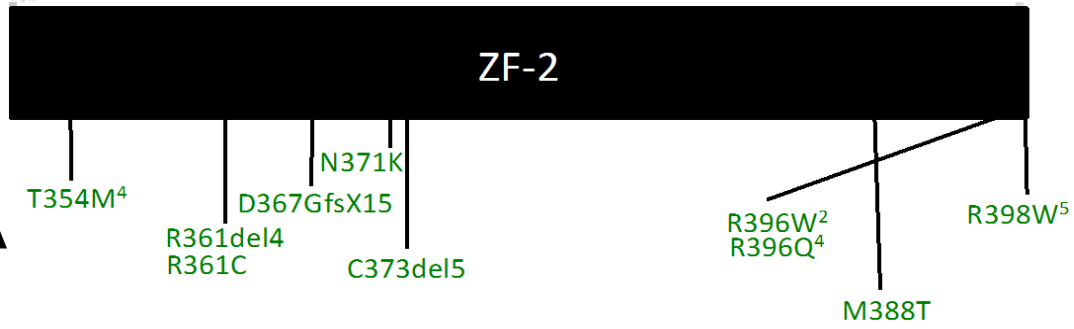


Intron 5 enhancer mutation:

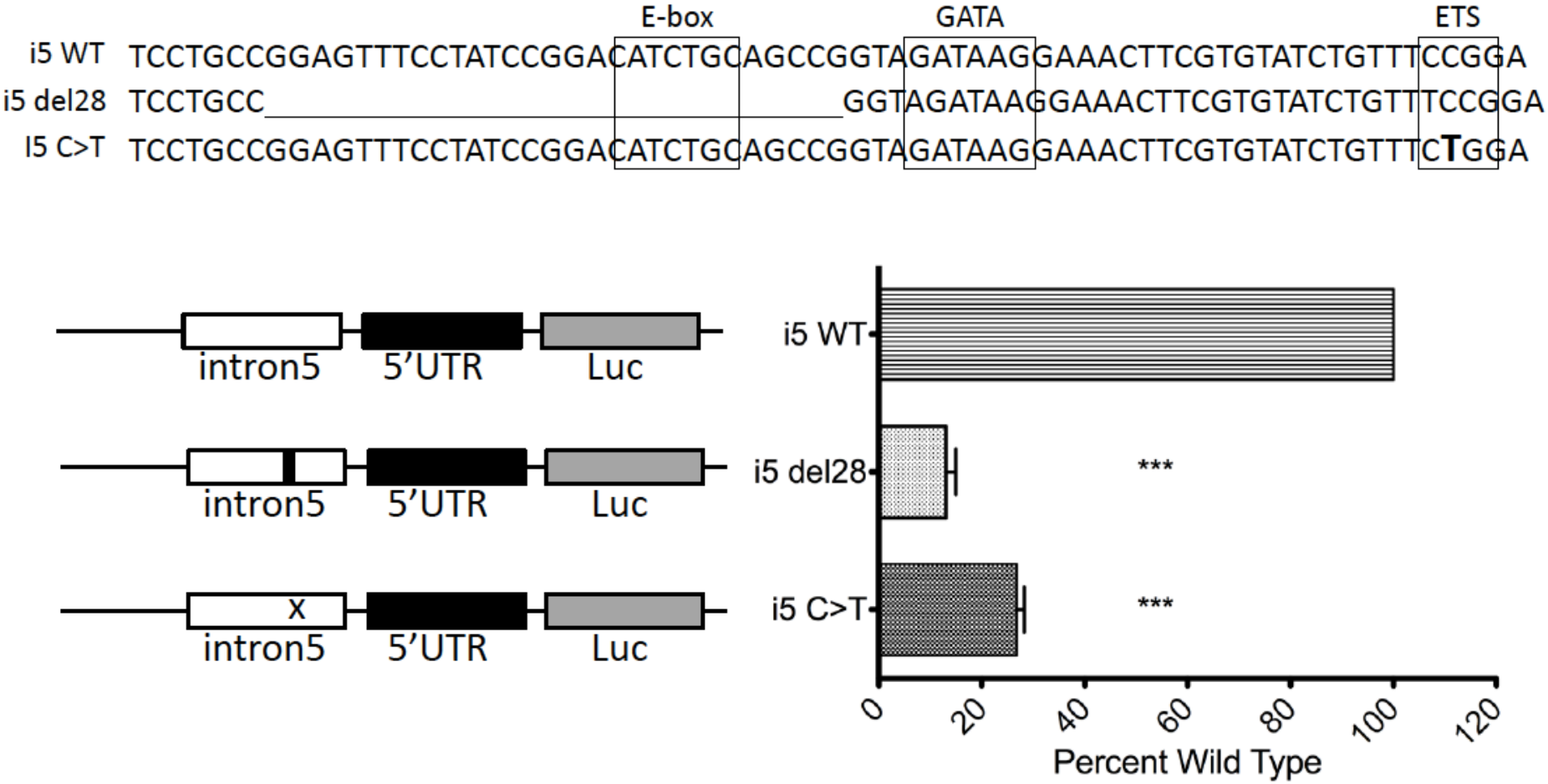
~25% cases

normal cDNA

Just less of it



GATA2 intron 5: *cis* enhancer of GATA2 expression

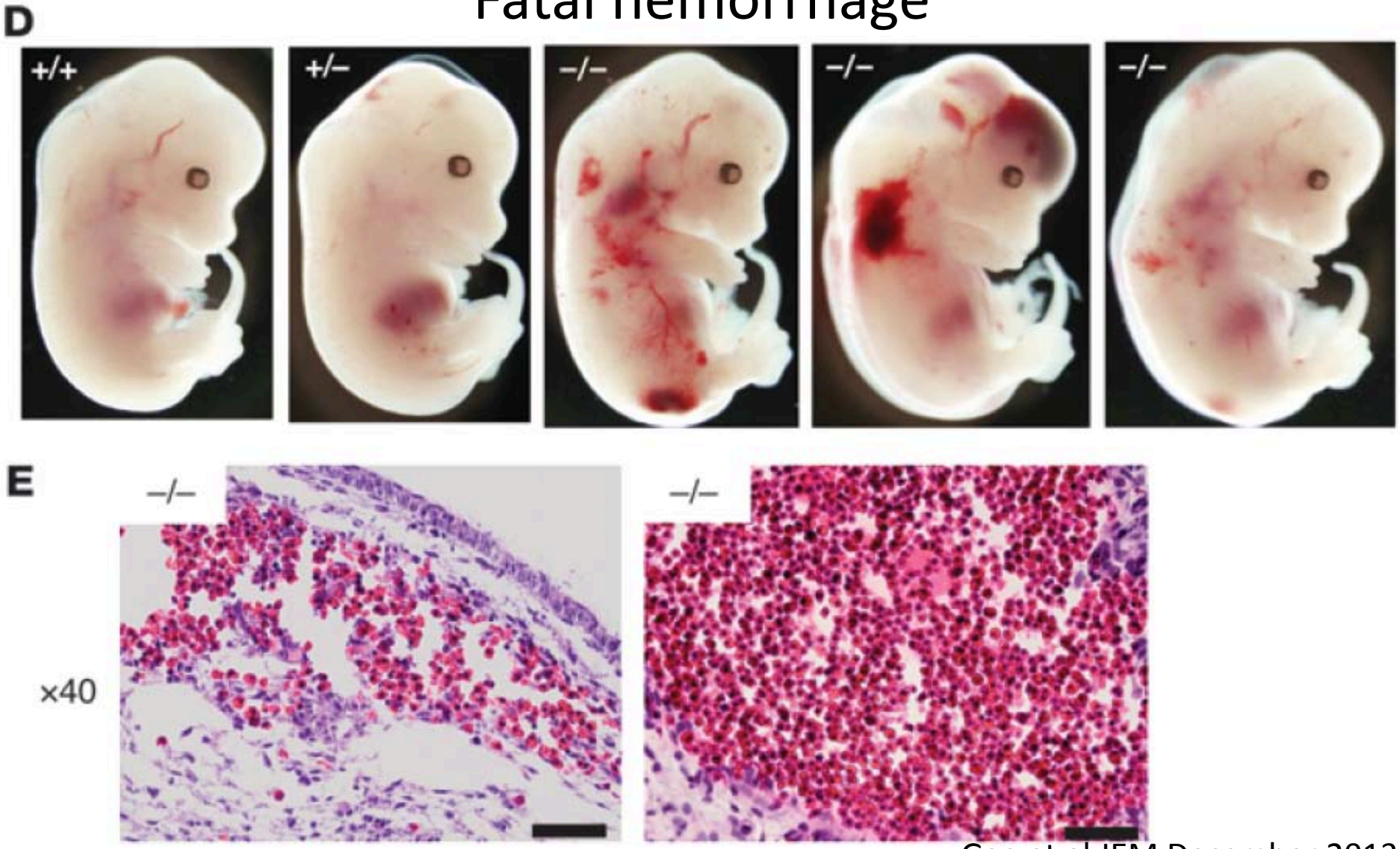


Hsu et al Blood. 2013 May 9;121(19):3830-7

Gata2$^{i5/i5}$ die d13.5b

Intron 5 cis element homozygous KO:

Fatal hemorrhage



Gao et al JEM December 2013

GATA2 is a Disease of Haploinsufficiency

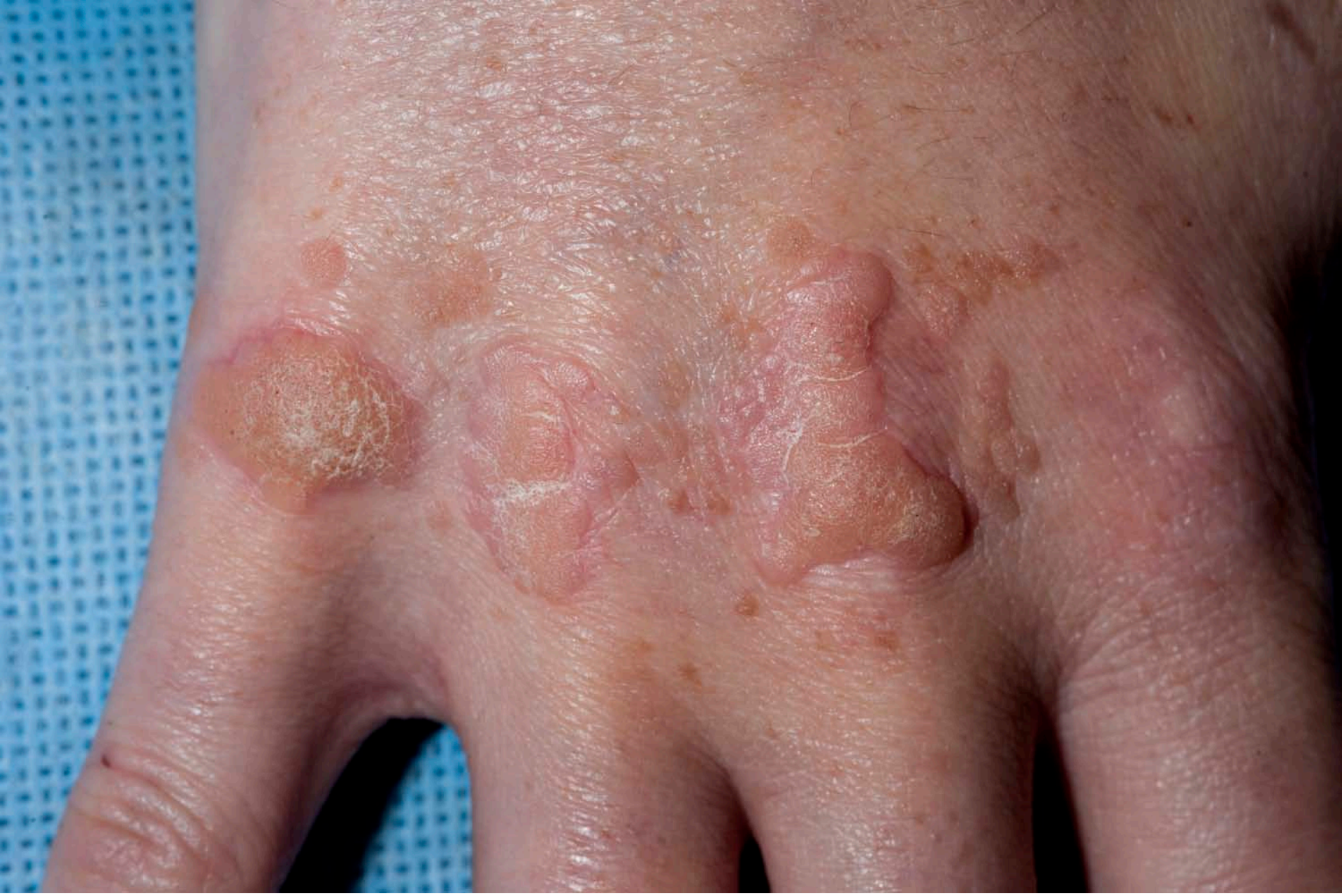
One copy is not enough

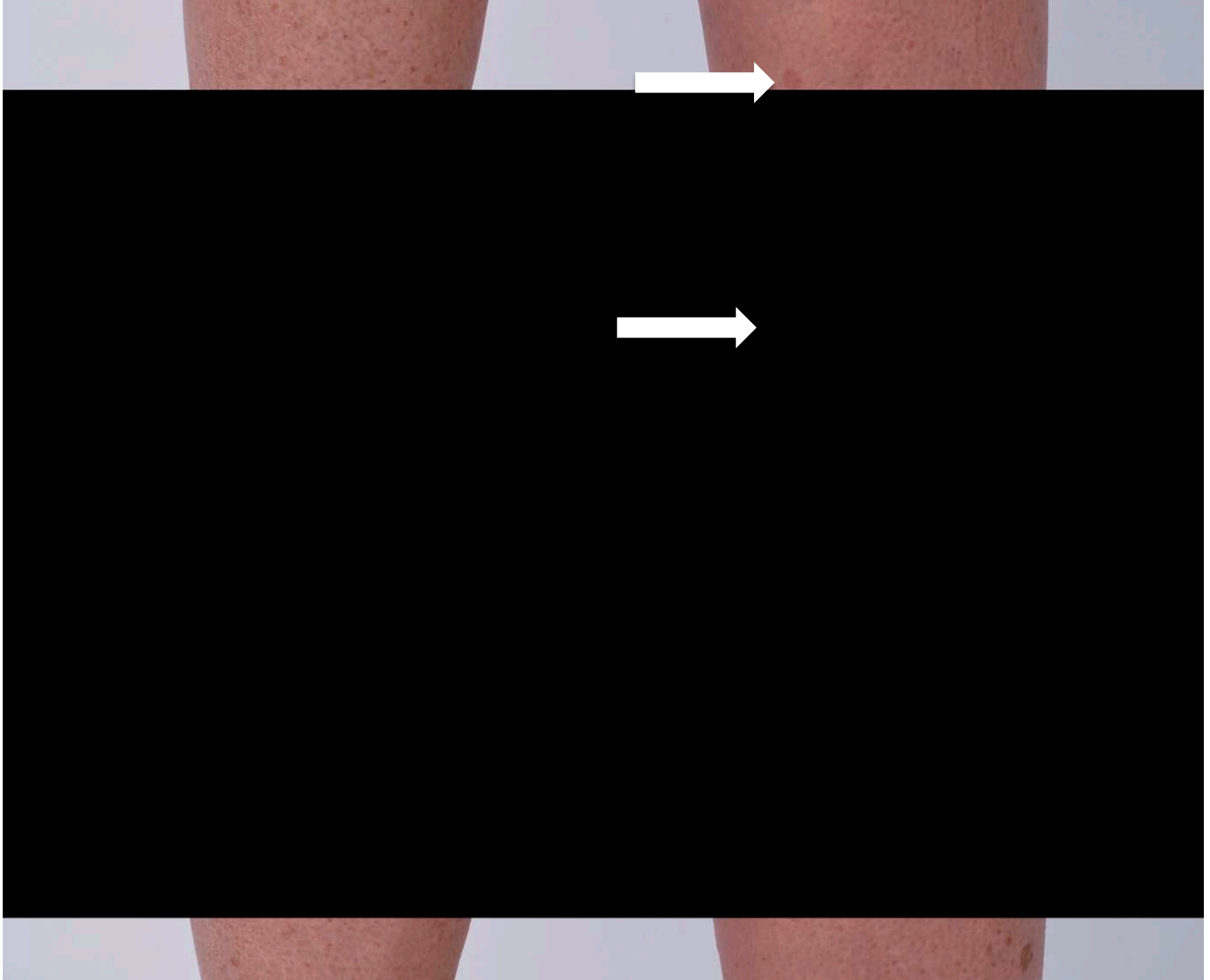
Intronic mutations:

Completely intact mRNA, but low levels

>70% GATA2 levels are required for normal hematopoiesis, lymphatic development, NK function

Stringent need for GATA2 expression

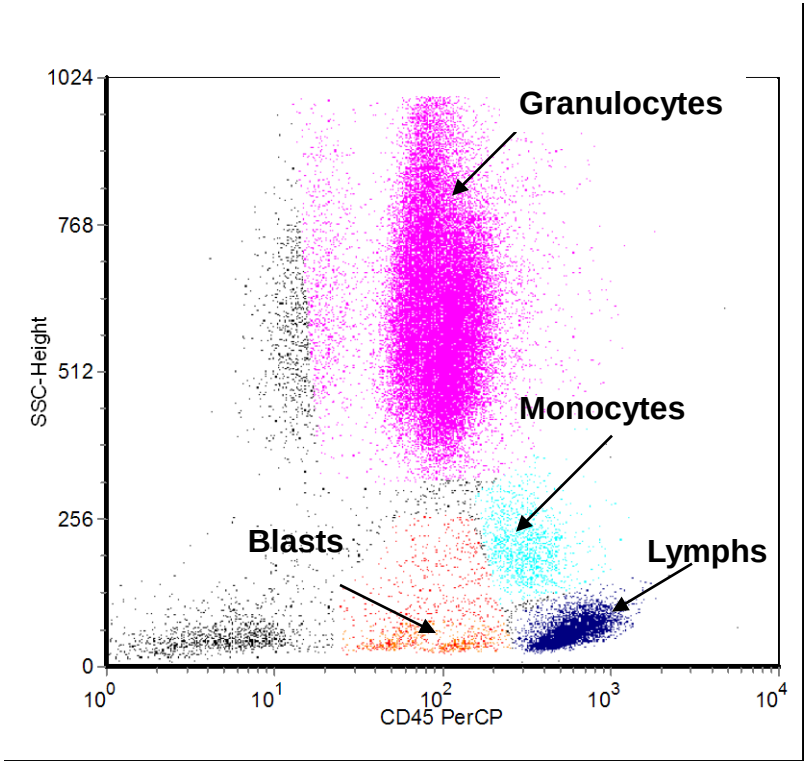




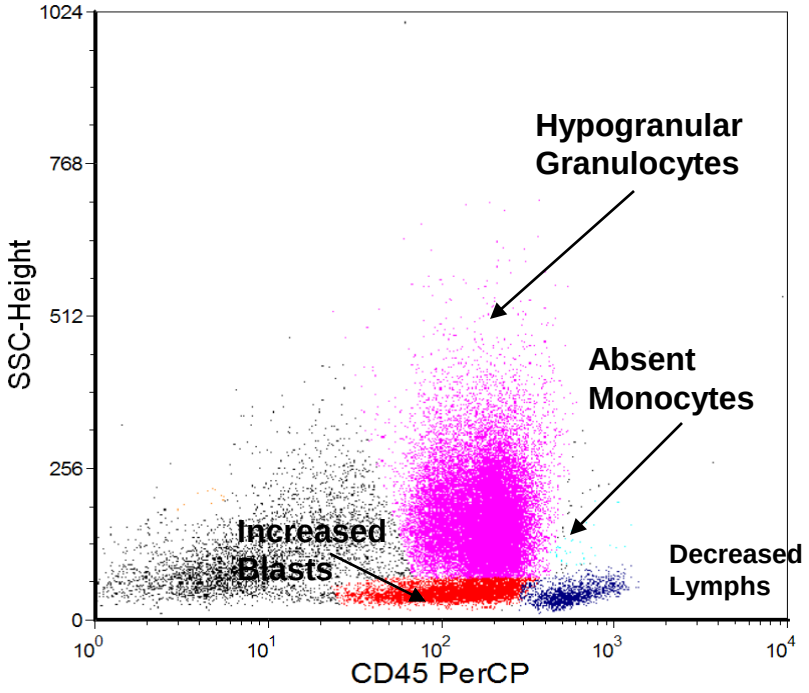
Myelodysplasia in autosomal dominant and sporadic monocytopenia immunodeficiency syndrome: diagnostic features and clinical implications

Katherine R. Calvo,[1] Donald C. Vinh,[2] Irina Maric,[1] Weixin Wang,[1] Pierre Noel,[1] Maryalice Stetler-Stevenson,[3] Diane C. Arthur,[3] Mark Raffeld,[3] Amalia Dutra,[4] Evgenia Pak,[4] Kyungjae Myung,[5] Amy P. Hsu,[2] Dennis D. Hickstein,[6] Stefania Pittaluga,[3] and Steven M. Holland[2]

Normal Marrow



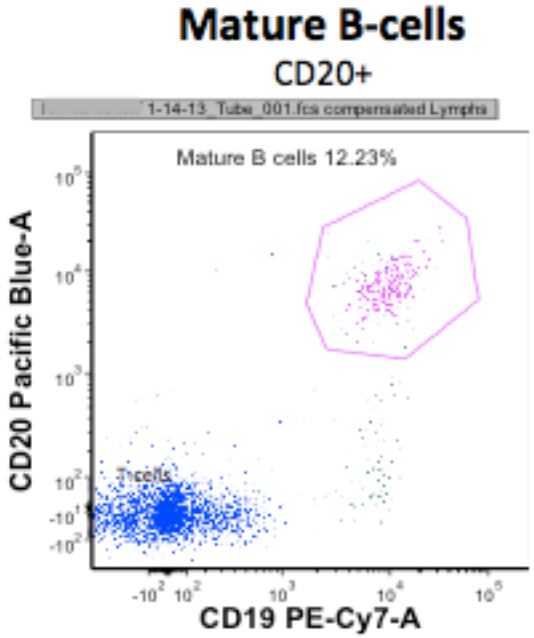
GATA2 deficiency

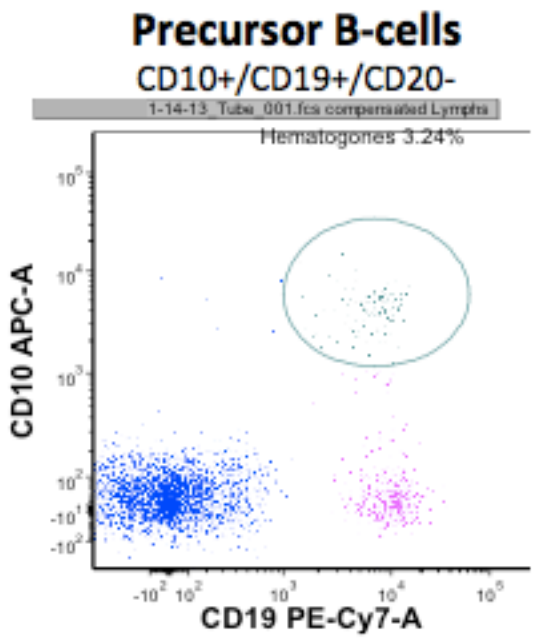


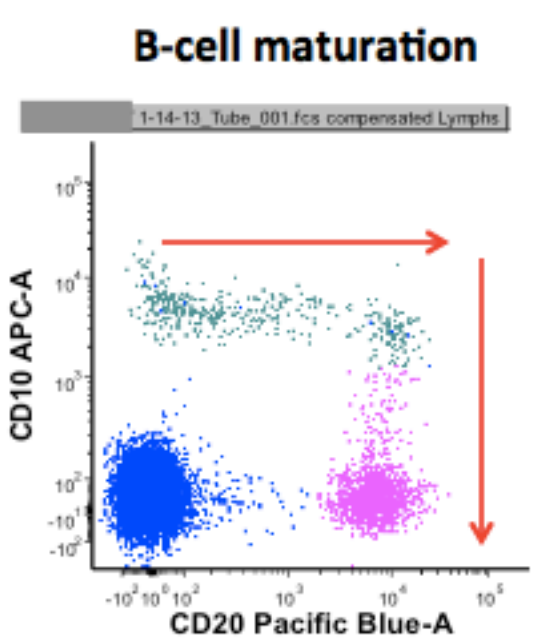
Heamatologica 2011;96:1221

Absent B cell Precursors

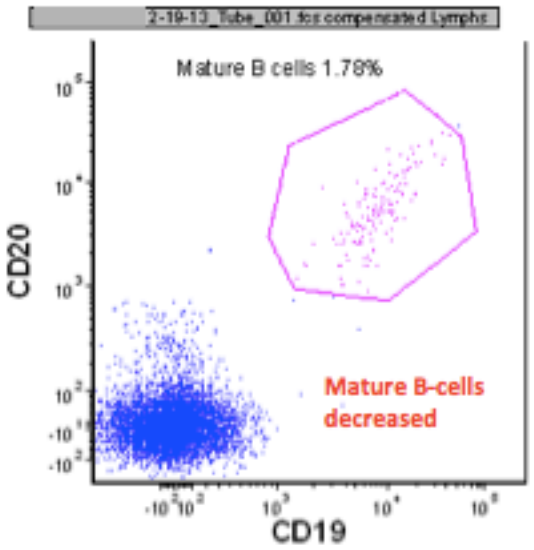
Normal adult marrow

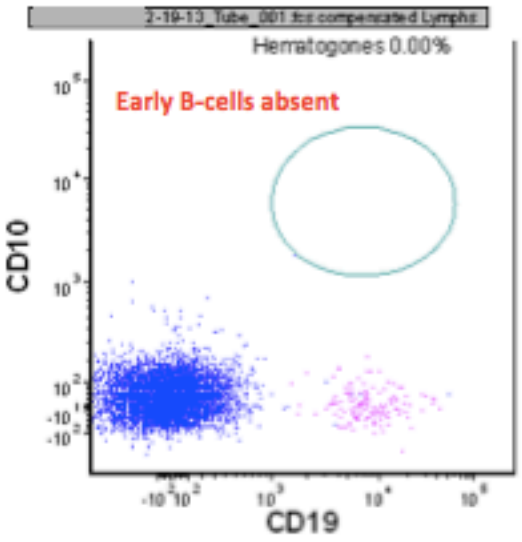


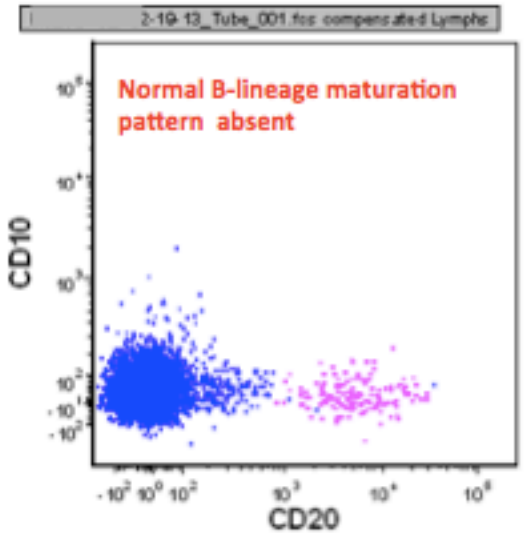




Patient marrow







Kathy Calvo, Hematology

GATA2 Deficiency

It’s also

Pediatric neutropenia

Pediatric MDS (especially tri8, mono7)

AML

ALL

CMML

5 New Things about GATA2 Deficiency

Severe EBV Infection

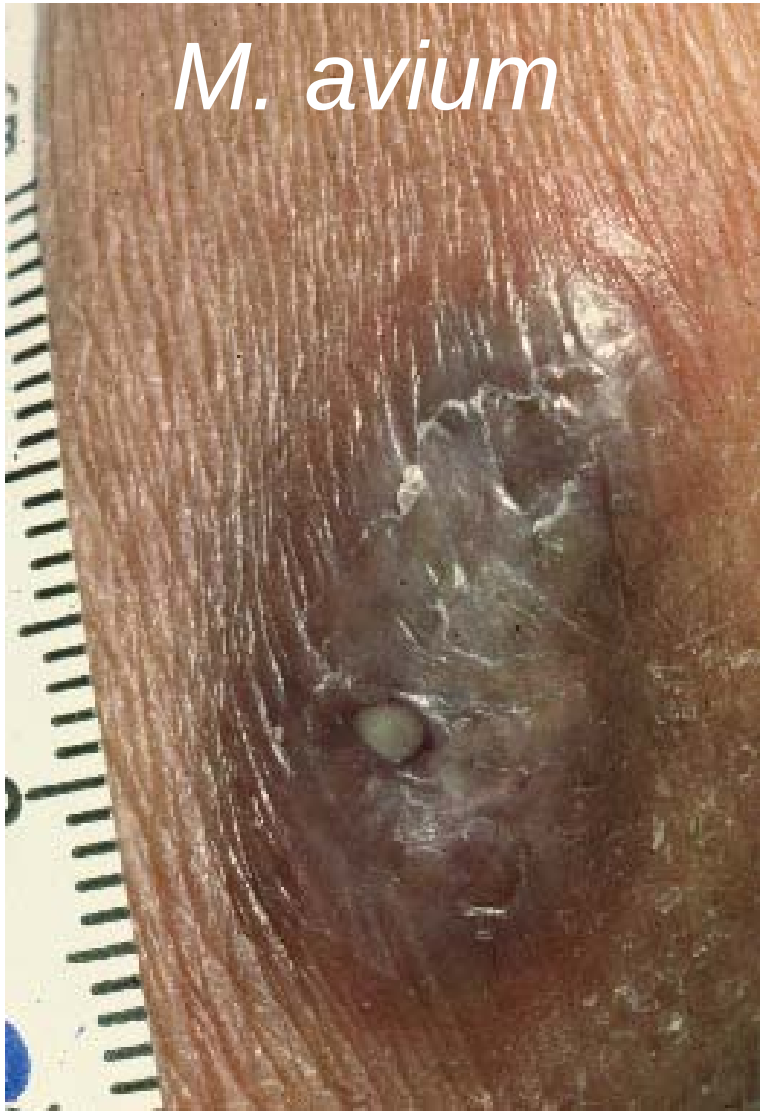
Severe *Mycobacterium kansasii* infection

Common Lung Abnormalities (not PAP)

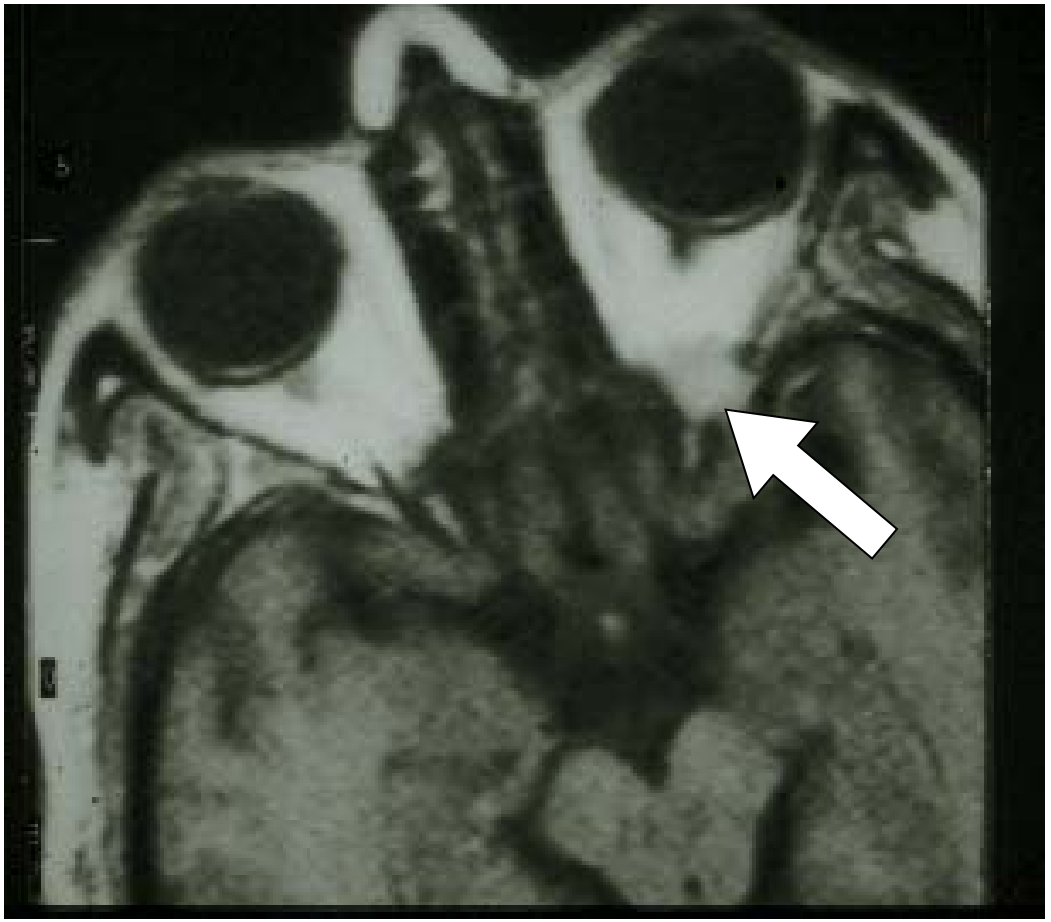
Severe *C. difficile* infection

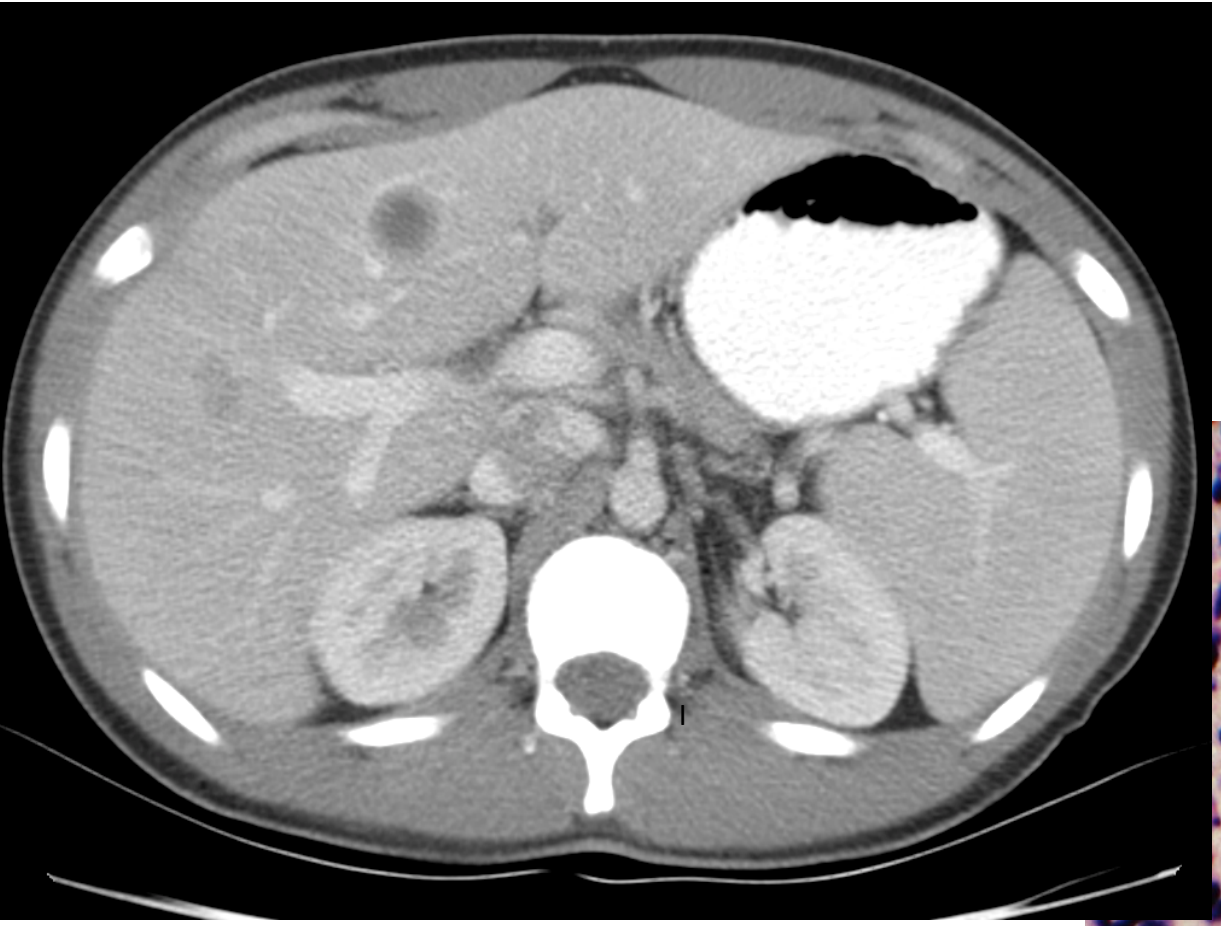
GATA2 Deficiency Imitation

1992: 41 yo Woman Refractory MAC Infection

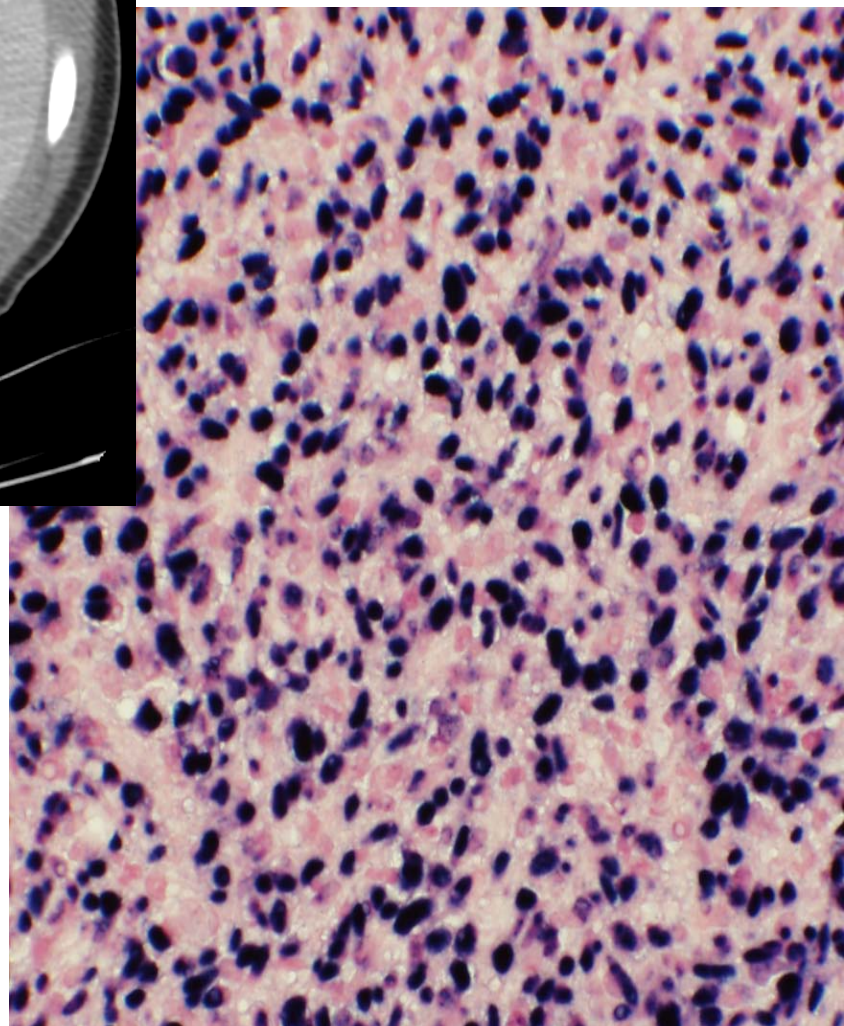


EBV+ Smooth Muscle Tumor



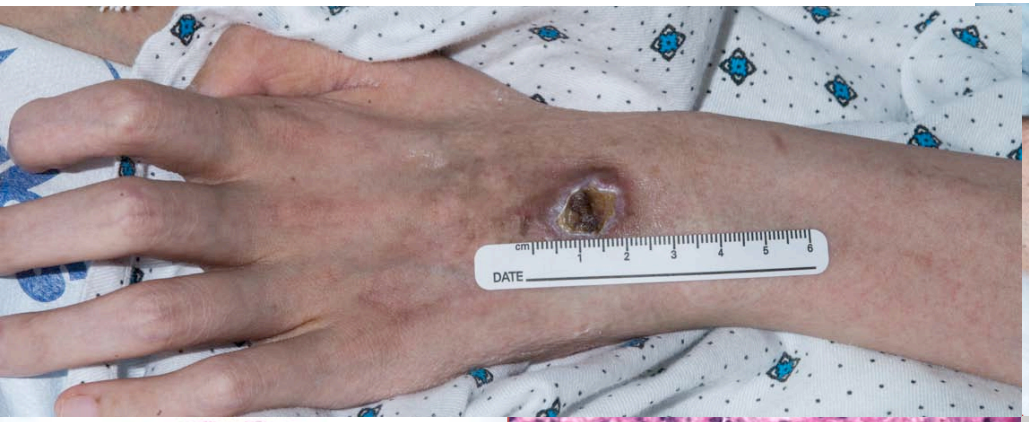


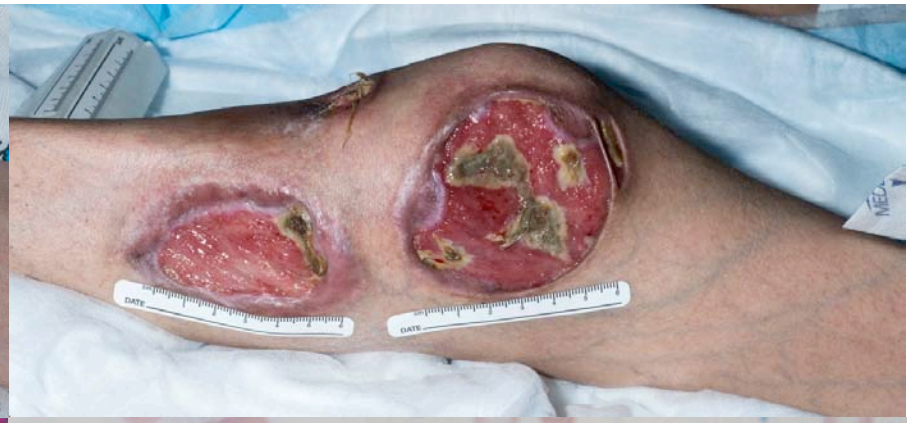
EBV

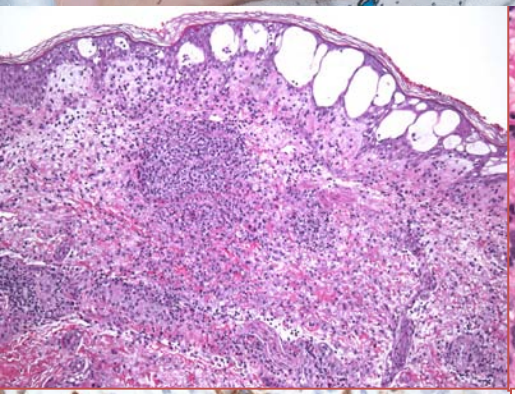


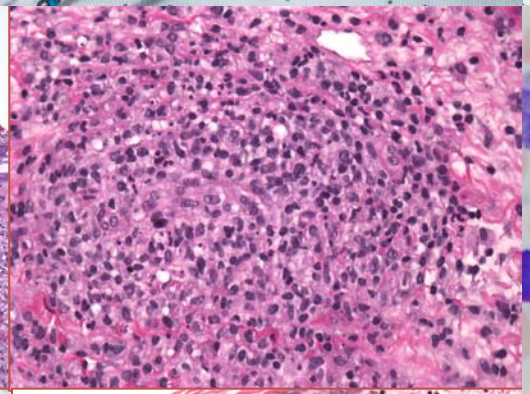
26 yo man

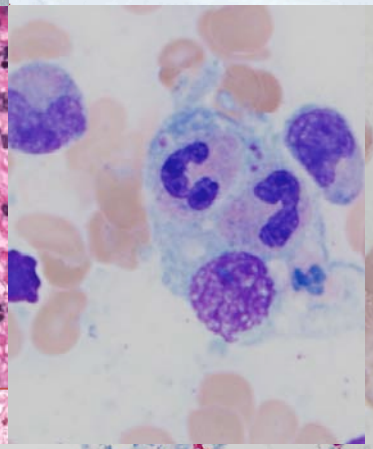
20 yo Cantonese Woman with Hydroa Vacciniforme and HLH

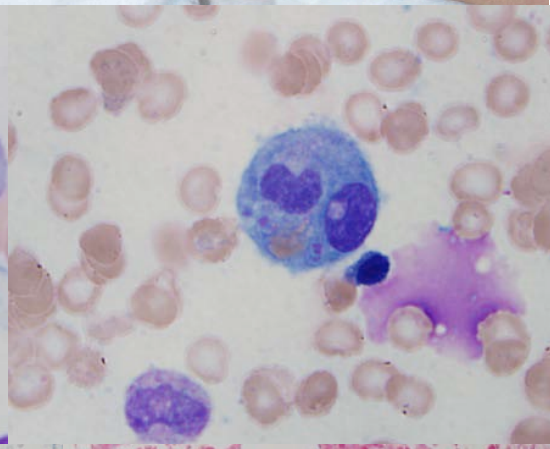


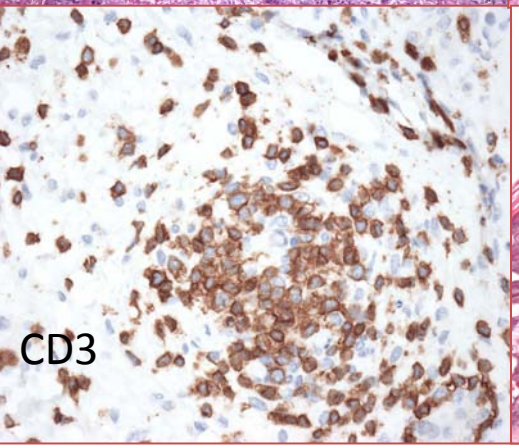


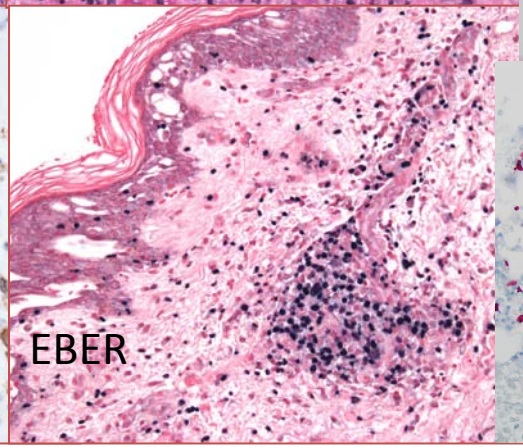


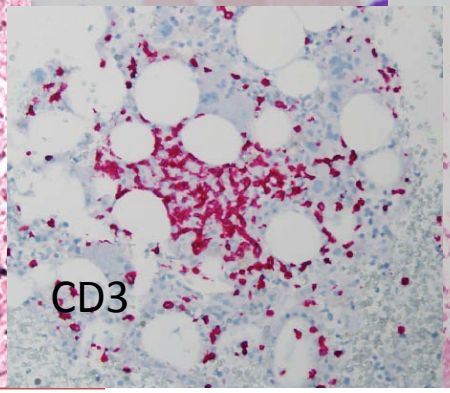


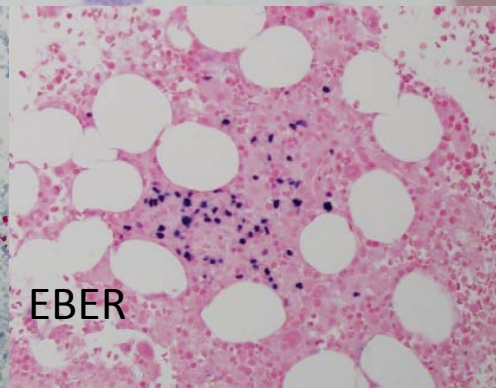












Cohen JI et al, CID in press

GATA-2 Deficiency is Associated with Severe Primary Epstein-Barr Virus (EBV) Infection and Malignant EBV Disease

General GATA2 patient EBV viral load 117 copies/ml

	Severe EBV Infectious Mononucleosis			CAEBV	Hydroa vacciniforme-like lymphoma/HLH	EBV-Positive Smooth Muscle Tumors	
Patient	1	2	3	4	5	6	7
Race/Sex	HF	WF	WF	WM	AF	HF	AM
Age Onset	6	19	23	20	20	41	24
Treatment	Steroids	HSCT	HSCT	None	HLH94/HSCT	HSCT	HSCT
Age at Death (yr)/Cause	Alive	Alive	Alive	22; mycobacterial infection	Alive	46; post HSCT viral infection	Alive
Peak EBV DNA in Blood copies/ml	44,000	20,600	8,900	2,770*	6.4 million	ND	3,350
GATA2 mutation	c.1187G>A R396Q	c.988C>T R330X (stop)	c.988C>T R330X	c.1061C>T T354M	Unialleleic expression.	R398W	C.1186 C>T R396W

Cohen JI, et al. CID, in press

Revised List for EBV Susceptibility, Chronic Active EBV, EBV malignancies

SH2D1

BIRC4

ITK

MAGT1

CD27

PRF1

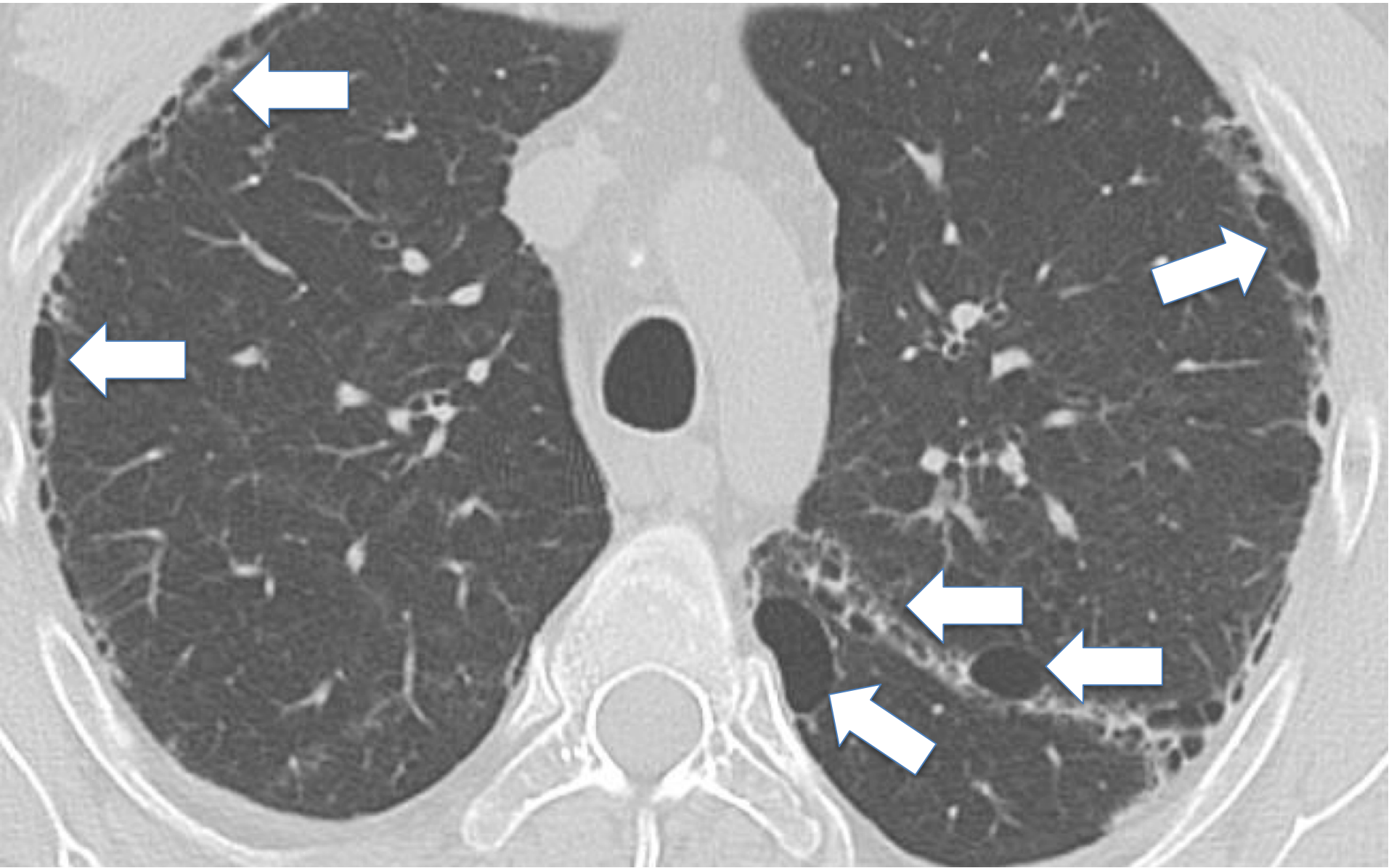
PIK3CD

CORO1A

MST1/STK4

GATA2

GATA2: Subpleural Blebs and Emphysema



Subpleural Blebs and Emphysema

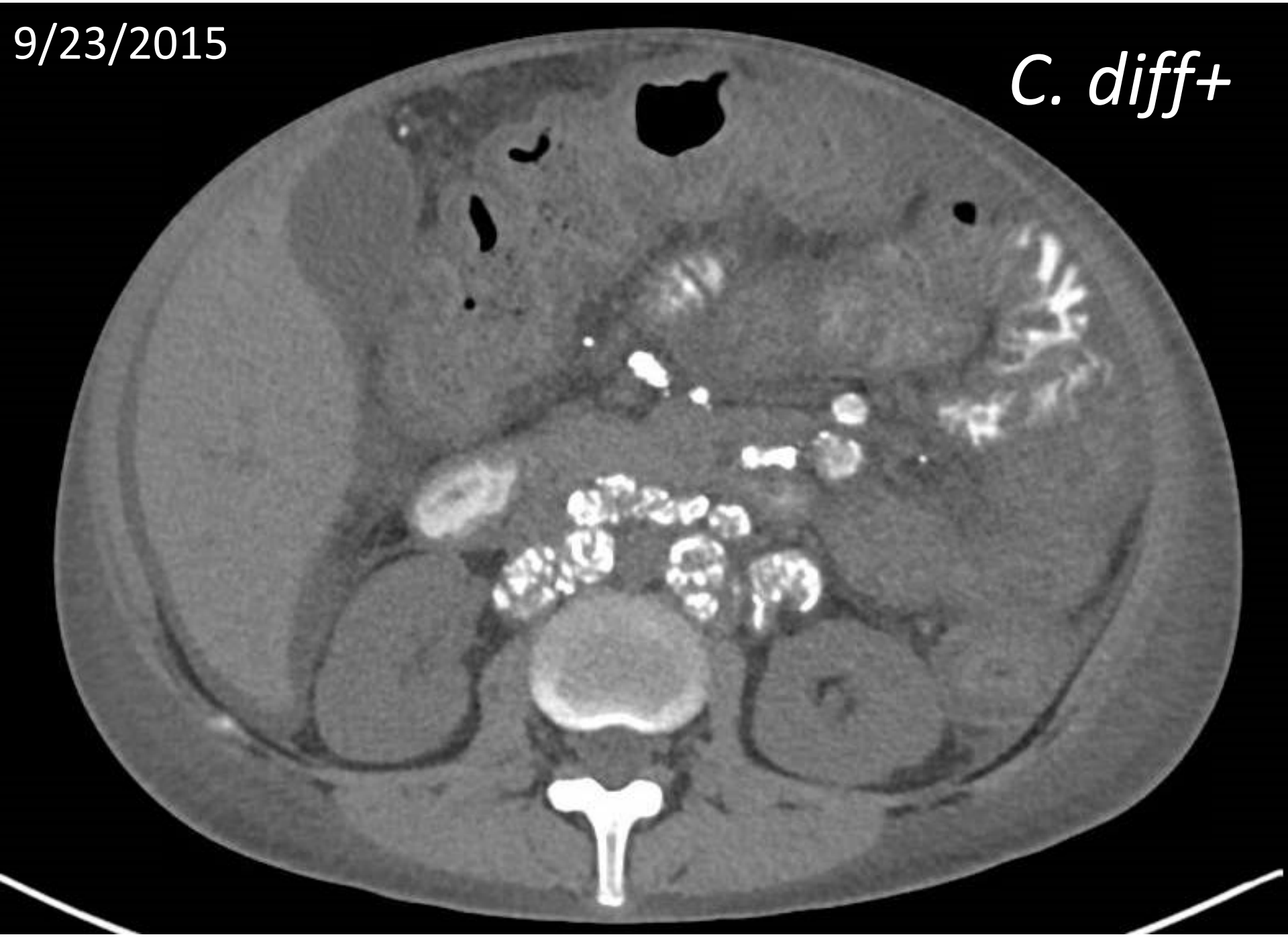
30% of patients

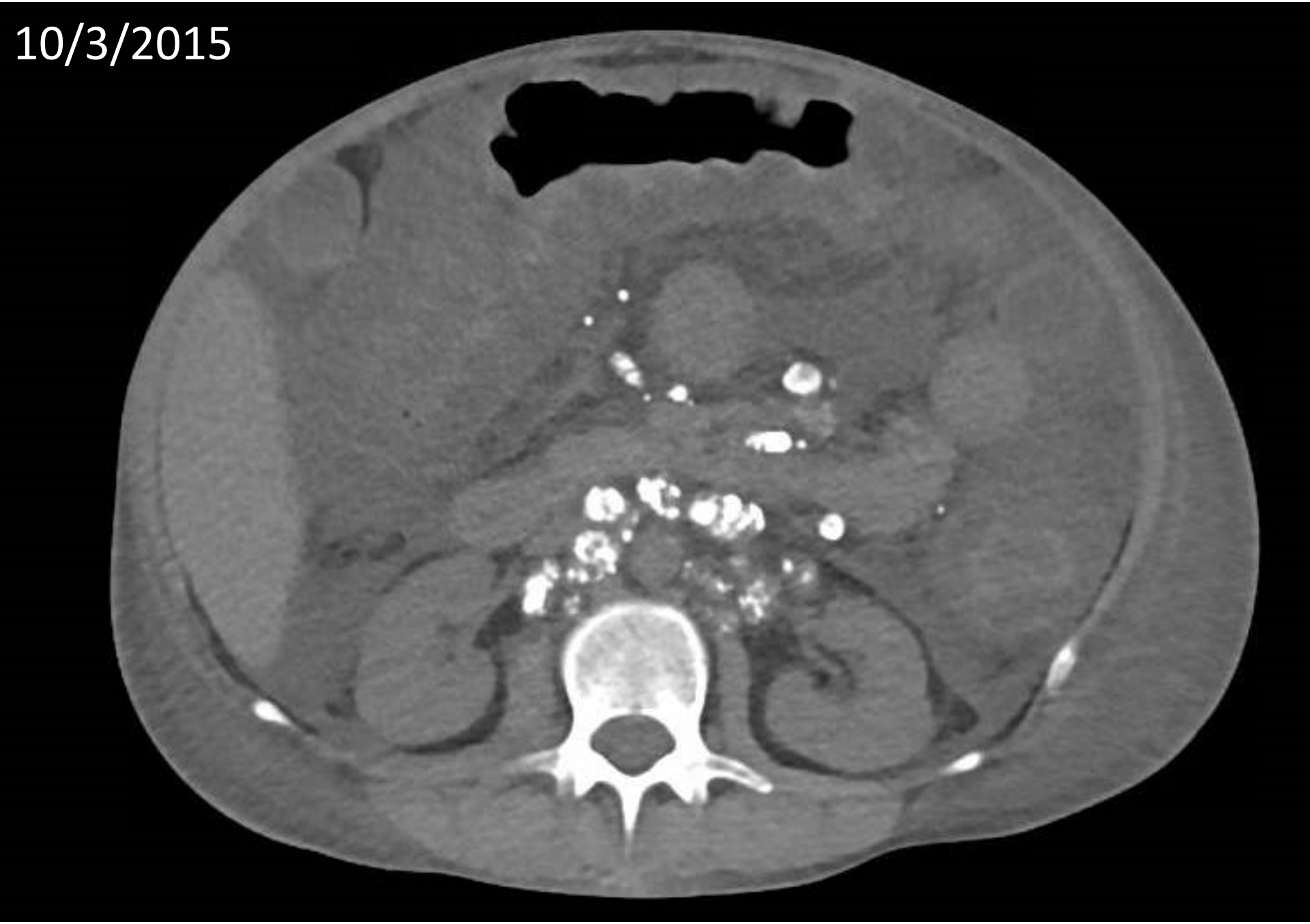
Begins early in life

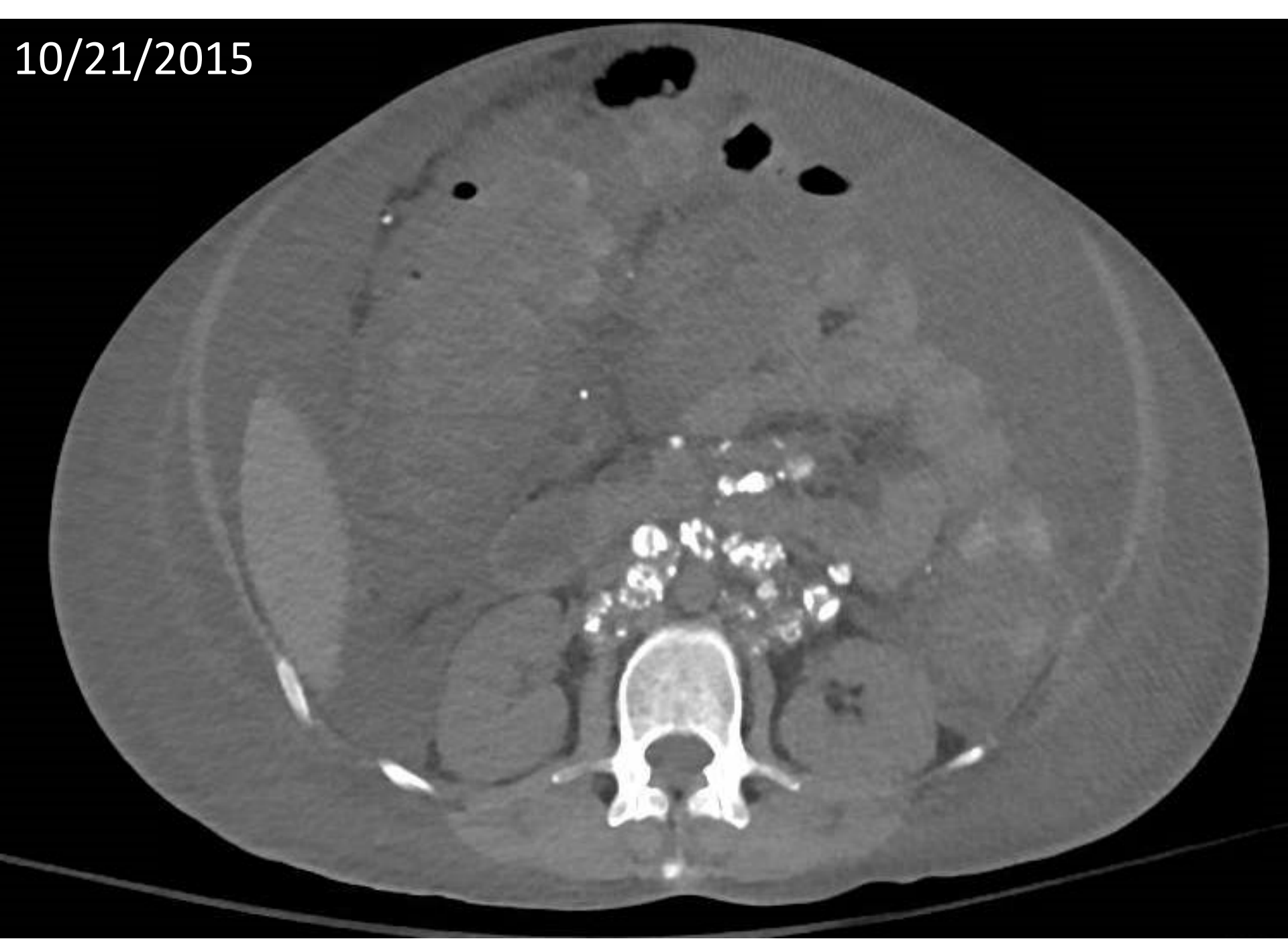
At tissue junctions: interlobar, apical

Can lead to emphysematous changes

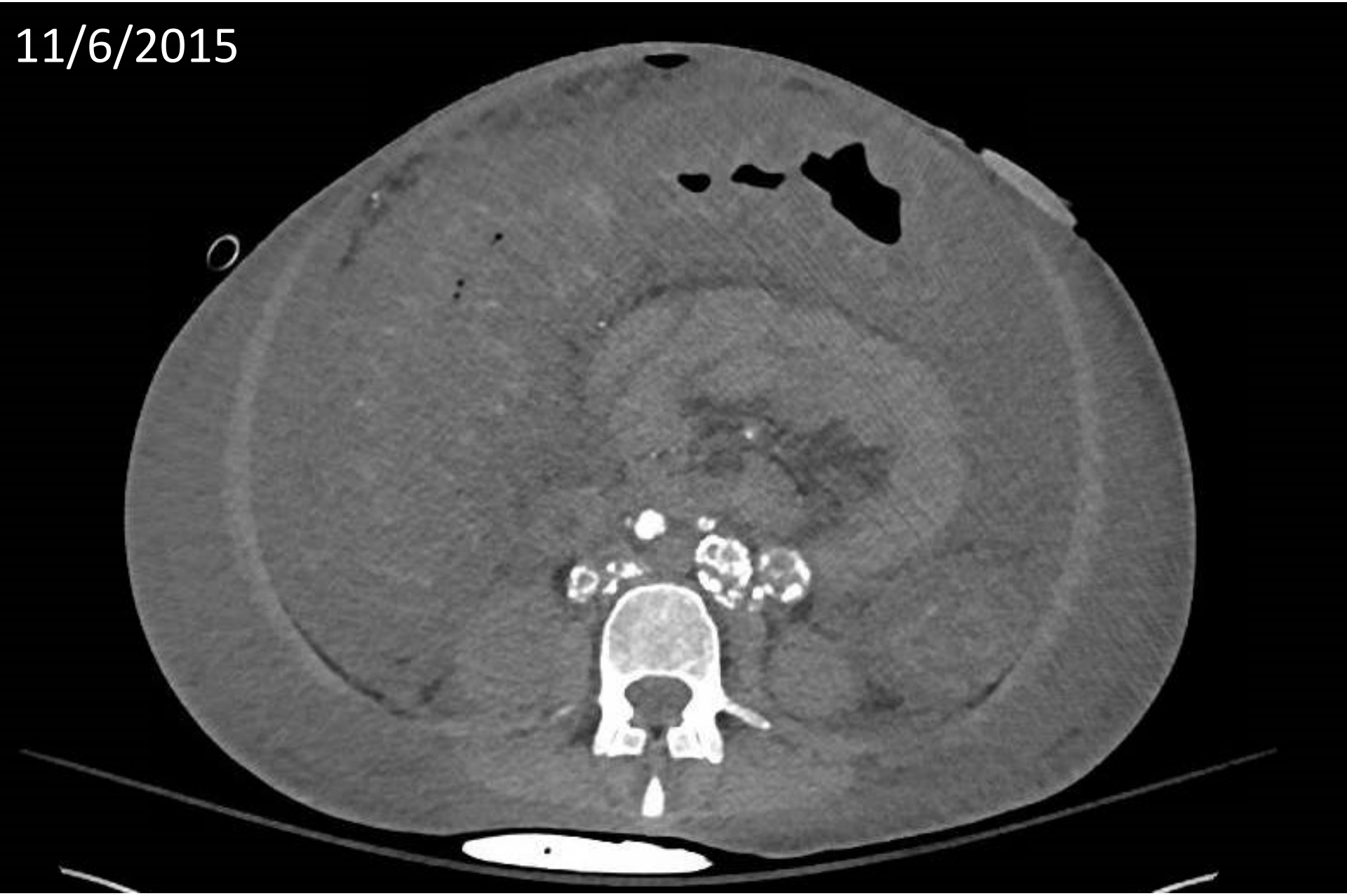
Etiology? Not apparently infectious

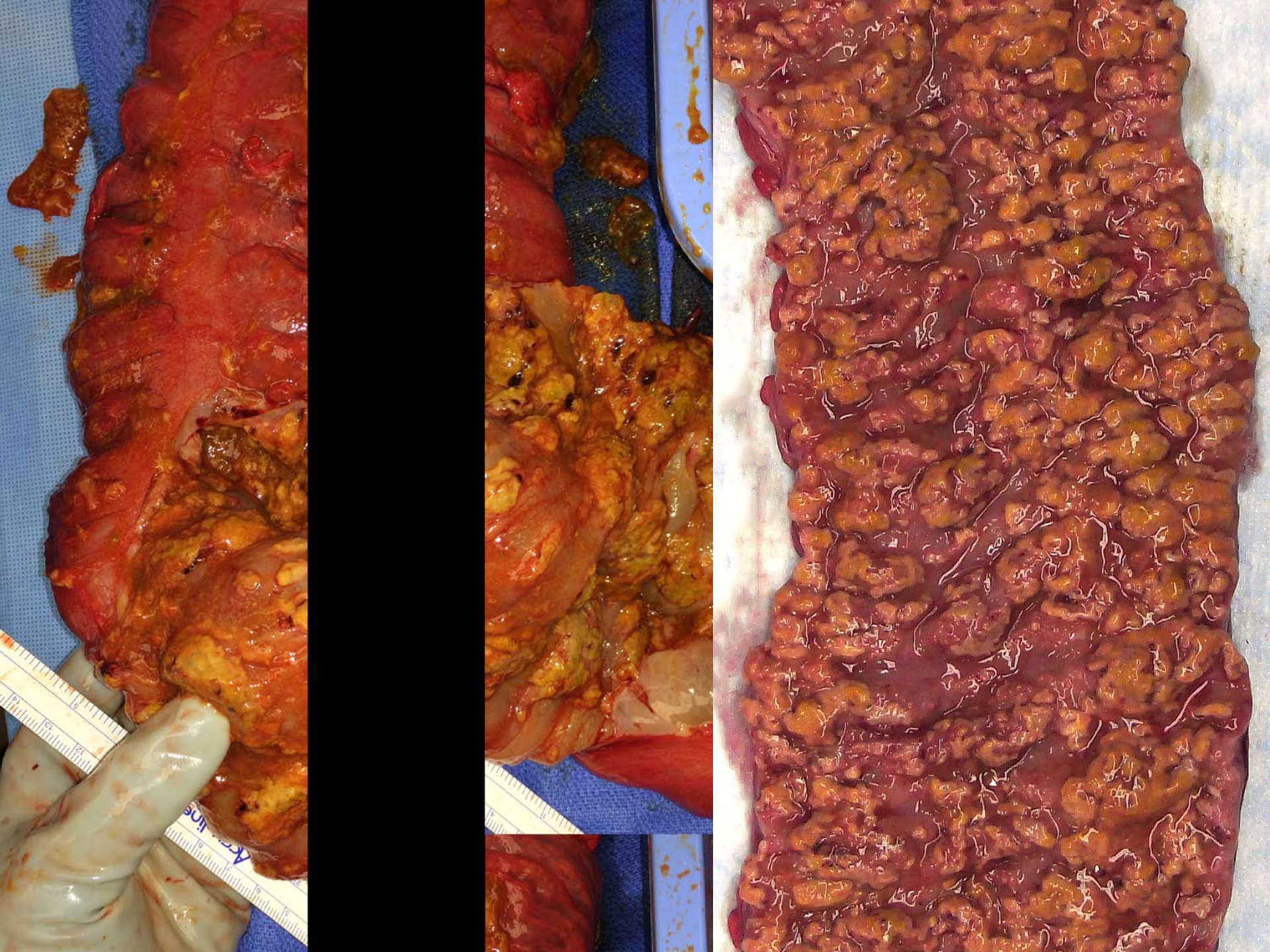

9/23/2015
C. diff+

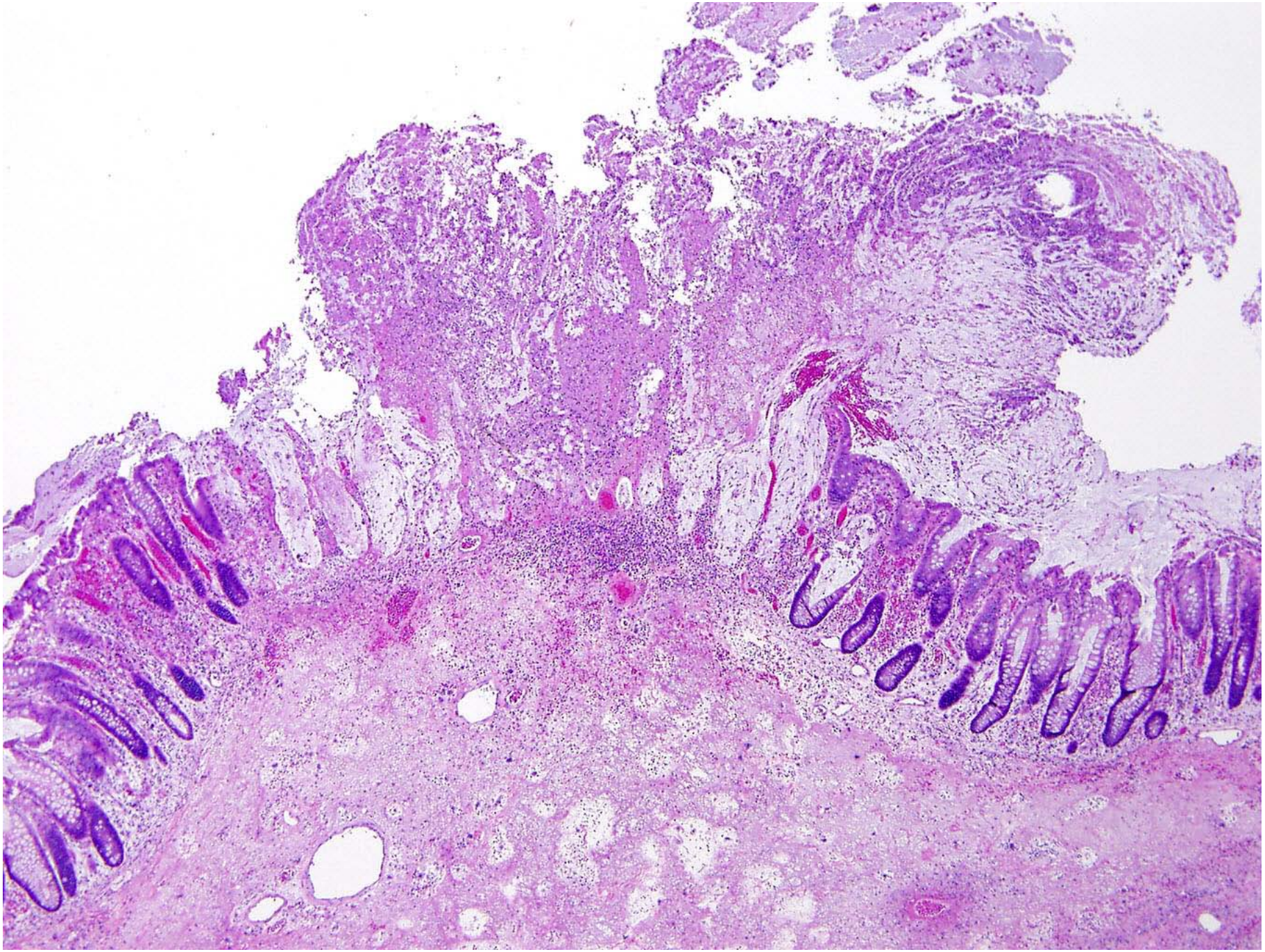

10/3/2015


10/21/2015

11/6/2015







Why are we discussing this common hospital acquired infection?

4/70 GATA2 patients seen here have had severe *C. difficile* colitis (6%)

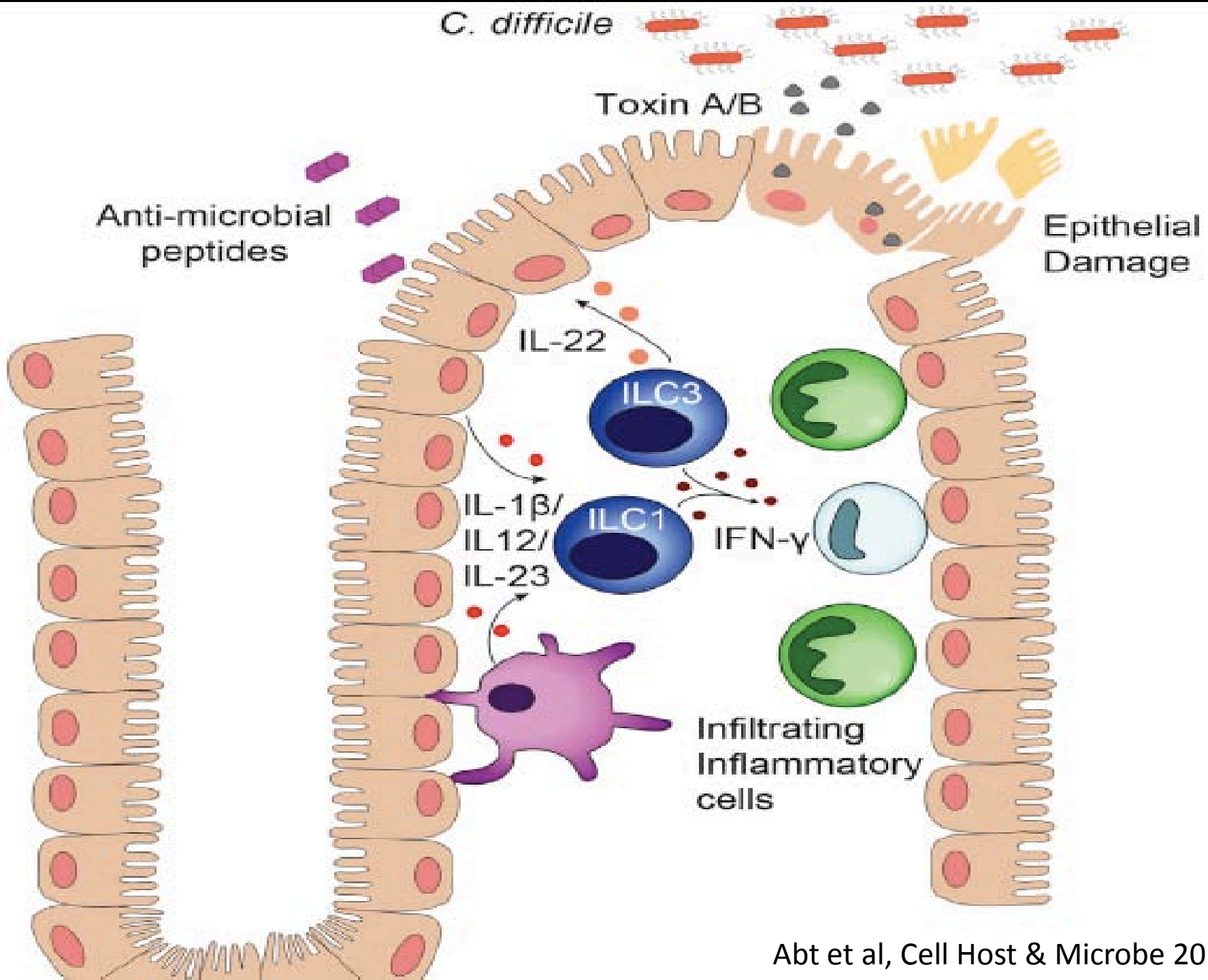
14 yo boy: *C. diff* after MAC therapy-colectomy

17 yo girl: *C. diff* after abx, ICU with chest tubes

59 yo woman: fatal *C. diff* colitis

28 yo woman: *C. diff* in MK therapy-colectomy

(in comparison at NIH, 0 in CGD, ~1 in STAT3)



Abt et al, Cell Host & Microbe 2015

C. difficile infection in GATA2

Can be very severe, even in childhood

Severe edema bowel wall

Recurrent

Mouse model underway

I'VE LEARNED SO MUCH FROM MY MISTAKES...

I'M THINKING OF MAKING A FEW MORE.

20 yo woman neutropenia, anemia, fungal infection

7 yo "CVID"

19 yo fever, neutropenia, invasive fungal sinusitis

E. coli sepsis, shock, ventilation

NIH transfer:

Fusarium proliferatum sinusitis

Neutrophils	0	cells/μl
Monocytes	1	cells/μl
NK cells	32	cells/μl
B cells	0	cells/μl

Clinical Course

Persistent fever, neutropenia

Clinically Consistent with GATA2 deficiency but no mutation found

Successful haploidentical HSCT from 17 yo sister

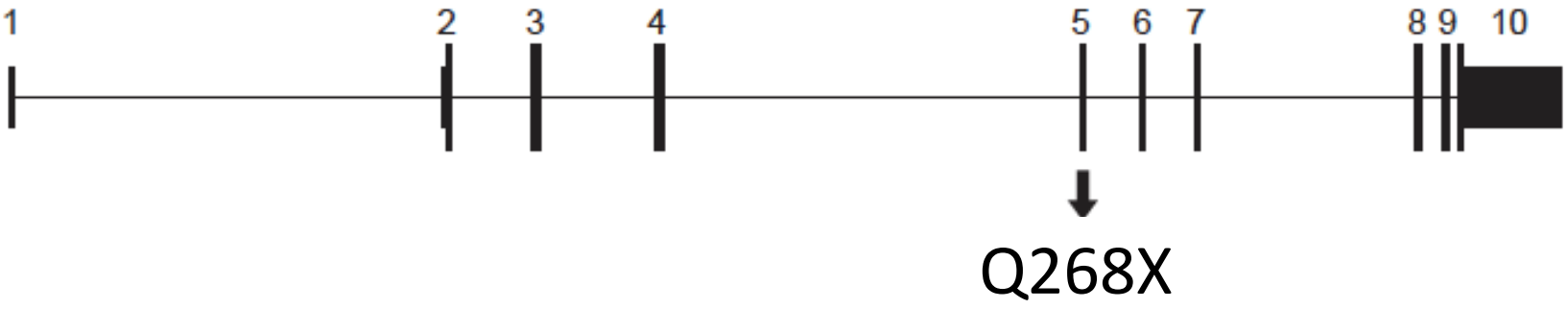
(busulfan, cylclophosphamide, 200cGy,

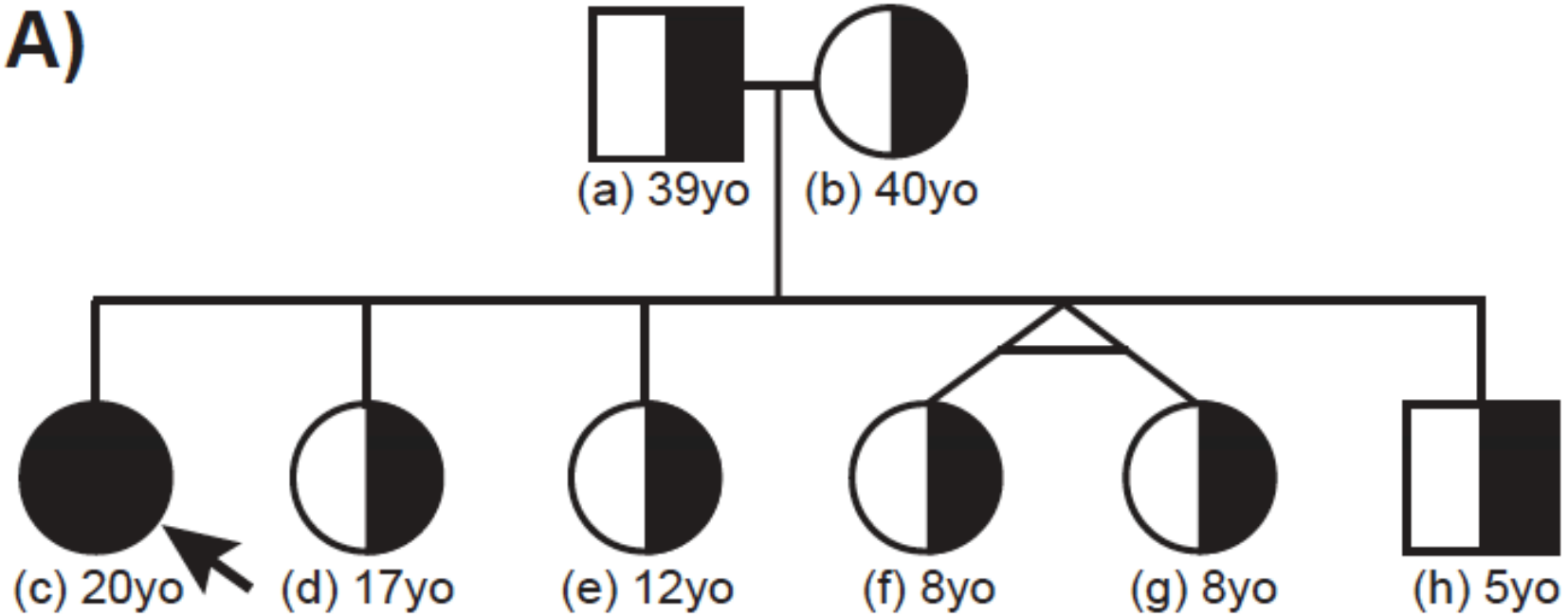
post-transplant cyclophosphamide)

Bacteremia, ventilation, but complete recovery

But where was her problem in *GATA2*?

Homozygous Null *CECR1* (ADA2 deficiency)





ORIGINAL ARTICLE

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

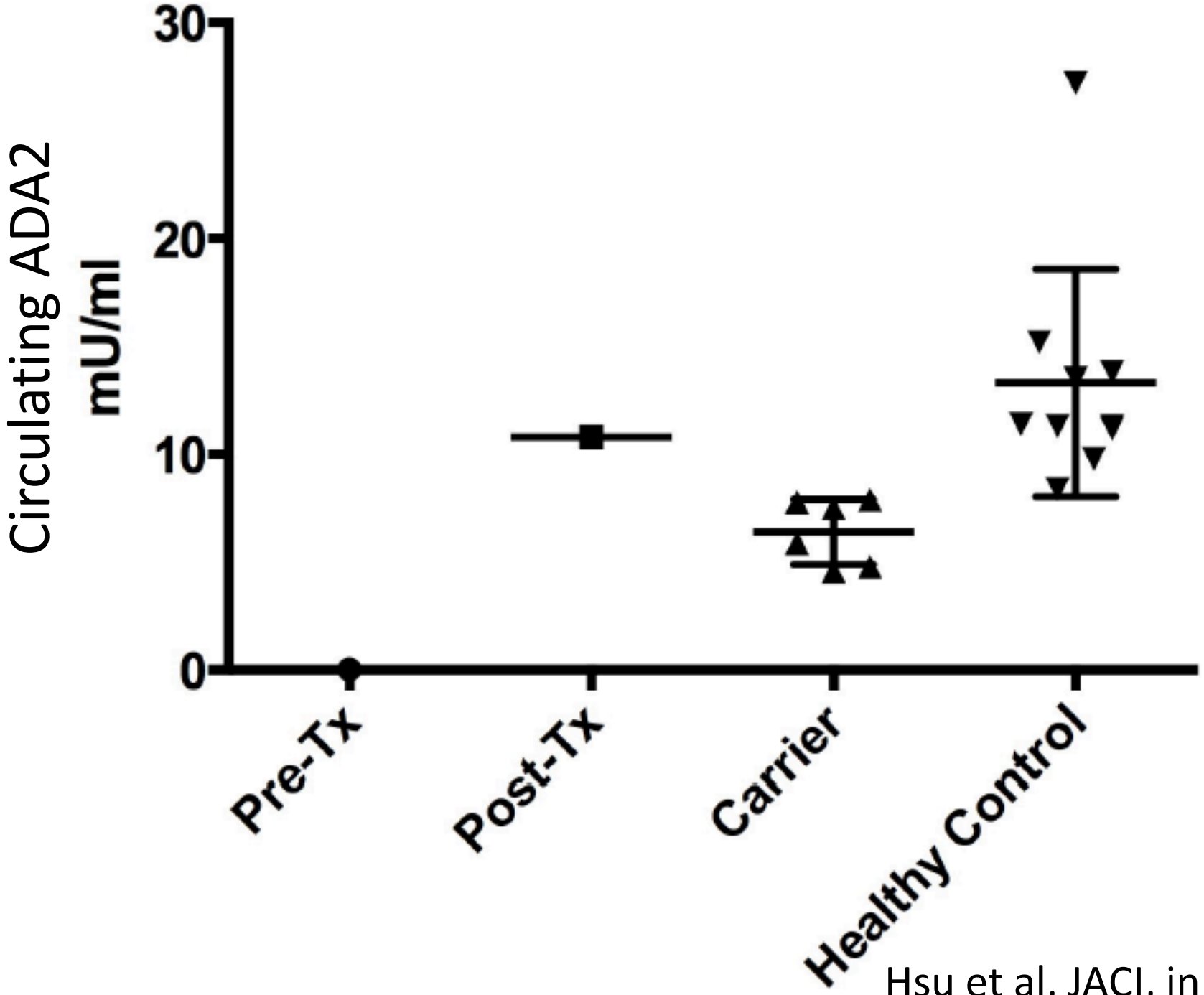
Q. Zhou, D. Yang, A.K. Ombrello, Andrey V. Zavialov, C. Toro, Anton V. Zavialov, D.L. Stone, J.J. Chae, S.D. Rosenzweig, K. Bishop, K.S. Barron, H.S. Kuehn, P. Hoffmann, A. Negro, W.L. Tsai, E.W. Cowen, W. Pei, J.D. Milner, C. Silvin, T. Heller, D.T. Chin, N.J. Patronas, J.S. Barber, C.-C.R. Lee, G.M. Wood, A. Ling, S.J. Kelly, D.E. Kleiner, J.C. Mullikin F. Candotti, M.M. Quezado, K.R J.F. Meschia, B.B. Worrall, S.E. Kasner E. Chalom, A.C. Gotte, M. Punaro, N.G. Singer, T.R. Gershon, S. Ozen S.M. Burgess, S.L. Moir, M. Gadir D.L. Kastner,

March 2014

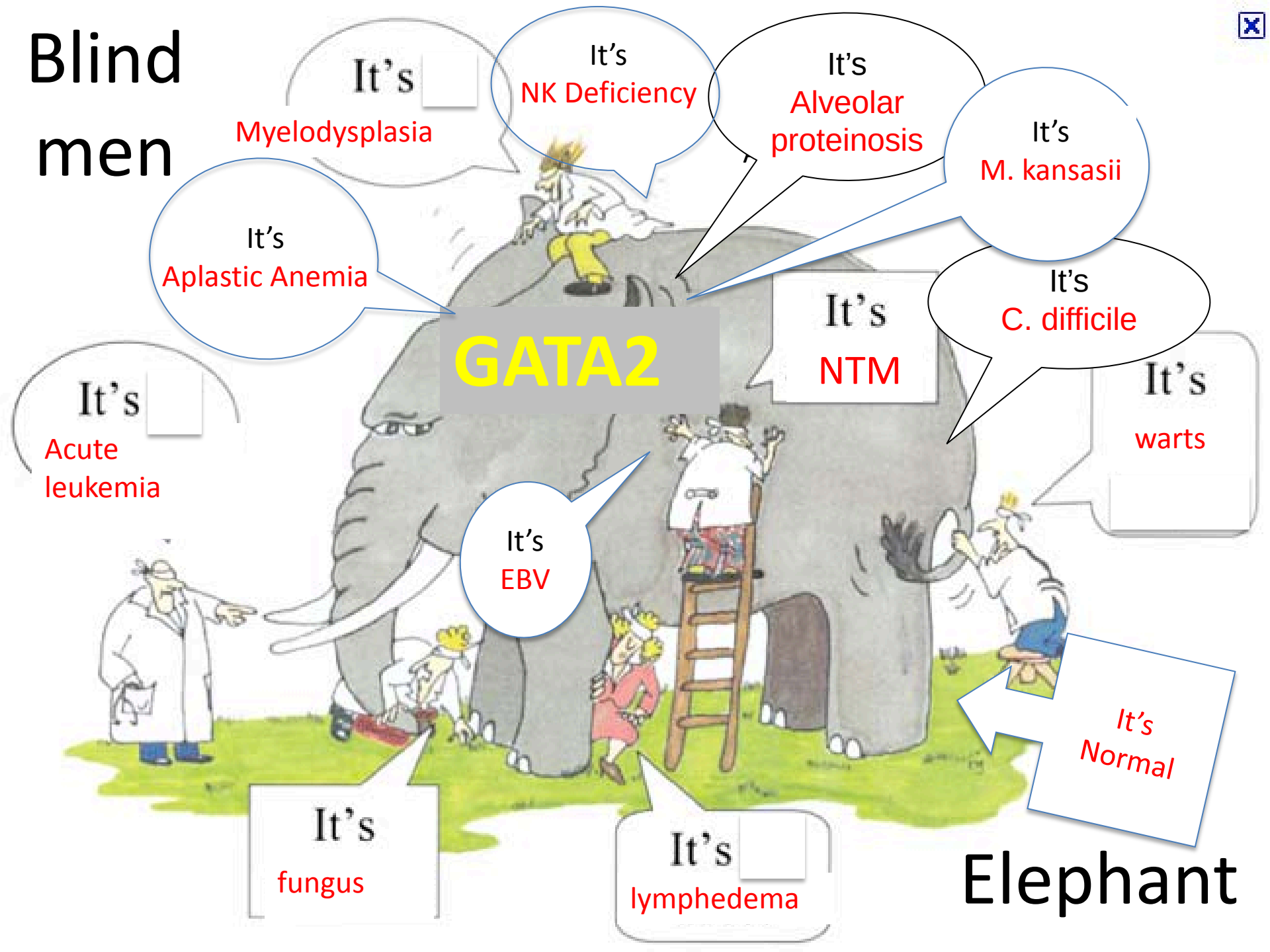
ORIGINAL ARTICLE

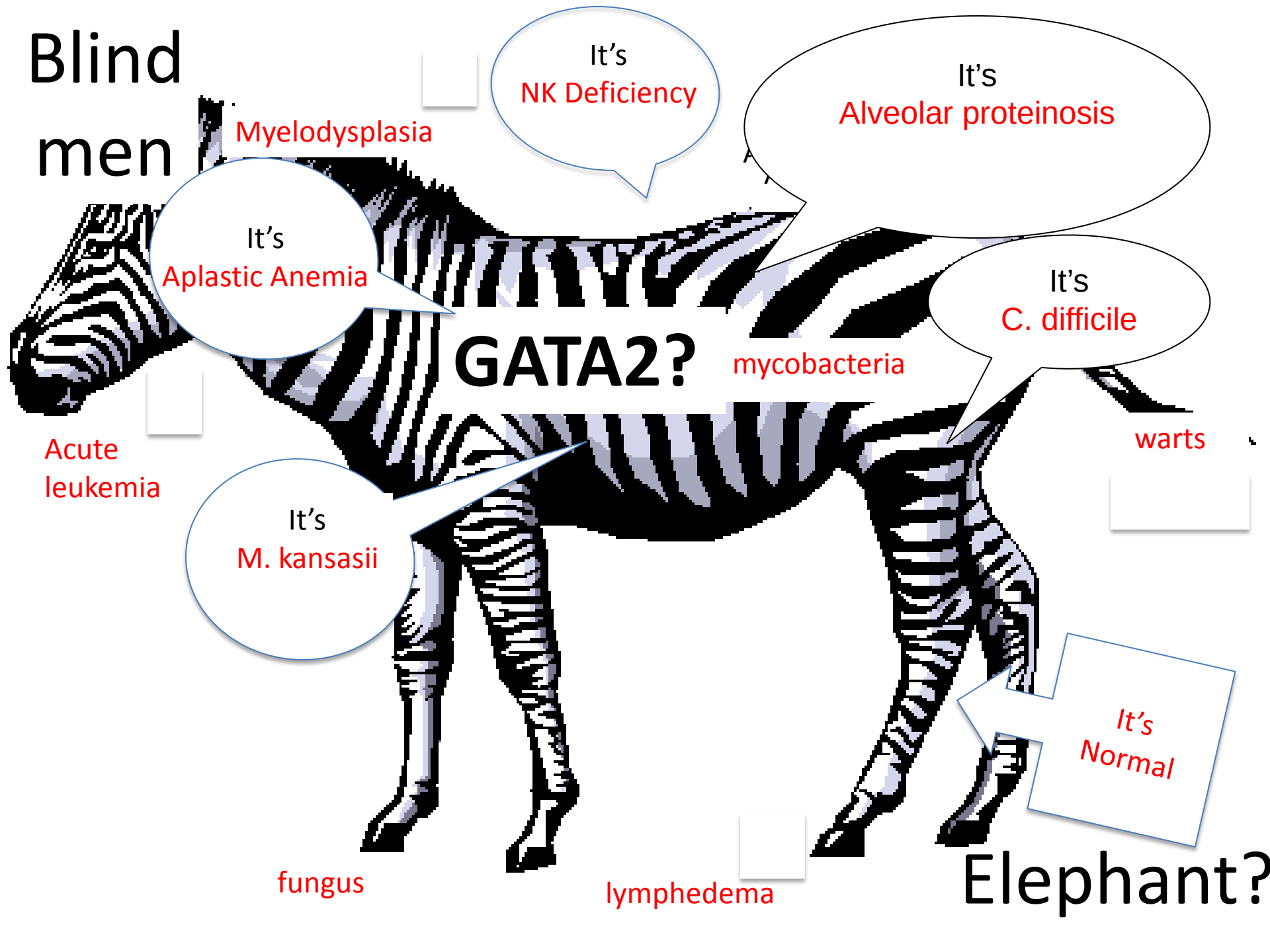
Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubinow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.



Hsu et al, JACI, in press


Blind men
It's Myelodysplasia
It's NK Deficiency
It's Alveolar proteinosis
It's M. kansasii
It's Aplastic Anemia
GATA2
It's NTM
It's C. difficile
It's Acute leukemia
It's warts
It's EBV
It's Normal
It's fungus
It's lymphedema
Elephant


Blind men
Myelodysplasia
It's NK Deficiency
It's Alveolar proteinosis
It's Aplastic Anemia
GATA2?
mycobacteria
It's C. difficile
Acute leukemia
warts
It's M. kansasii
It's Normal
fungus
lymphedema
Elephant?

GATA2 Haploinsufficiency

It is already complex and getting more complex

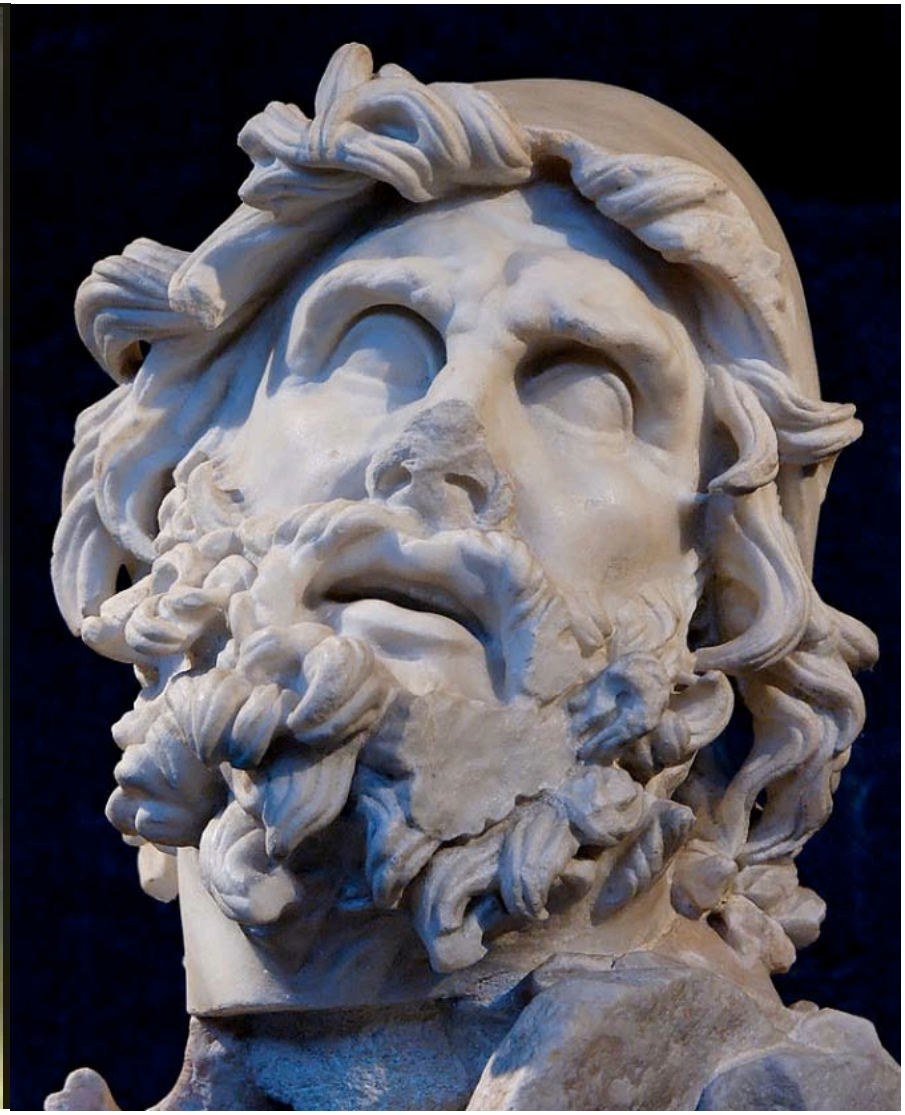
We are still learning about its phenotypes

It does seem to have exquisite susceptibilities

(*M. kansasii*, *C. difficile*, HPV, EBV)

It is not the only disease that can have similar features

Phenotype Changes with Time, Exposure, Perspective



But the origin of the story stays the same

Acknowledgements

Amy P. Hsu
Elizabeth Sampaio
Lauren Sanchez
Michael Spinner
Kathy Calvo
Diane Arthur
Mark Raffeld
Stefania Pittaluga
Li Ding
Lisa McReynolds
Smita Patel
Josh Milner
Liana Falcone
Ken Olivier
Blanche Alter
Neelam Giri
Inga Hoffman
Tom Fleisher
Gulbu Uzel
Christa Zerbe
Alexandra Freeman
Sergio Rosenzweig
Janine Daub
Lisa Barnhart
Reggie Claypool
Cathleen Frein
Vickey Anderson
Maria L. Turner
Emery Bresnick
Kirby Johnson
Danielle Townsley
Neal Young
Emily Mace
Jordan Orange
Jennifer Cuellar-Rodriguez
Dennis Hickstein