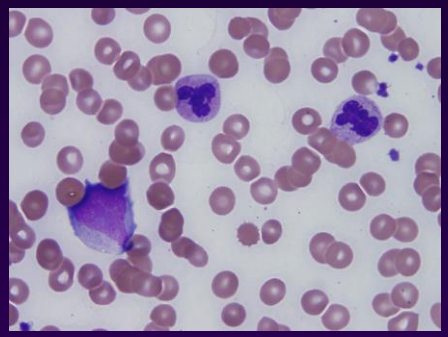
GATA2 transplant- "the past is prologue to the future"



Dennis D. Hickstein, M.D.

12 July 2019

NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTES OF HEALTH

Disclaimer

Happiness = Reality - Expectation

Car Talk circa 1992

GATA2 deficiency AKA "MonoMAC"

- Young adults present with atypical mycobacterial infections (MAC), HPV, cytopenias, etc.

- PBL: Monocytes — low to 0
  - B-lymphocytes (CD19+) — low to 0
  - NK cells (CD56+) — low to 0
  - T-lymphocytes (CD3+) — normal

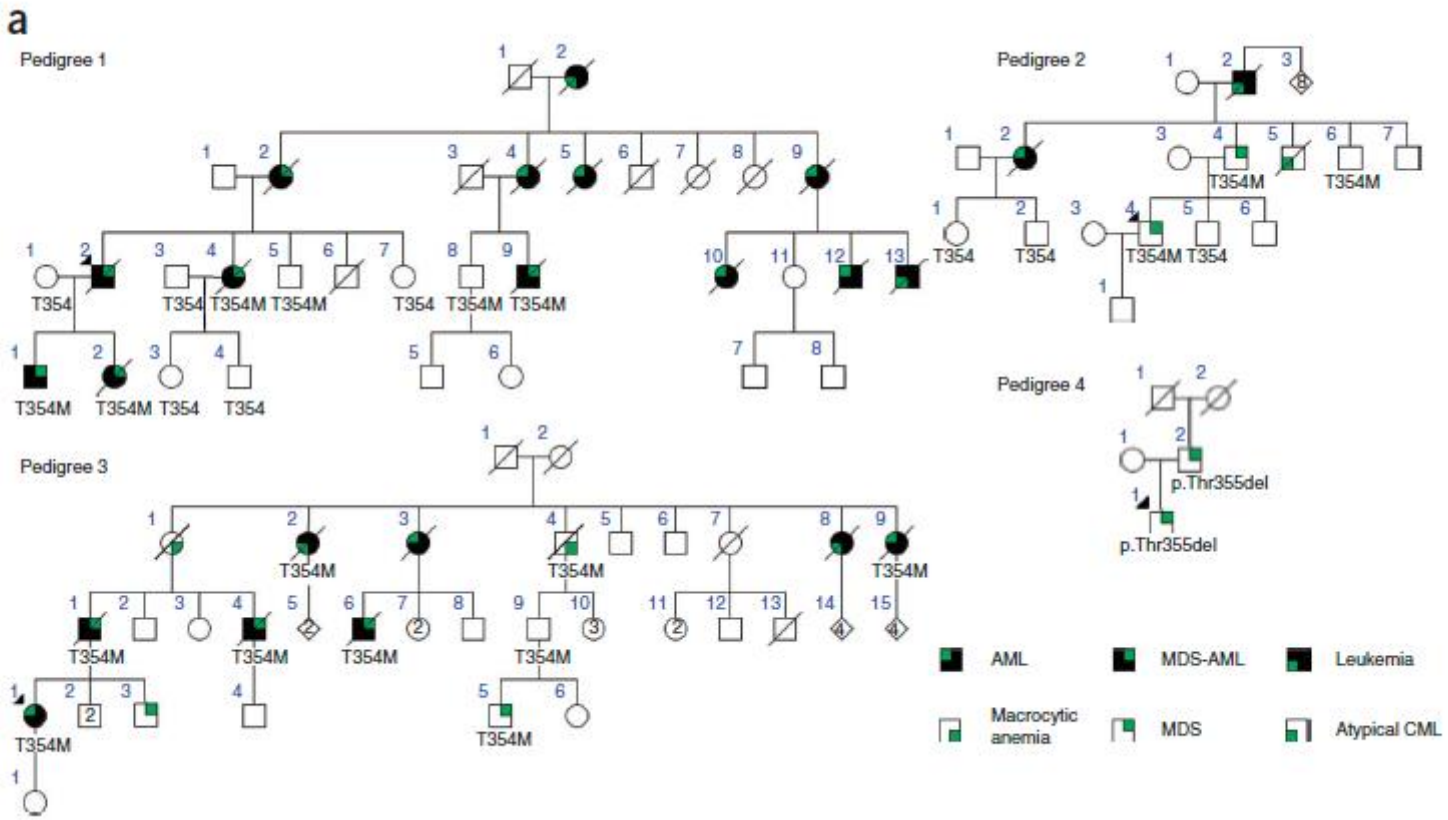
- 50% Sporadic or new mutation and 50% are familial
- Develop MDS, AML, CMML
- Mutations on one allele of GATA2- haploinsufficiency

Questions re GATA2 deficiency

- What's the mutation?
- What's the natural history of disease?
- What's the role of stem cell transplant ?

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]



Nature Genetics 2011

blood

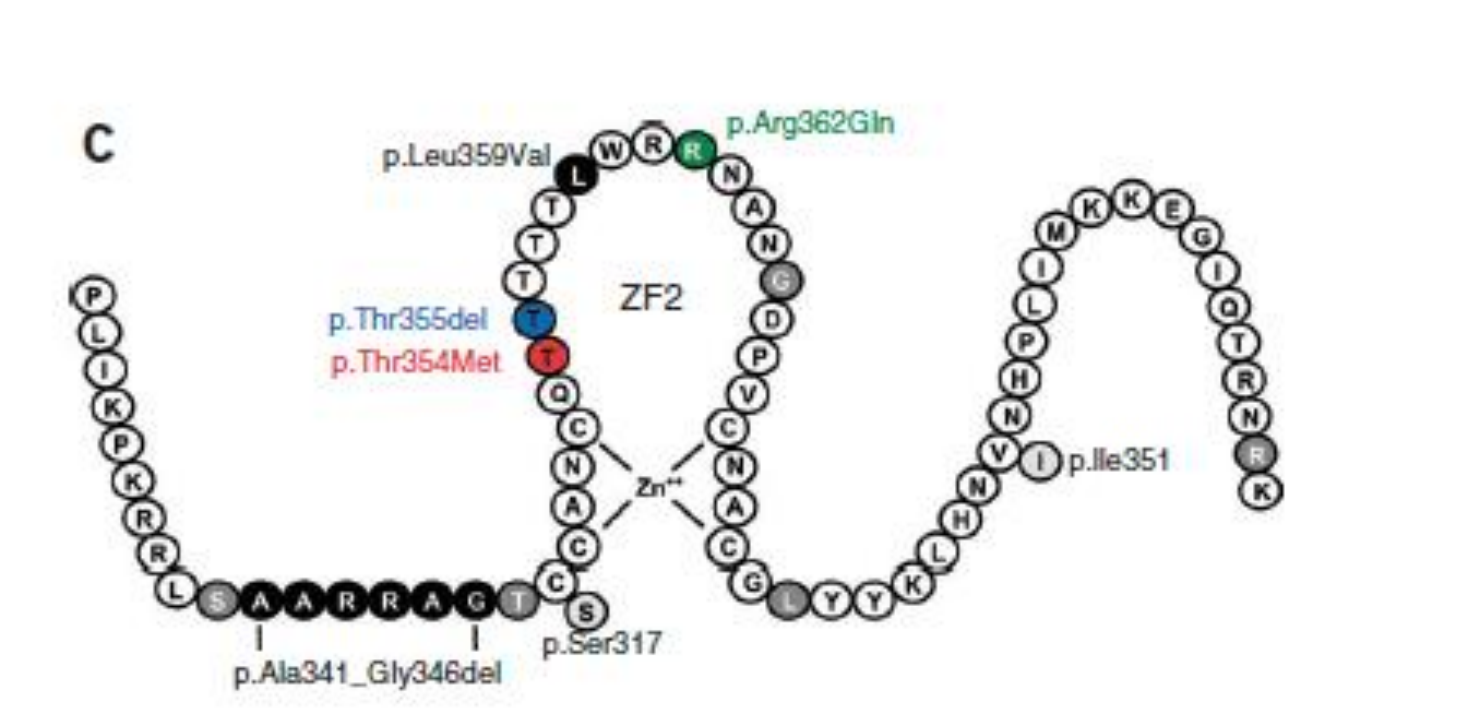
Prepublished online June 13, 2011;
doi:10.1182/blood-2011-05-356352

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

12 distinct heterozygous mutations in GATA2
-Missense mutations in 2nd ZNF
- 4 insertion/deletion mutations leading to premature stops

Mutations cluster in 2nd ZNF of GATA2

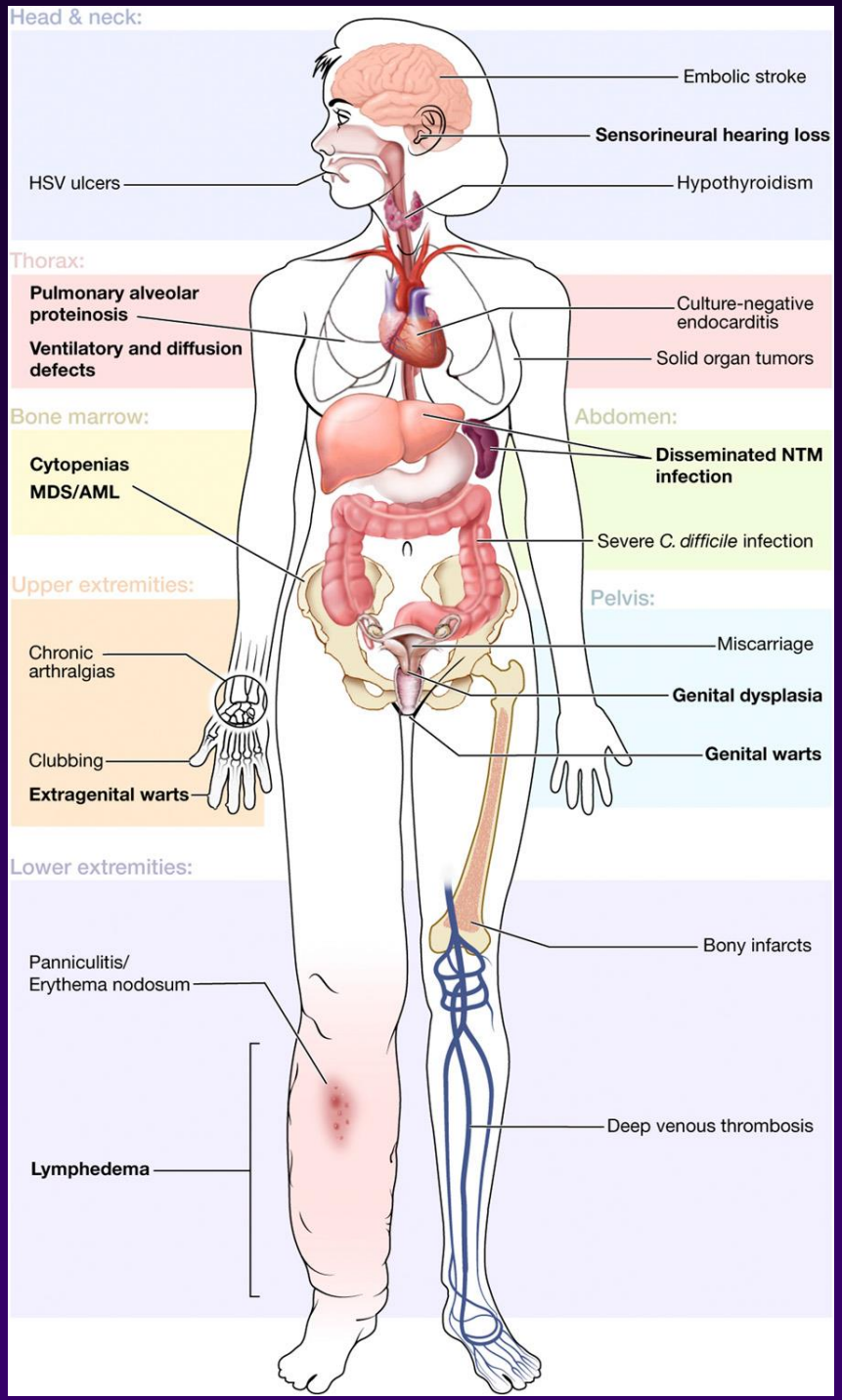


R362X
R=CGA
X=TGA

R398W
R =CGG
W=TGG

- > 100 different mutations identified
- missense, nonsense, indels, intronic, and enhancer mutations
- In general, mutation type does not correlate with phenotype

Spinner M A et al. Blood 2014;123:809-821



blood

Names for GATA2 deficiency

- MonoMAC *(Monocytopenia, Mycobacterium avium complex*
- Dendritic cell, Monocyte, B and NK lymphoid def (DCML)
- Emberger syndrome- lymphedema and monosomy 7
- Familial myelodysplastic syndrome/AML

- ** Now it is known as GATA2 deficiency

"Biologists would rather share a toothbrush than a gene name"

- David Botstein

Haploinsufficiency means that when you lose one of the two copies of a gene, you get disease because.. . .

Transcription factor haploinsufficiency: when half a loaf is not enough

Commentary

See related articles, pages 469–473 and 475–480.

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[2]Division of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts, USA

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Phone: (617) 432-7871; Fax: (617) 432-7832; E-mail: seidman@rascal.med.harvard.edu.

J. Clin. Invest. **109**:451–455 (2002). DOI:10.1172/JCI200215043.

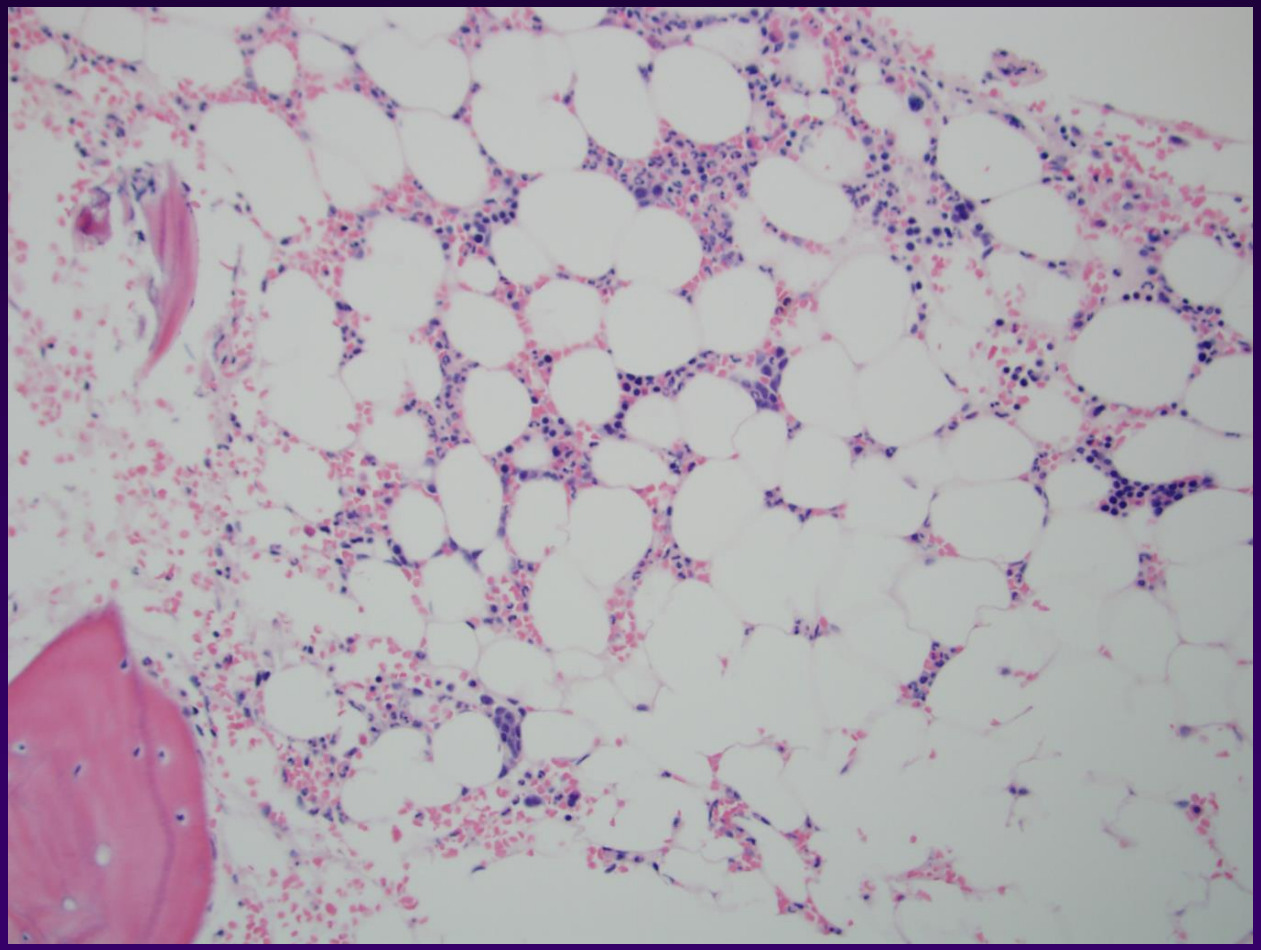
Questions re GATA2 deficiency

- What's the mutation?
- What's the natural history of disease?
- What's the role of stem cell transplant ?

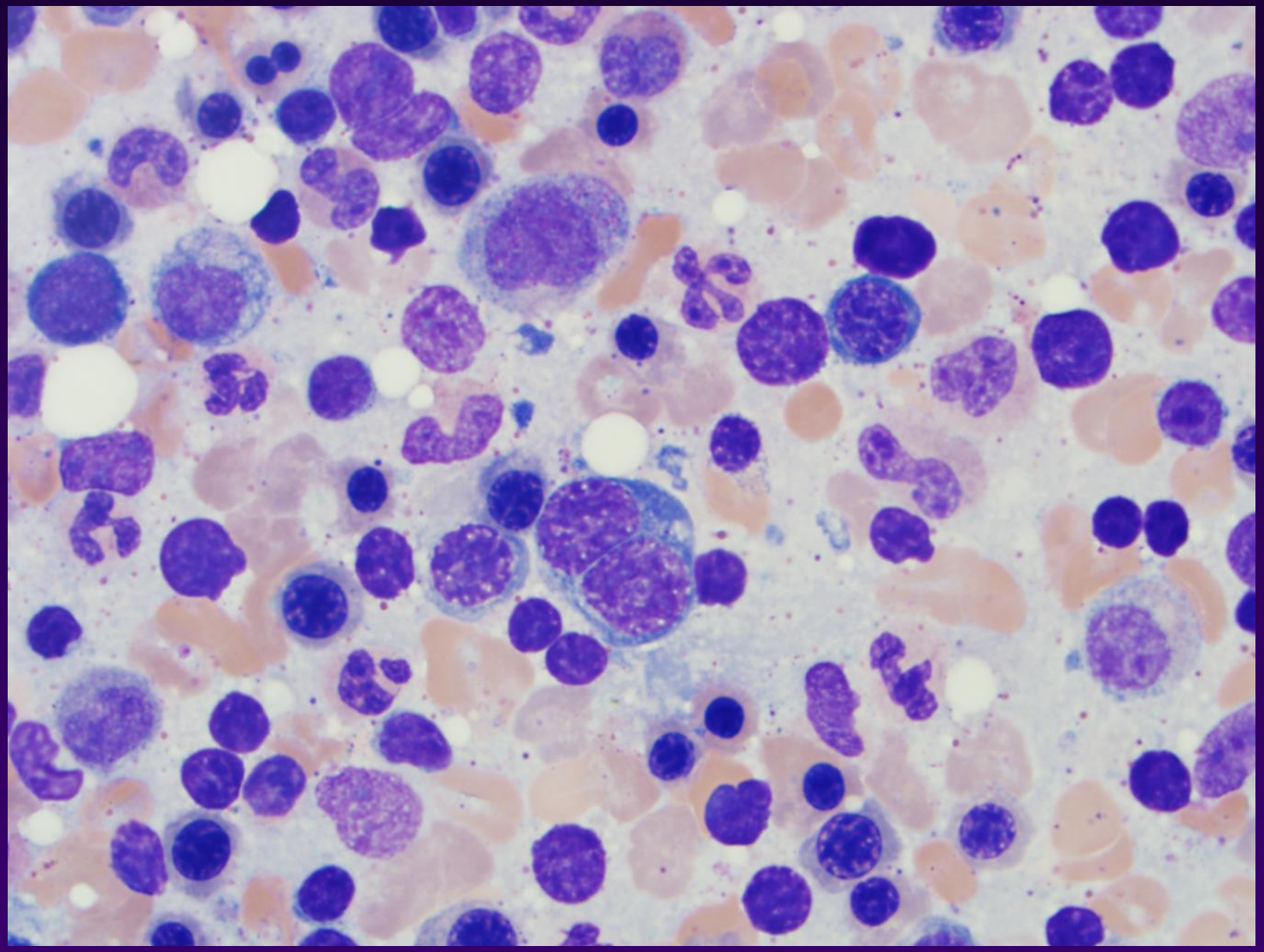
Natural history of *GATA2* deficiency

- Symptoms generally first appear in childhood, and worsen through early adulthood
- Disease manifestations and progression highly variable, even within a family with the same mutation
- Progress from normal marrow to hypoplastic MDS to AML

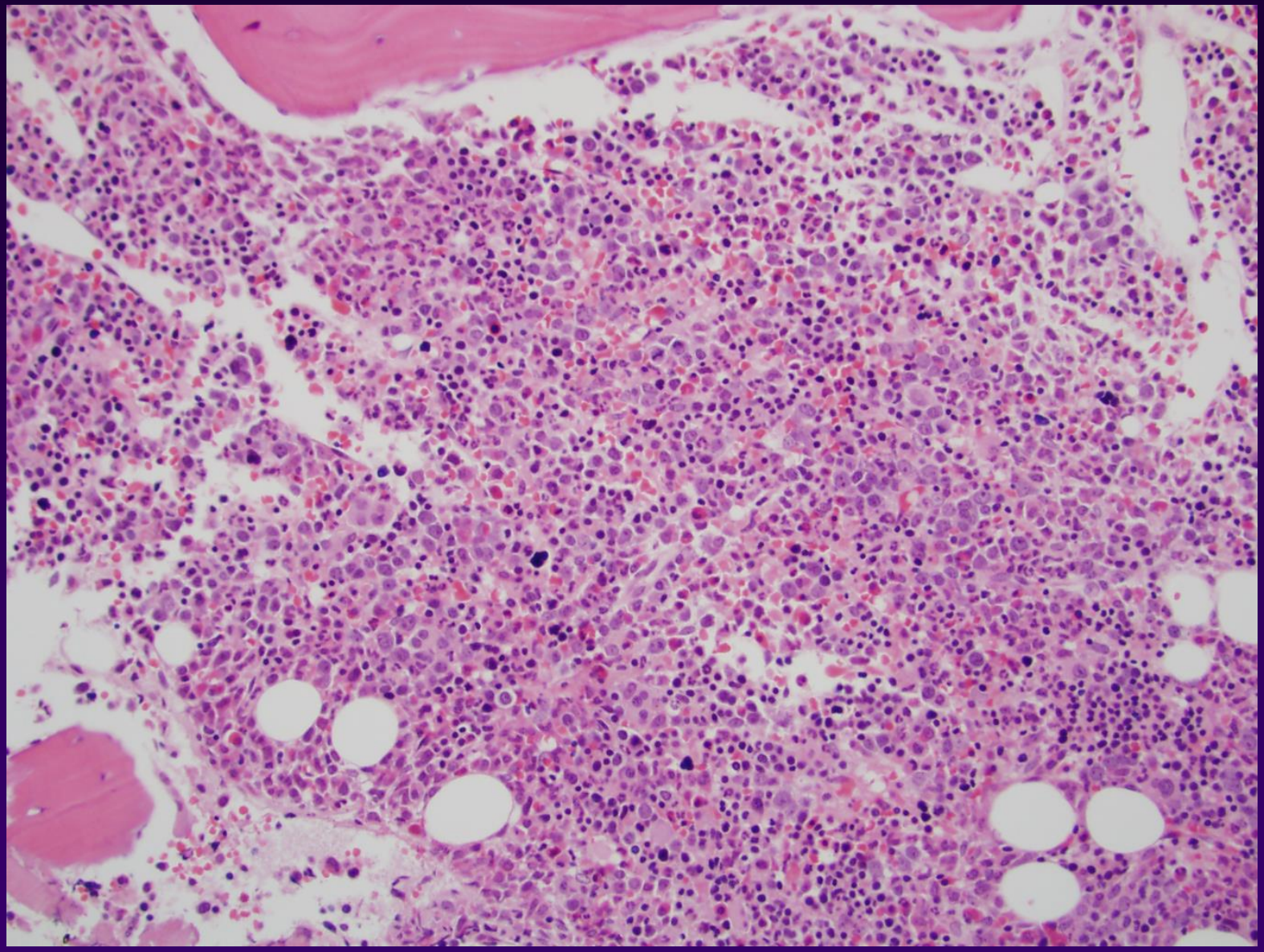
Case #1: Bone marrow 2009 hypocellular



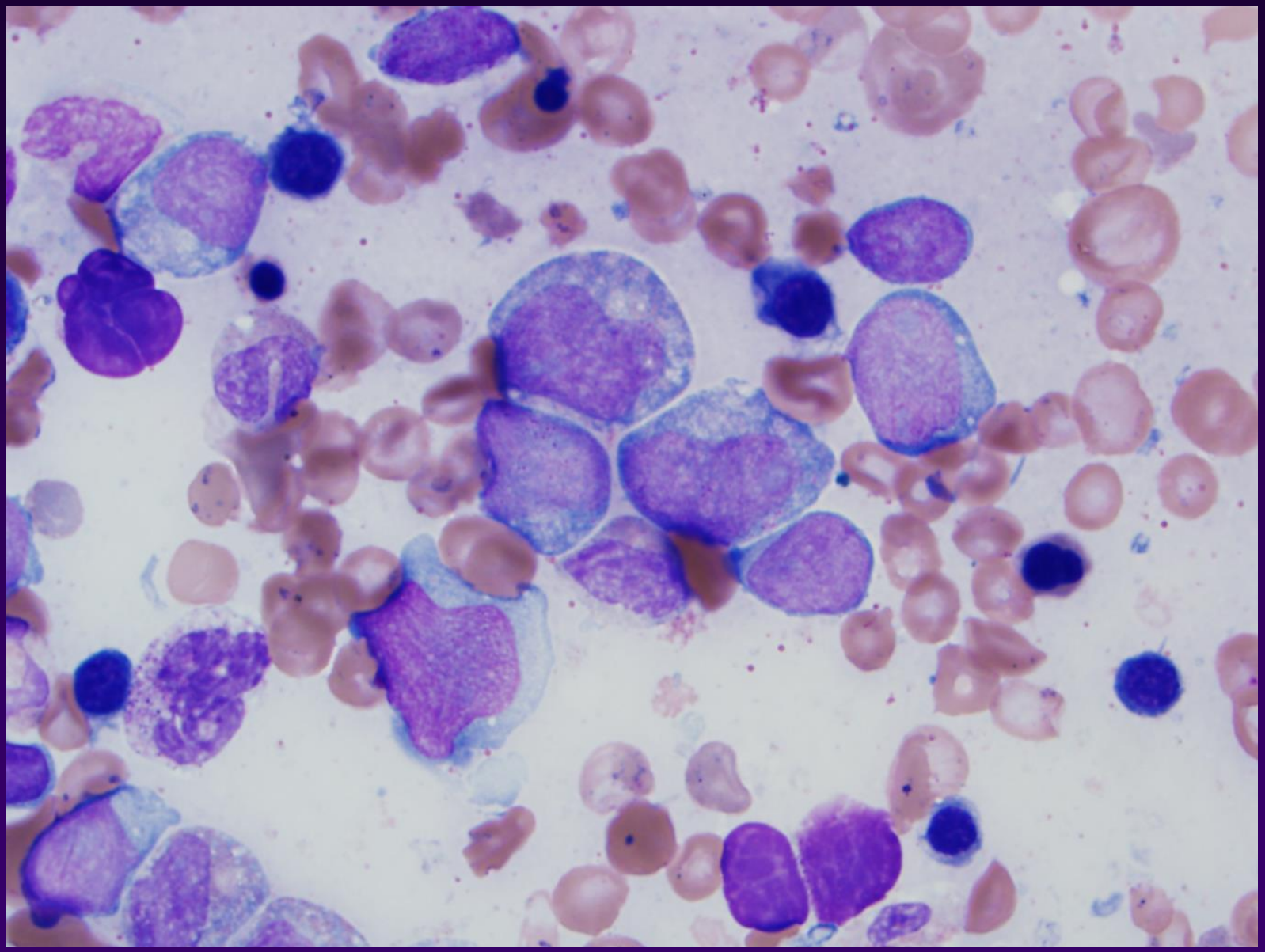
Case #1: Bone marrow in 2009 hypocellular with no increase in blasts



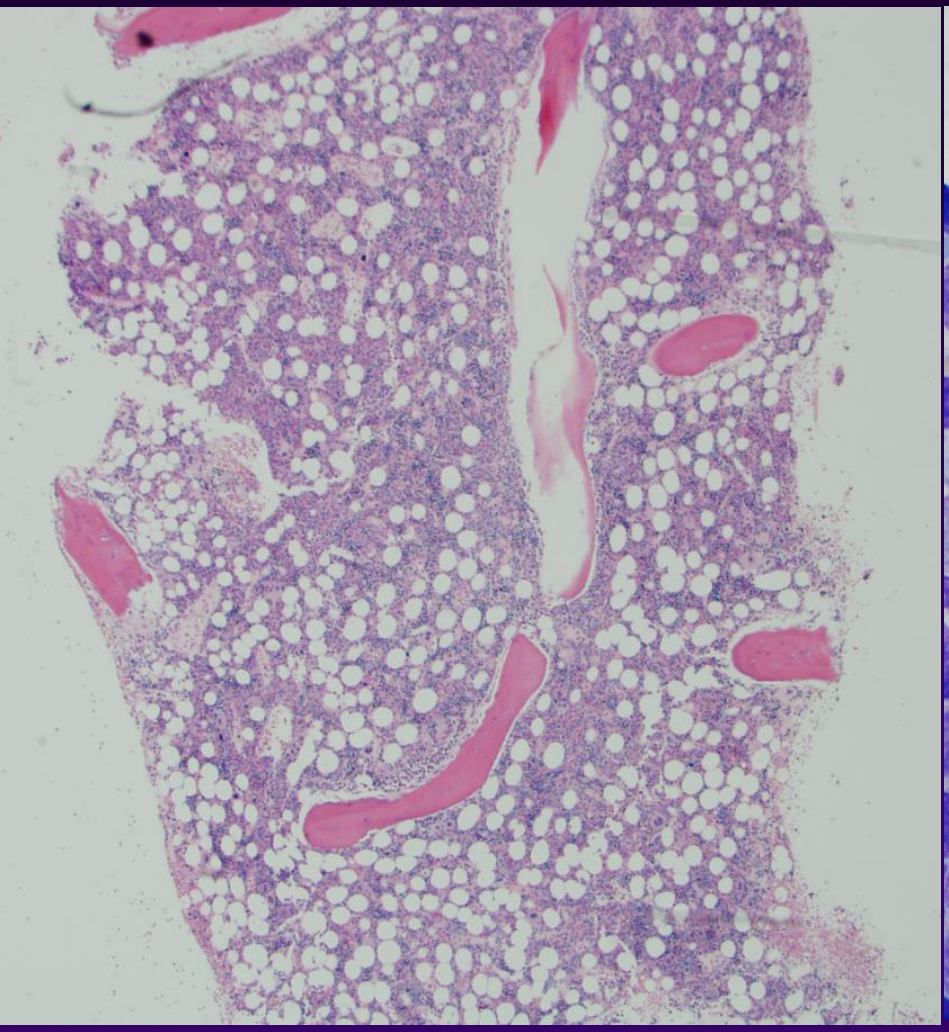
Case 1: Bone marrow 2 years later- hypercellular



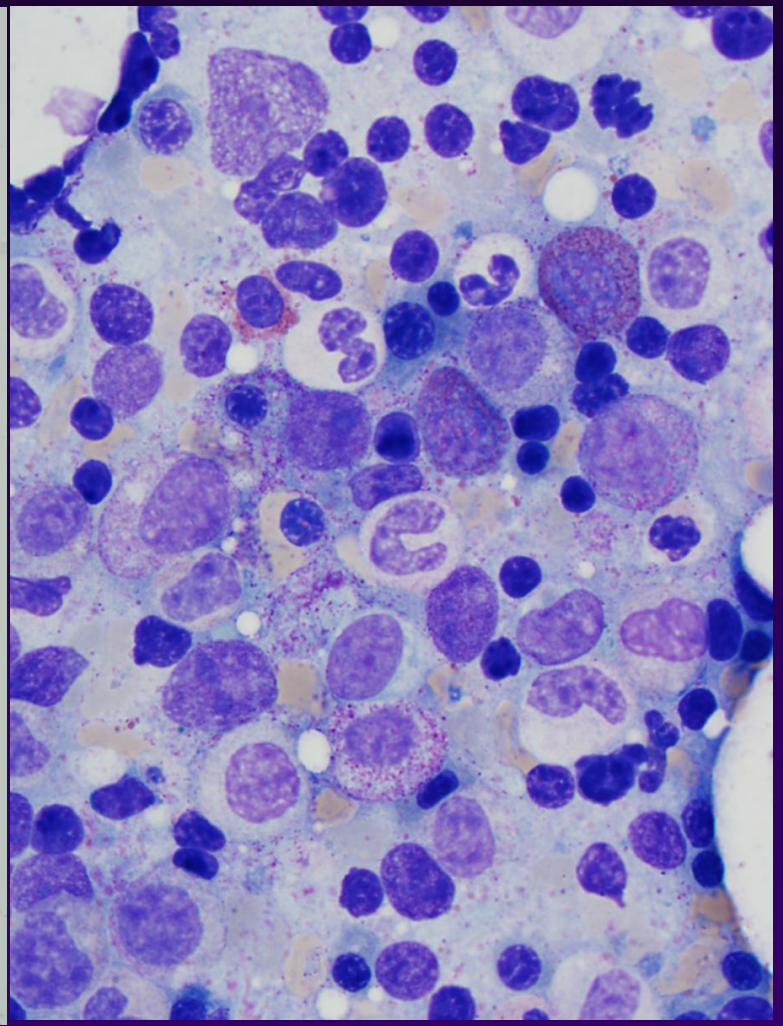
Case 1: Bone marrow 2 years later- blasts



24 yo long history of MDS and trisomy 8 March 25, 2014

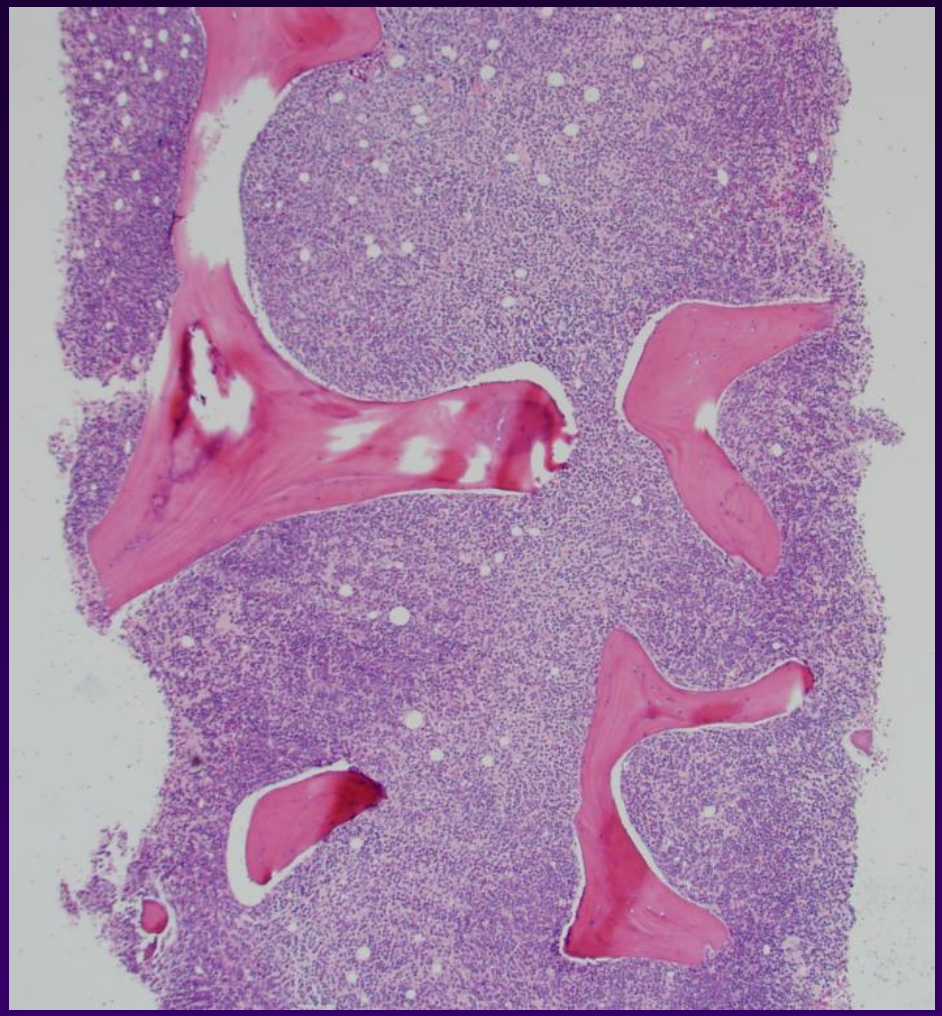


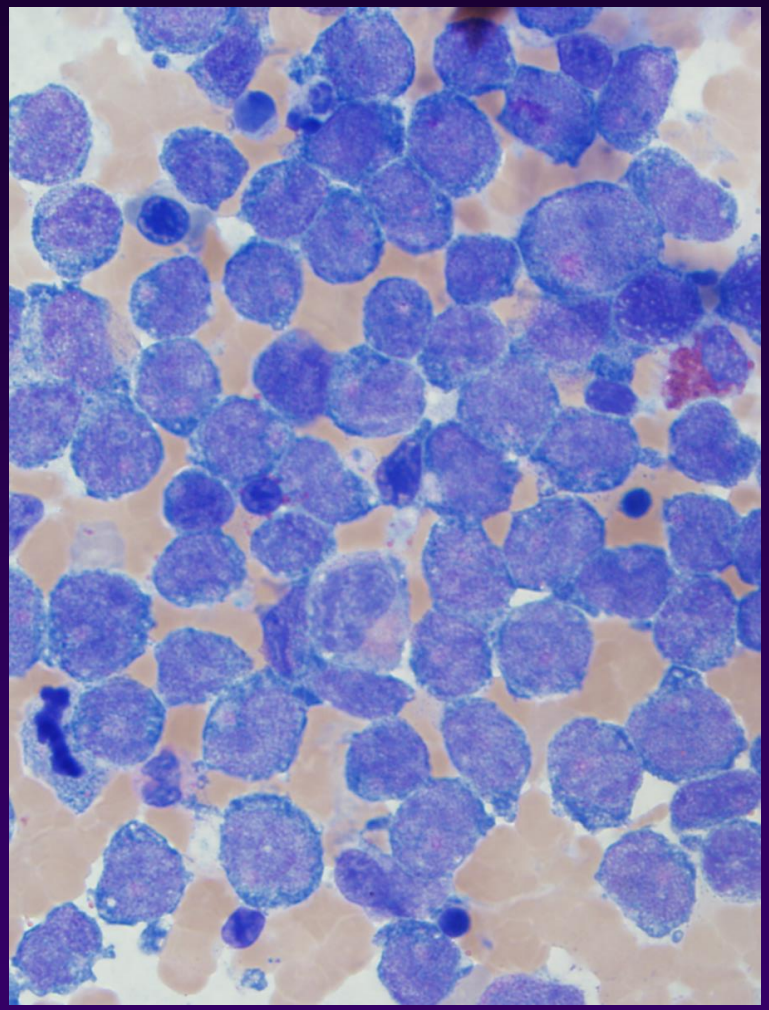
Biopsy Normocellular



Trilineage hematopoiesis, no increase in blasts

August 5, 2014





Hypercellular biopsy

86% blasts: AML (monoblastic)

Acquired *ASXL1* mutations are common in patients with inherited *GATA2* mutations and correlate with myeloid transformation

Robert R. West,[1] Amy P. Hsu,[2] Steven M. Holland,[2] Jennifer Cuellar-Rodriguez,[2] and Dennis D. Hickstein[1]

[1]Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; and [2]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

ABSTRACT

Inherited or sporadic heterozygous mutations in the transcription factor *GATA2* lead to a clinical syndrome characterized by non-tuberculous mycobacterial and other opportunistic infections, a severe deficiency in monocytes, B cells and natural killer cells, and progression from a hypocellular myelodysplastic syndrome to myeloid leukemias. To identify acquired somatic mutations associated with myeloid transformation in patients with *GATA2* mutations, we sequenced the region of the *ASXL1* gene previously associated with transformation from myelodysplasia to myeloid leukemia. Somatic, heterozygous *ASXL1* mutations were identified in 14/48 (29%) of patients with GATA2 deficiency, including four out of five patients who developed a proliferative chronic myelomonocytic leukemia. Although patients with *GATA2* mutations had a similarly high incidence of myeloid transformation when compared to previously described patients with *ASXL1* mutations, GATA2 deficiency patients with acquired *ASXL1* mutation were considerably younger, almost exclusively female, and had a high incidence of transformation to a proliferative chronic myelomonocytic leukemia. These patients may benefit from allogeneic hematopoietic stem cell transplantation before the development of acute myeloid leukemia or chronic myelomonocytic leukemia. (*ClinicalTrials.gov identifier NCT00018044, NCT00404560, NCT00001467, NCT00923364.*)

Haematologica February 2014

Questions re GATA2 deficiency

- What's the mutation?
- What's the natural history of disease?
- What's the role of stem cell transplant ?

Should GATA2 deficiency patients be transplanted?

- Patients are at high risk of death due to underlying infections, pulmonary alveolar proteinosis, and leukemia
- It is a stem cell disease, and normal donor hematopoietic stem cells should reverse the phenotype
- Allogeneic hematopoietic stem transplant can cure both immunodeficiency diseases and leukemia

When to transplant for *GATA2* ?

1) recurrent, severe opportunistic infections from cytopenias drives transplant about 50% of time

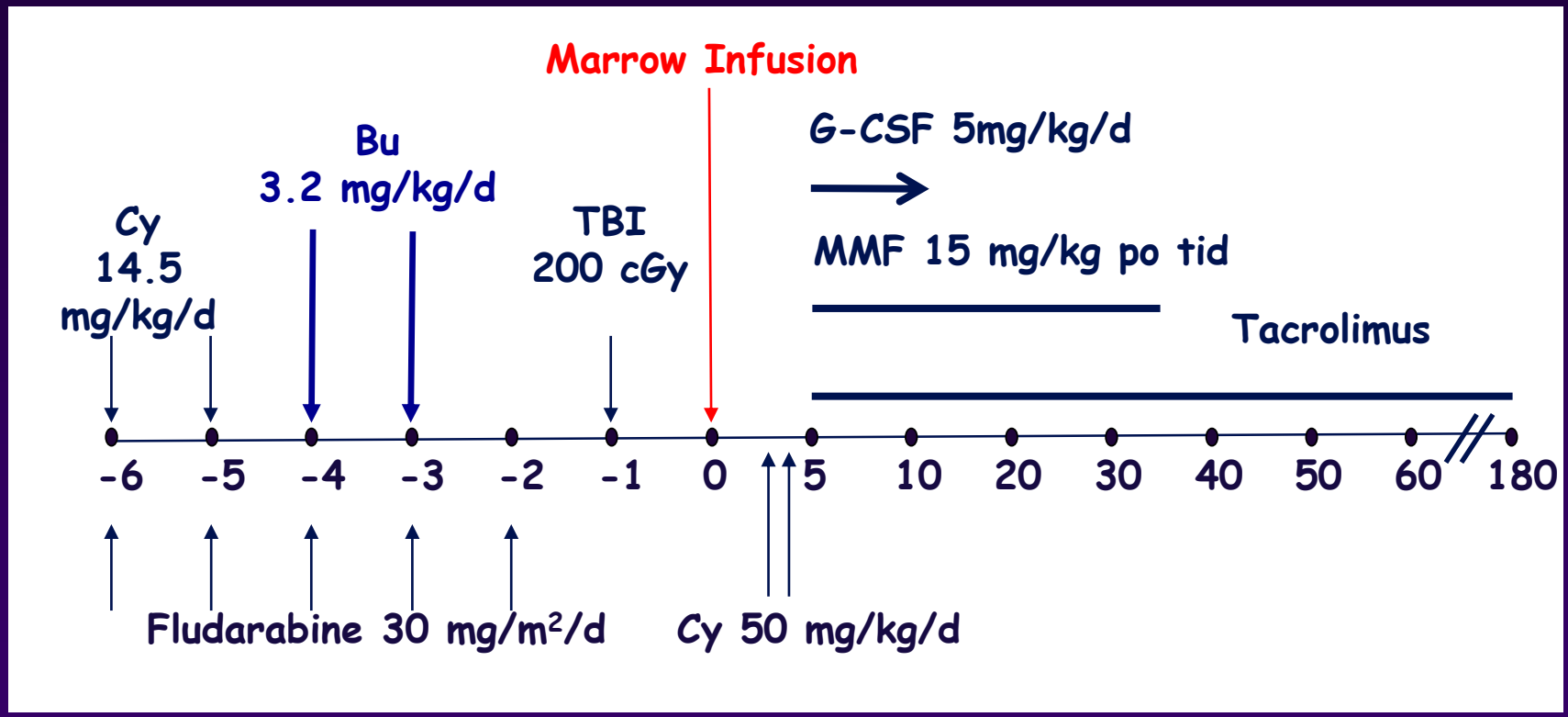
2) pulmonary disease requiring lavage

3) marrow changing to MDS/AML, e.g. increase blasts, cellularity increasing, or cytogenetics drives transplant about 50%

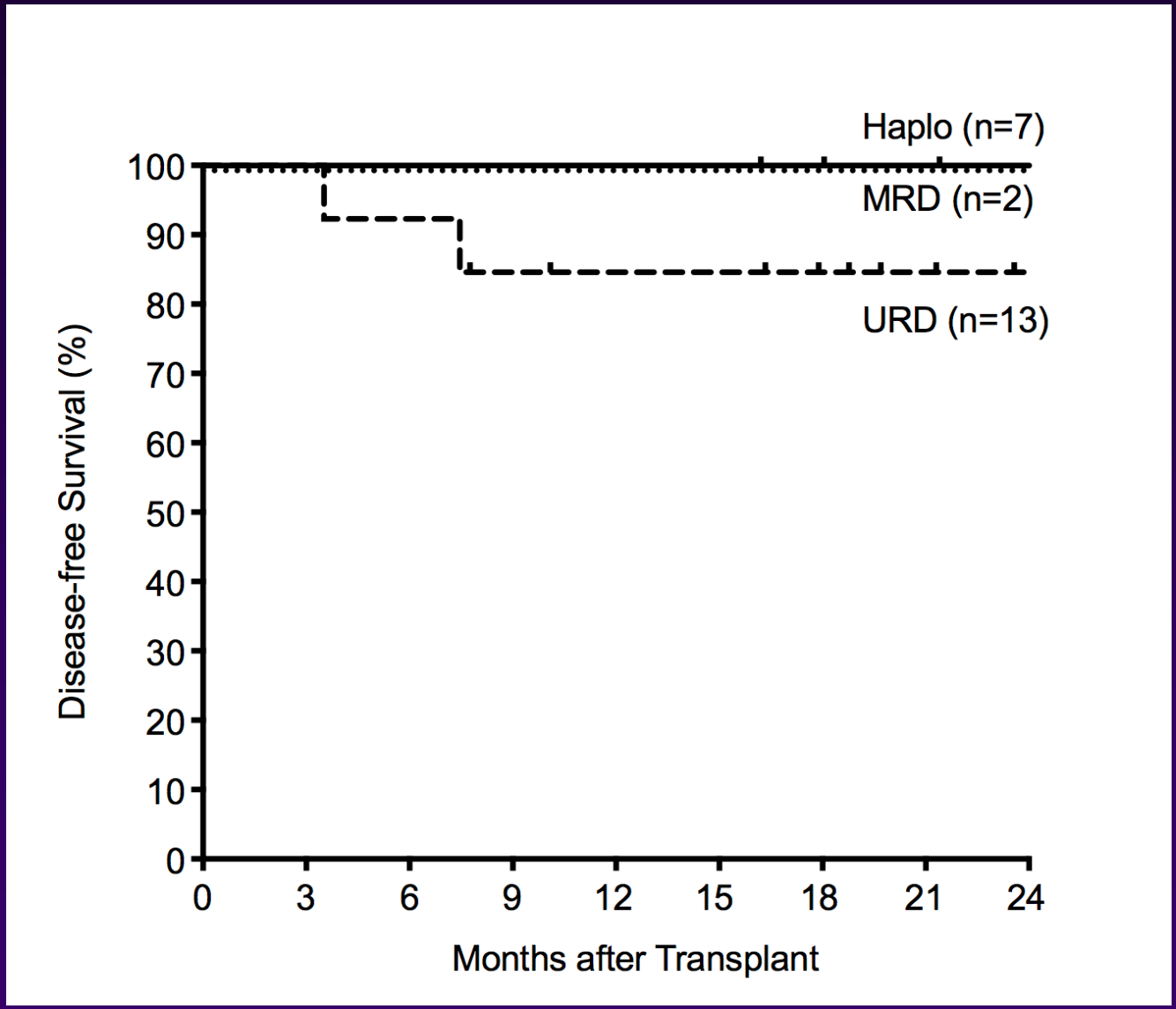
New protocol using a myeloablative regimen for transplanting *GATA2* deficient patients 2013

- Busulfan + Fludarabine x 4 days for matched related and unrelated donors (myeloablative regimen)- AUC 3600-4800
- Haploidentical related donors ala JHMI added 2 days of busulfan conditioning
- Now treated 52 patients!

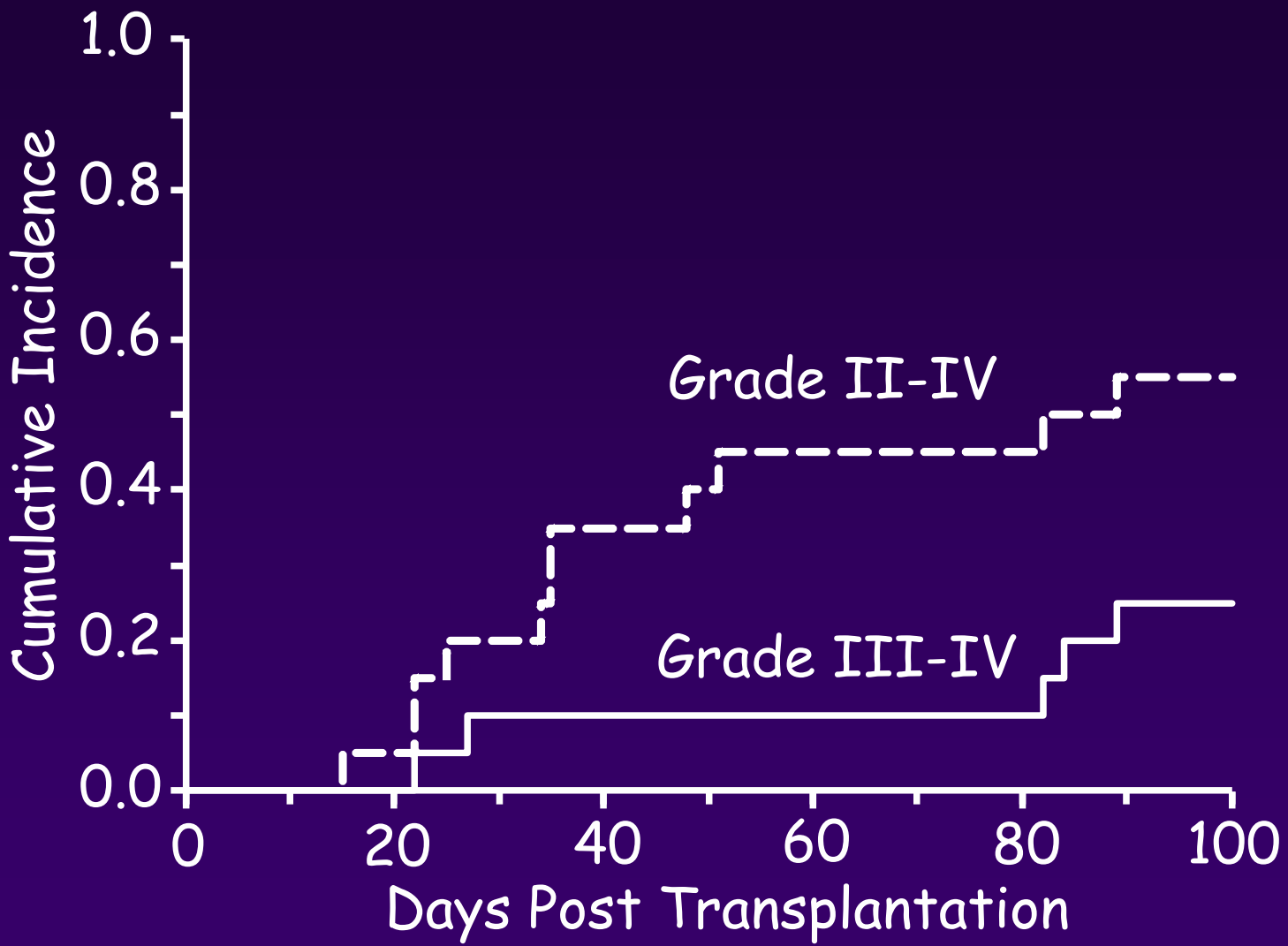
Haploidentical transplant for GATA2 ala JHMI: added busulfan 3.2 mg/kg on days +3 and +4



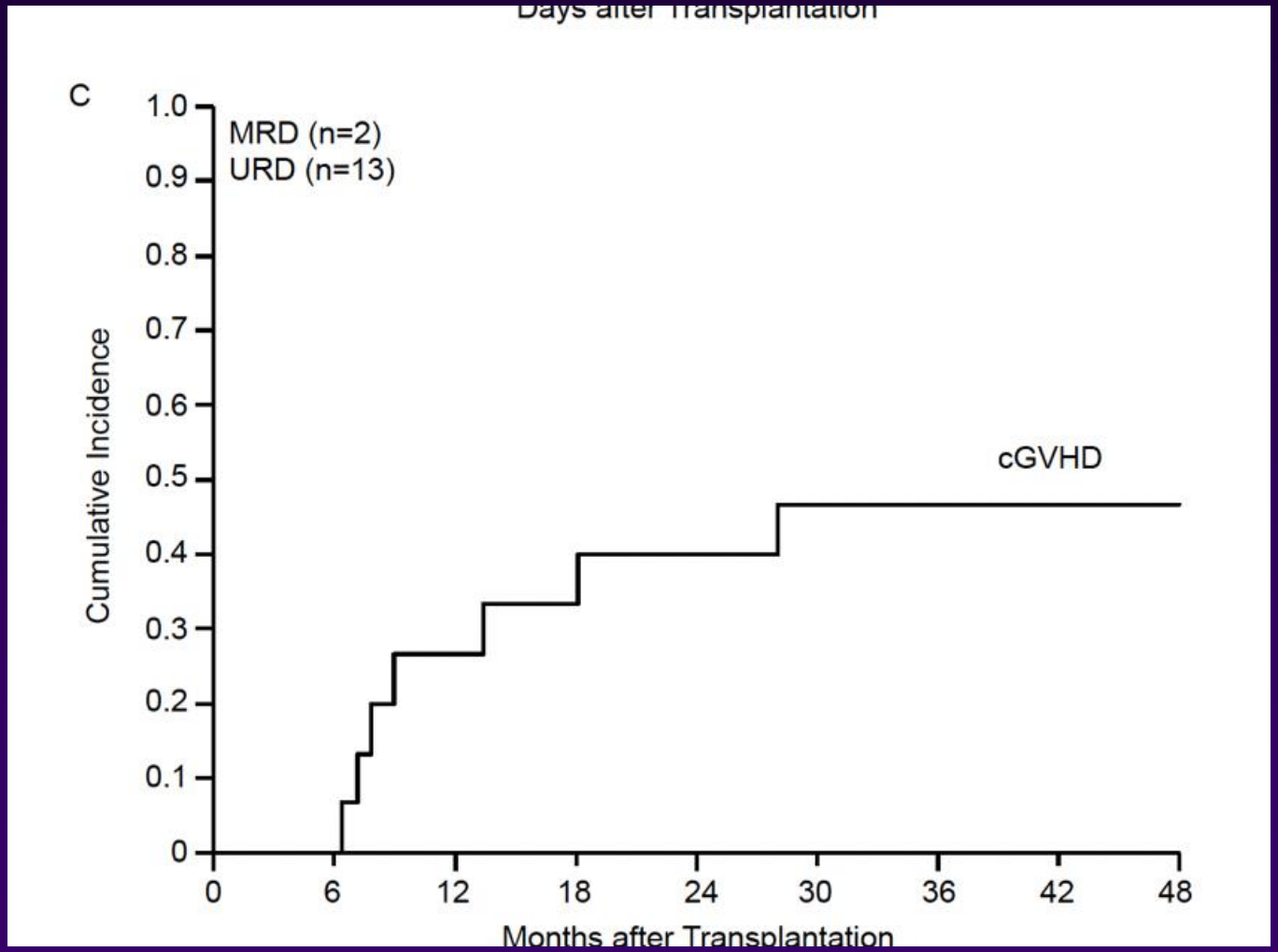
Disease-free survival of first 22 pts (Tacro/MTX)



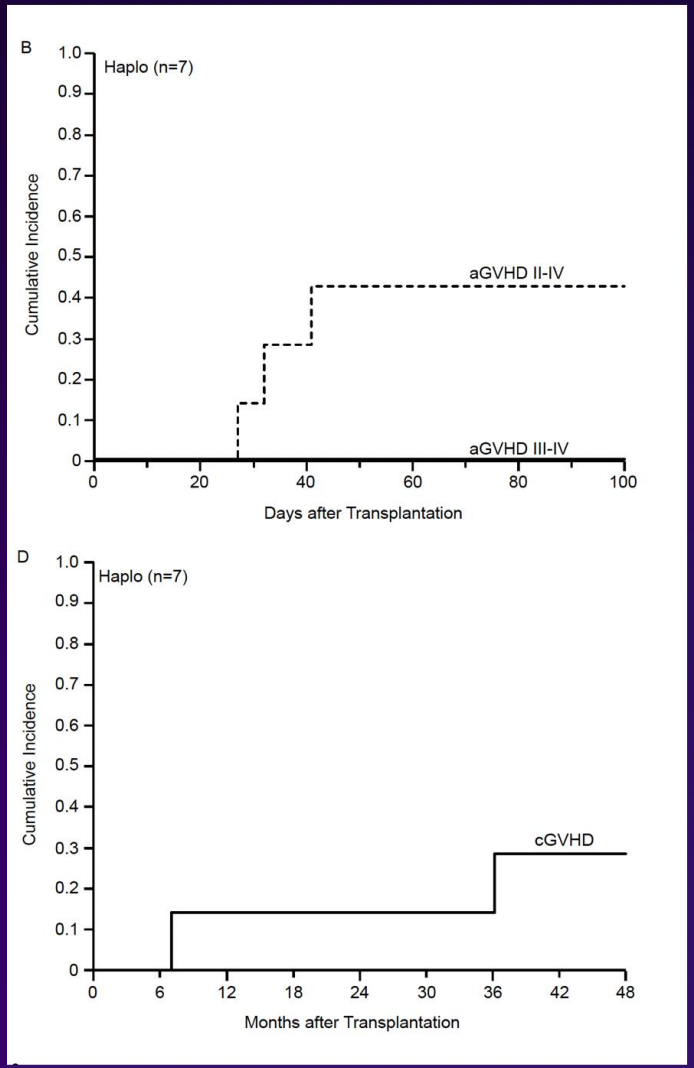
Acute GVHD in MRD and URD donor recipients receiving Tacrolimus / MTX



Chronic GVHD in MRD and URD donor recipients receiving Tacrolimus / MTX



Acute and chronic GVHD in Haplos



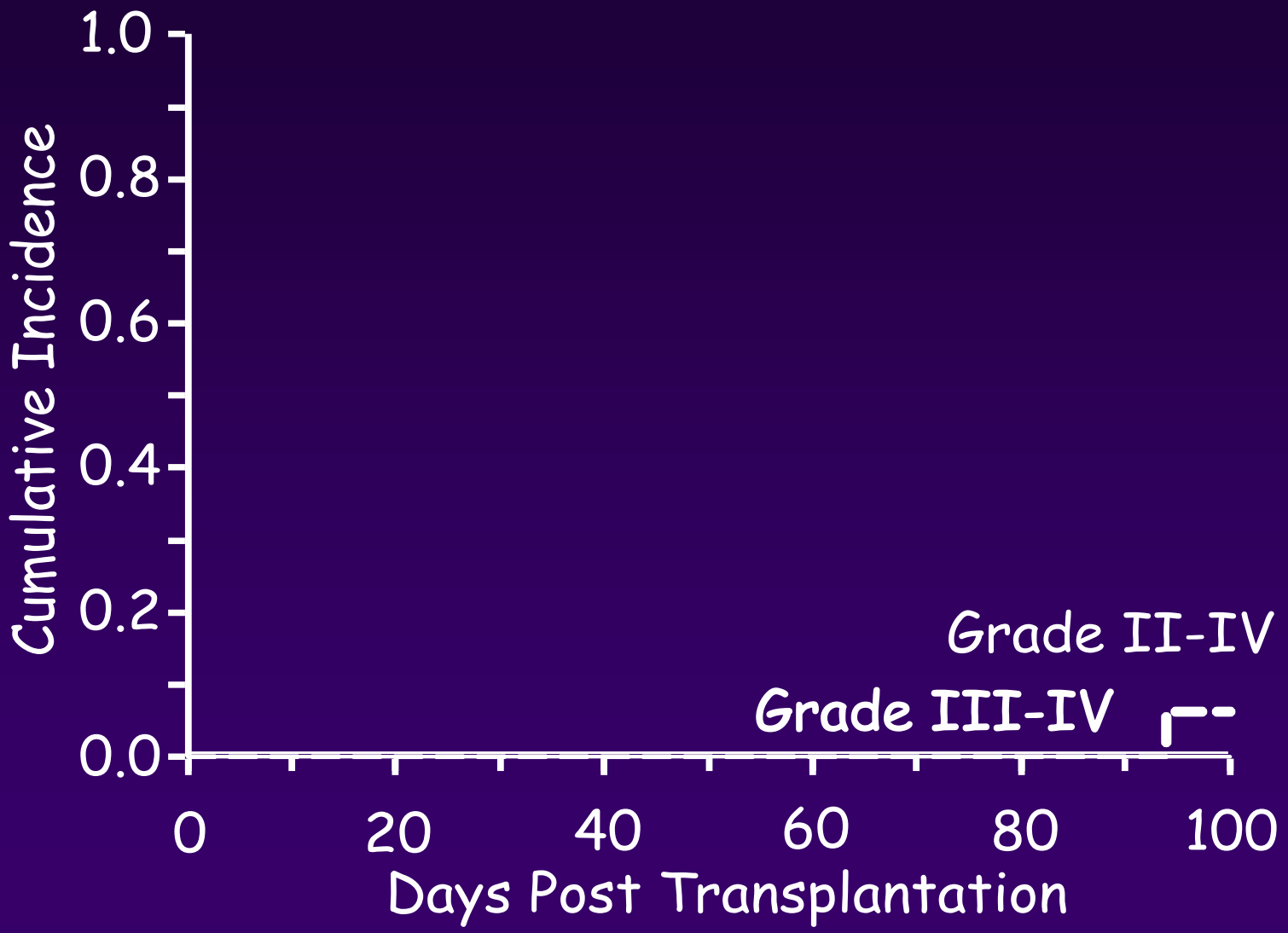
Amendment I January 2017

- MRD and URD recipients with normal cytogenetics, favorable, or intermed cytogenetics will receive PT/Cy followed by Tacro/MMF
- MRD and URD recipients with unfavorable cytogenetics will continue to receive Tacro/MTX

Total GATA2 patients transplanted since 2013 n=53

- 9 Matched related donors (1 death- rectal cancer)
- 27 Unrelated donors (5 deaths- 2 GVHD, 1 AML,1 sepsis, 1 MAC
- 16 Haploidentical related donors- all alive and disease-free with two cGVHD
- 89 % disease-free survival overall

Acute GVHD in MRD and URD Patients Treated with Post-Transplant Cyclophosphamide n=16



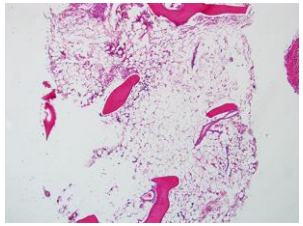
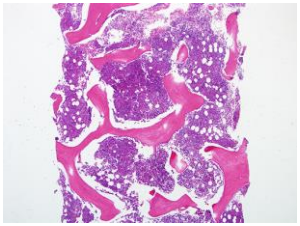
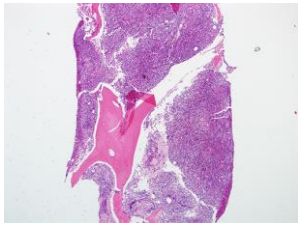
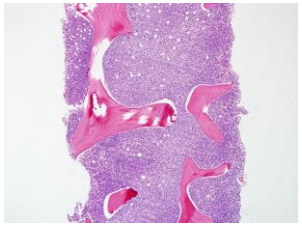
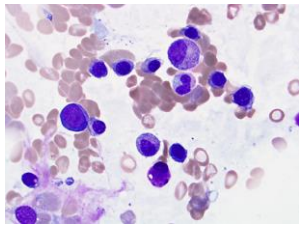
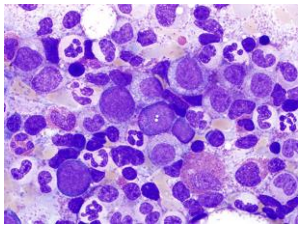
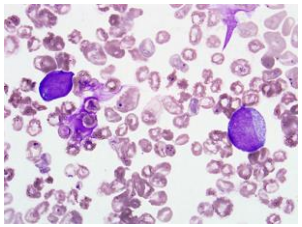
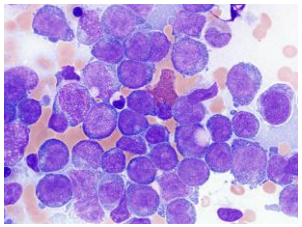
Comment on Tholouli et al, page XXX

HSCT for GATA2 deficiency across the pond

Dennis Hickstein | National Cancer Institute

In this issue of *Blood*, Tholouli et al describe successful in vivo T-cell–depleted allogeneic hematopoietic stem cell transplant (HSCT) in 4 patients with GATA2 deficiency using a reduced-intensity conditioning (RIC) regimen including serotherapy with alemtuzumab.[1] Three immediate questions come to mind when contemplating the first sentence, namely: what is GATA2 deficiency, what is the natural history of the disease that leads to HSCT, and what makes HSCT so special for GATA2 deficiency that it warrants a commentary?

The Spectrum of Bone Marrow Findings in GATA2 Deficiency

	Patient 1	Patient 2	Patient 3	Patient 4
Biopsy				
Aspirate				
	- Hypocellular marrow - <5% Blasts - Normal cytogenetics	- Hypercellular marrow - <5% Blasts - -X, trisomy 8, trisomy 1q	- Hypercellular marrow - <5% Blasts - Monosomy 7	- Acute monoblastic leukemia - 85% Blasts - Trisomy 8, trisomy 20

How to improve outcome in MRD and URD 's ?

- Dose reduce Bu in sub-groups
- Post-transplant Cytoxan in matched related and unrelated donor group to prevent GVHD
- Transplant before they get AML or CMML
- Transplant after MAC under control- high ∂-IFN
- Transplant before co-morbidities like colostomy

"Professor:
one who talks in someone else's sleep"

W.H. Auden

"The past is prologue to the future"

The phrase comes from Shakespeare's *The Tempest* and indicates that all of their lives up to this point was merely a prologue - an introduction - to the great story to come and that everything that came before doesn't matter because a new and glorious future awaits.

Unfortunately, it has since taken on the *exact opposite* meaning. The way it is used today is that the past is of great importance because it defines the present and therefore sets the stage for the future.