What Helps You Helps Your Patients
- Familial Myeloid Neoplasms In the Era of NGS Testing

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Learning Objectives

- Updates on myeloid neoplasms with germline predisposition in 5th WHO and ICC
- Updates on AML and MDS in 5th WHO and ICC
- Characteristic clinical and pathologic features of “rare” types of familial myeloid neoplasms in pediatric and adult patients
- Clinical utility of NGS based testing for myeloid neoplasms
- Current recommendations on clinical management

Presentation Outline

- Clinical utilities of NGS testing
- Different types of NGS based testing for tumors
- Updates in common myeloid neoplasms with germline predisposition
- Challenges and future directions
- Take home message

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Precision Medicine in Oncology

Diagnosis & prognosis

5th WHO and ICC classification of myeloid neoplasms

Therapeutic targets

Known drugs & new drugs in trials for 20% patients not responding to standard treatment

Pharmaco-genetics

Pharmacokinetics
DPD
UGT1A1
TPMT
CDA
CYP2D6

Surveillance

Monitoring response and resistance to therapy

Genetic Counseling

Family member genetic testing and early cancer screening

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What Is Next Generation Sequencing and Why

Next generation sequencing (NGS), or **massively parallel** or **deep sequencing**

Why molecular testing is moving toward to NGS

- Massive output
- Faster and sensitive
- Sequencing with quantification
- Relatively inexpensive
- NGS testing has been clinically used for genomic and genetic studies

NGS Based Testing For Tumors

- Whole genome sequencing
- Whole exome sequencing
- Targeted gene panels for somatic mutations in cancers
- Targeted gene panels for hereditary cancers
- Targeted RNA-sequencing
- Cell free DNA/RNA testing

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Acute Myeloid Leukemia Updates in 5th WHO

- AML with defining genetic abnormalities
  - RUNX1-RUNX1T1 fusion
  - CBFB-MYH11 fusion
  - KMT2A rearrangement
  - DEK-NUP214 fusion
  - RBM15-MKL1 fusion
  - BCR-ABL1 fusion
  - NUP98 rearrangement
  - Other defined driver gene alterations
  - AML MRC
- AML, defined by differentiation
- Myeloid sarcoma and others

Acute Myeloid Leukemia Updates in WHO

WHO Revised 4th Ed.	WHO 5th Ed.	ICC
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1	AML with RUNX1::RUNX1T1 fusion	AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 ≥10%
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	AML with CBFB::MYH11 fusion	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 ≥10%
APL with PML-RARA	Acute promyelocytic leukemia (APL) with PML::RARA fusion	APL with t(15;17)(q24.1;q21.2)/PML::RARA ≥10%
Not included	Currently mentioned in text	APL with other RARA rearrangements[1] ≥10%
AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3	Included in AML with KMT2A rearrangement	AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A ≥10%
Not included	AML with KMT2A rearrangement	AML with other KMT2A rearrangements[2] ≥10%
AML with t(6;9)(p23;q34.1); DEK-NUP214	AML with DEK::NUP214 fusion	AML with t(6;9)(p22.3;q34.1)/DEK::NUP214 ≥10%
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	Included in AML with MECOM rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1) ≥10%
Mentioned in text	AML with MECOM rearrangement	AML with other MECOM rearrangements[3] ≥10%
AML with t(1;22)(p13.3;q13.1); RBM15-MKL1	AML with RBM15::MRTFA fusion	Included in AML with other rare recurring translocations ≥10%
AML with BCR-ABL 1	AML with BCR::ABL1 fusion*	AML with t(9;22)(q34.1;q11.2)/BCR::ABL1 ≥20% blasts*
Not included	**AML with NUP98 rearrangement**	Included in AML with other rare recurring translocations ≥10%
Not included	**AML with other defined genetic alterations**	**AML with other rare recurring translocations**
AML with mutated NPM1	AML with NPM1 mutation	AML with mutated NPM1 ≥10%
AML with biallelic mutation of CEBPA	AML with **CEBPA mutation***	AML with **in-frame bZIP** CEBPA mutations ≥10%
AML with mutated RUNX1	**Not included**	**Not included**
Not included	Not included	**AML and MDS/AML with mutated TP53 10-19% (MDS/AML) and ≥ 20% (AML): at least one TP53 mutation with VAF >10%**

Acute Myeloid Leukemia Updates in WHO

WHO Revised 4th Ed.	WHO 5th Ed.	ICC
AML with MRC • **Morphologic multilineage dysplasia (at least in 50% of cells in at least two cell lines)** • **Defining cytogenetic abnormalities** • **History of MDS or MDS/MPN**	AML, myelodysplasia-related (AML-MR) ✓ Removal of morphology alone as a diagnostic criterium ✓ defining mutations (new, 8 genes): SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2 ✓ defining cytogenetic criteria with updates ✓ History of MDS or MDS/MPN	AML (≥ 20%) and MDS/AML (10-19%) with ✓ Removal of morphology alone as a diagnostic criterium ✓ myelodysplasia-related gene mutations (**new, 9 genes**): RUNX1, SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2 ✓ myelodysplasia-related cytogenetic abnormalities with updates

• **Absence of specific cytogenetic abnormalities in AML with recurrent cytogenetic abnormalities**
• **Absence of prior cytotoxic therapy**
	✓ Absence of specific cytogenetic abnormalities of AML with recurrent cytogenetic abnormalities
	✓ Absence of prior cytotoxic therapy
		AML (≥ 20%) and MDS/AML (10-19%) with qualifiers
		• Therapy related
		  • Chemotherapy
		  • Radiation
		  • Immune interventions
		• Progressing from MDS or MDS/MPN
		• Germline predisposition

Therapy-related myeloid neoplasms (AML, MDS, MDS/MPN) • **Cytotoxic chemotherapy** • **Radiation therapy**	Myeloid neoplasms (MDS, MDS/MPN, and AML) post cytotoxic therapy (MN-pCT) • PARP1 inhibitors (new) in addition	Included in AML/MDS with myelodysplasia-related changes

AML defined by differentiation

WHO Revised 4th Ed.	WHO 5th Ed.	ICC
AML, NOS	AML defined by differentiation	AML (≥ 20), NOS
Acute myeloid leukemia with minimal differentiation	AML with minimal differentiation	Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation	AML without maturation	Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation	AML with maturation	Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia	Acute myelomonocytic leukemia	Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia	Acute monocytic leukemia	Acute monoblastic and monocytic leukemia
Pure erythroid leukemia	Pure erythroid leukemia	**Removed to AML with mutated *TP53***
Acute megakaryoblastic leukemia	Acute megakaryoblastic leukemia (AMKL)	Acute megakaryoblastic leukemia
Acute basophilic leukemia	Acute basophilic leukemia	Acute basophilic leukemia
Acute panmyelosis with myelofibrosis	Acute panmyelosis with myelofibrosis	Acute panmyelosis with myelofibrosis
Myeloid sarcoma	Myeloid sarcoma	Myeloid sarcoma

Updates in 5th WHO and ICC Classification

Myeloid neoplasms, secondary

- Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions
  - **Myelodysplastic neoplasm associated with germline predisposition**
  - Myeloid neoplasm post cytotoxic therapy
  - Acute myeloid leukemia following other hematolymphoid malignancy
  - Myeloid proliferation associated with Down syndrome
  - Myeloid neoplasms associated with malignant germ cell tumor

Genetic tumor syndromes

- Fanconi anemia
- Bloom syndrome
- Ataxia-telangiectasia syndrome
- RASopathies

Hematologic Neoplasms with Germline Predisposition

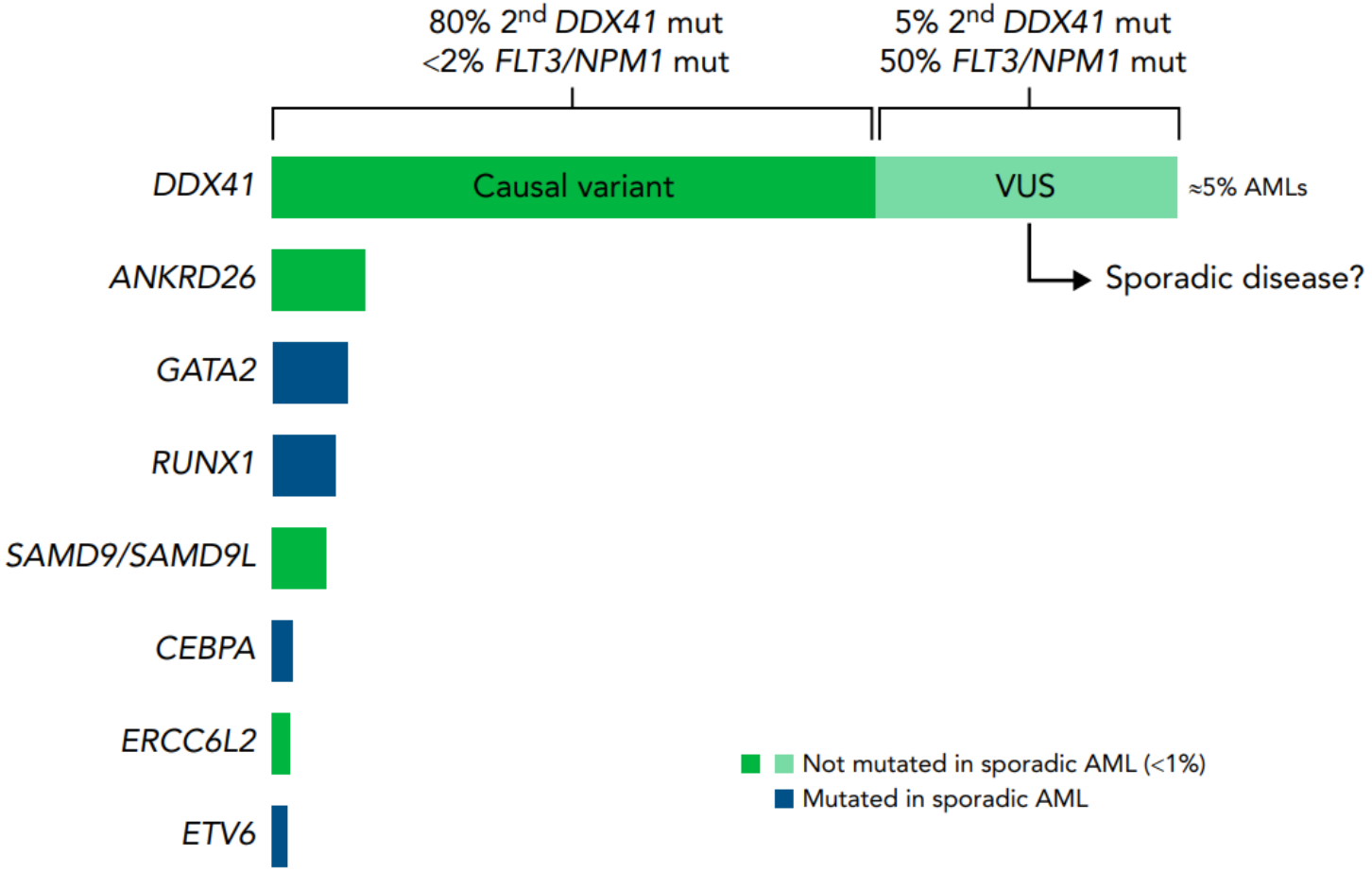
Diseases	Patterns	Genes	Penetrance
No pre-existing disorders or organ dysfunction			
Myeloid neoplasm with germline *DDX41* mutation	AD	*DDX41*	Unknown
Myeloid/lymphoid neoplasm with germline CEBPA mutation	AD	*CEBPA*	90%, AML only
Myeloid/lymphoid neoplasm with germline TP53 mutation	AD	*TP53*	50-70%
With pre-existing platelet disorders			
Myeloid neoplasm with germline *RUNX1* mutation	AD	*RUNX1*	20-60%
Myeloid neoplasm with germline *ANKRD26* mutation	AD	*ANKRD26*	Unknown
Myeloid neoplasm with germline *ETV6* mutation	AD	*ETV6*	Unknown
With other organ dysfunction			
Myeloid neoplasm with germline *GATA2* mutation	AD	*GATA2*	70%
Myeloid neoplasm with germline *SAMD9/SAMD9L* mutation	AD	*SAMD9/L*	Unknown
With inherited bone marrow failure syndrome and telomere biology disorders	Most AD	*Multiple*	Unknown
Acute lymphoblastic leukemia with germline predisposition	Most AD	*PAX5 and IKZF1*	Unknown

WHO 2016 and Fisher and Gramatges. Precision Molecular Pathology of Myeloid Neoplasm, 2017

Common Features of Inherited Myeloid Neoplasms

- Manifest at earlier ages
- Substantial familial clustering
- With or without syndromatic manifestation
- Rare disease

The most common familial aml



> 5% of all AML

7% of AML aged > 50 yr

10% of AML aged > 70 yr

Rio-Machin et al, Blood, 2022

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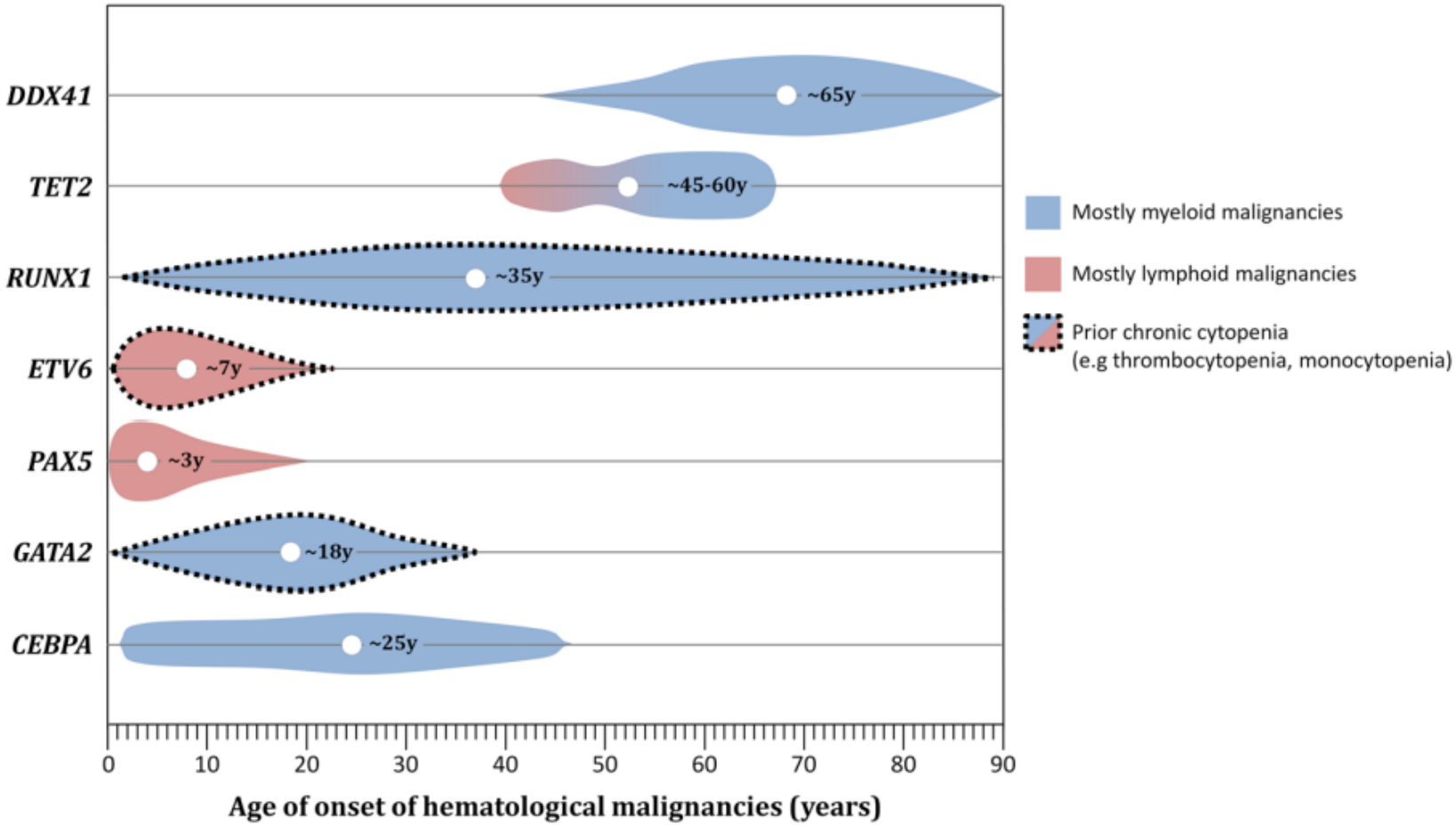
Age at Onset of Familial Hematologic Malignancy



Fenwarth, Hema Sphere, 2021

Common Features of Inherited Myeloid Neoplasms

- Manifest at earlier ages
- Substantial familial clustering
- With or without syndromatic manifestation (<50%)
- Rare disease

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Hereditary Predispositions of Myeloid Neoplasms

Patients with newly diagnosed MDS/AML

MDS dx at age < 40 yr (with exceptions)
Any potential germline variant with a persistent VAF >30% (with exceptions)
Or
Family History of MDS/AML
Early onset of cancers of any type
Multiple close relatives with cancers

Syndromatic manifestations
Personal or family history of

- Thrombocytopenia, pancytopenia
- Bleeding tendency
- Skin or nail abnormalities
- Unexplained liver disease
- Pulmonary fibrosis or alveolar proteinosis
- Limb anomalies
- Immune deficiency or atypical infections

Genetic counseling and testing

Bannon, Int J Mol Sci. 2016; Fenwarth, Hema Sphere, 2021

Presentation Outline

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Case #1

- 10 year old Caucasian male with URIs
- Persistent pancytopenia, macrocytic anemia
- A history of extensive warts
- Family history:
  - Maternal family history: significant for warts
  - Two healthy siblings

Case #1 – CBC and Peripheral Blood

WBC: 1.7 × 10^9/L (3.9–10.2 × 10^9/L) ⇩

ANC: 0.14 × 10^9/L (1.8–6.8 × 10^9/L) ⇩

Lymphocytes 1.19 × 10^9/L (1.0–3.6 × 10^9/L)

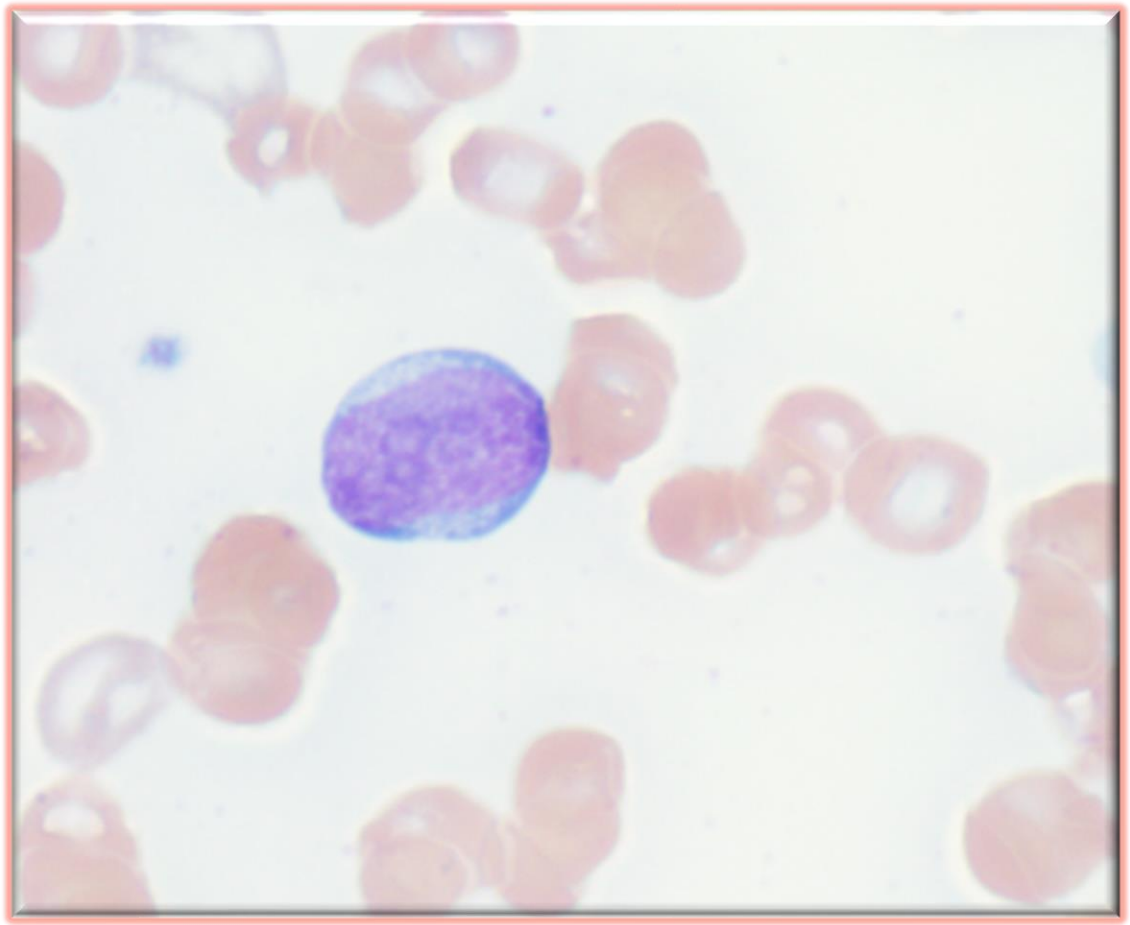
Monocytes 0.17 × 10^9/L (0.1–0.7 × 10^9/L)

Other (blasts) 0.09 × 10^9/L ⇧

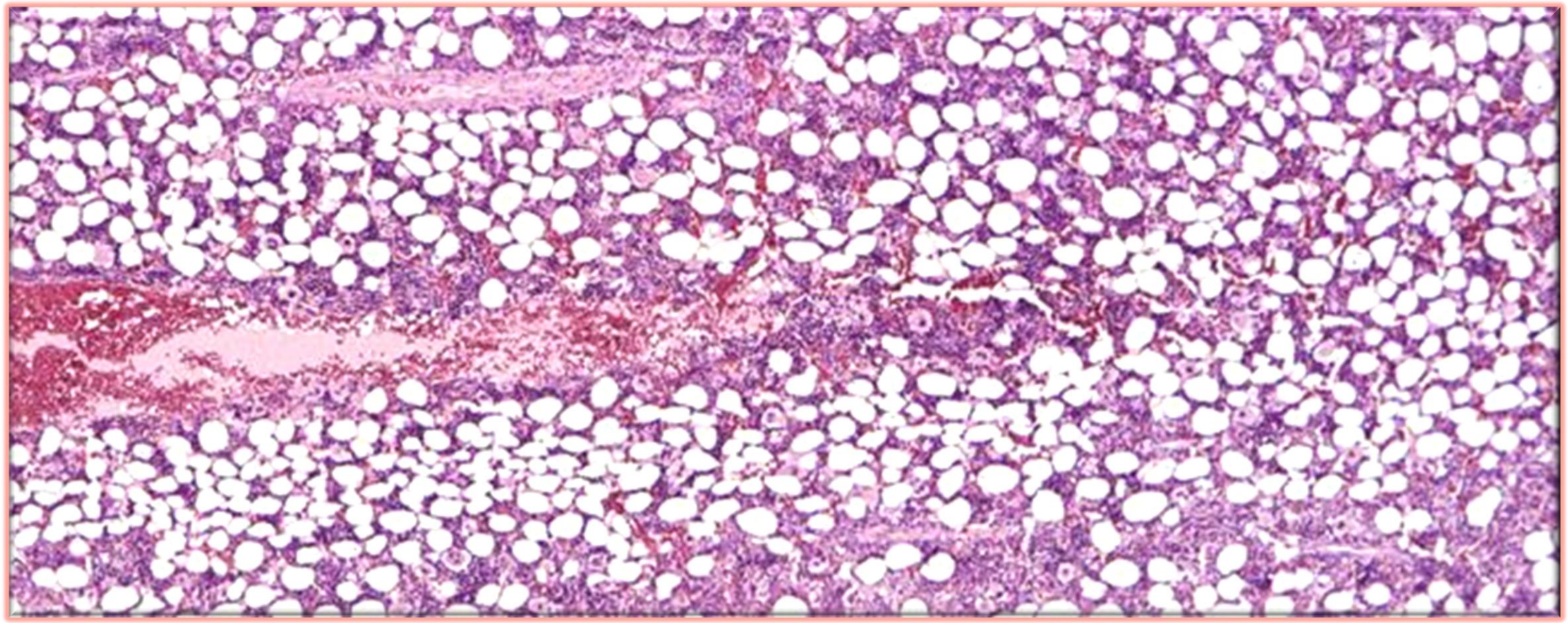
Hemoglobin: 98 g/L (131–169 g/L) ⇩

MCV: 101.5 fl (80–95 fl) ⇧

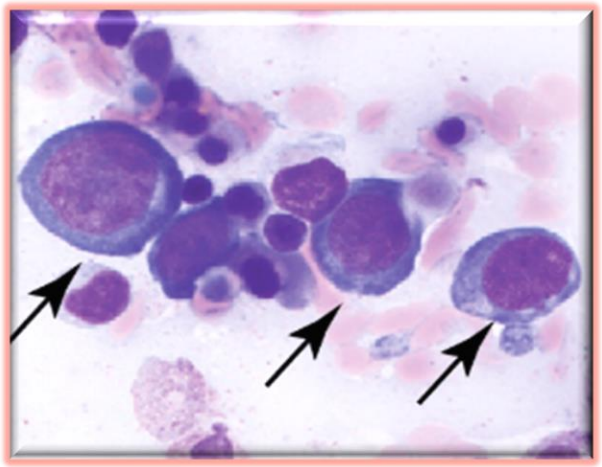
Platelets: 116 × 10^9/L (165–397 × 10^9/L) ⇩

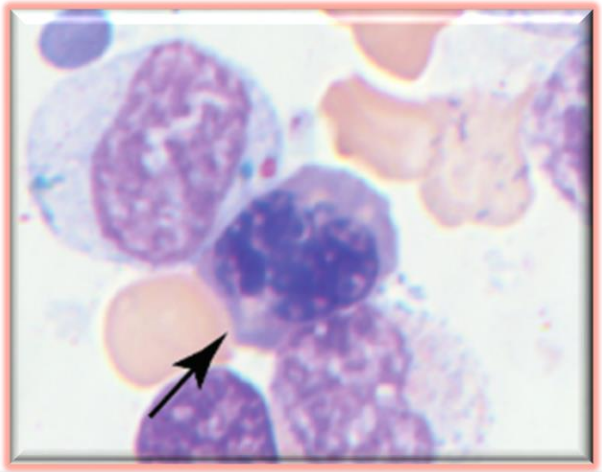


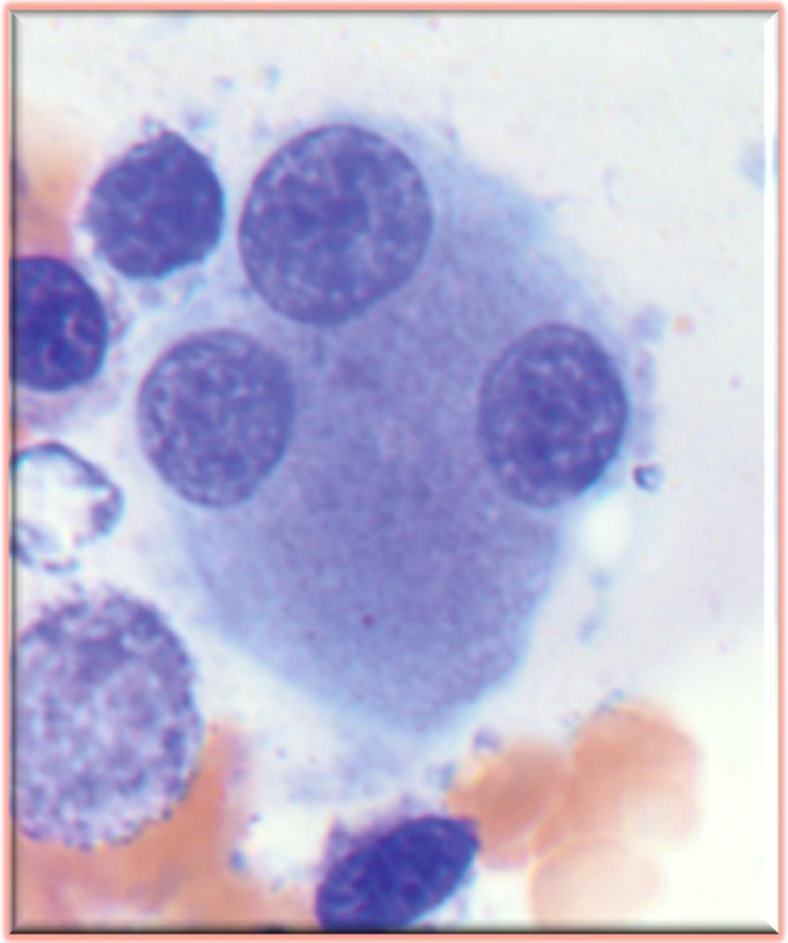
Case #1 – Bone Marrow Biopsy

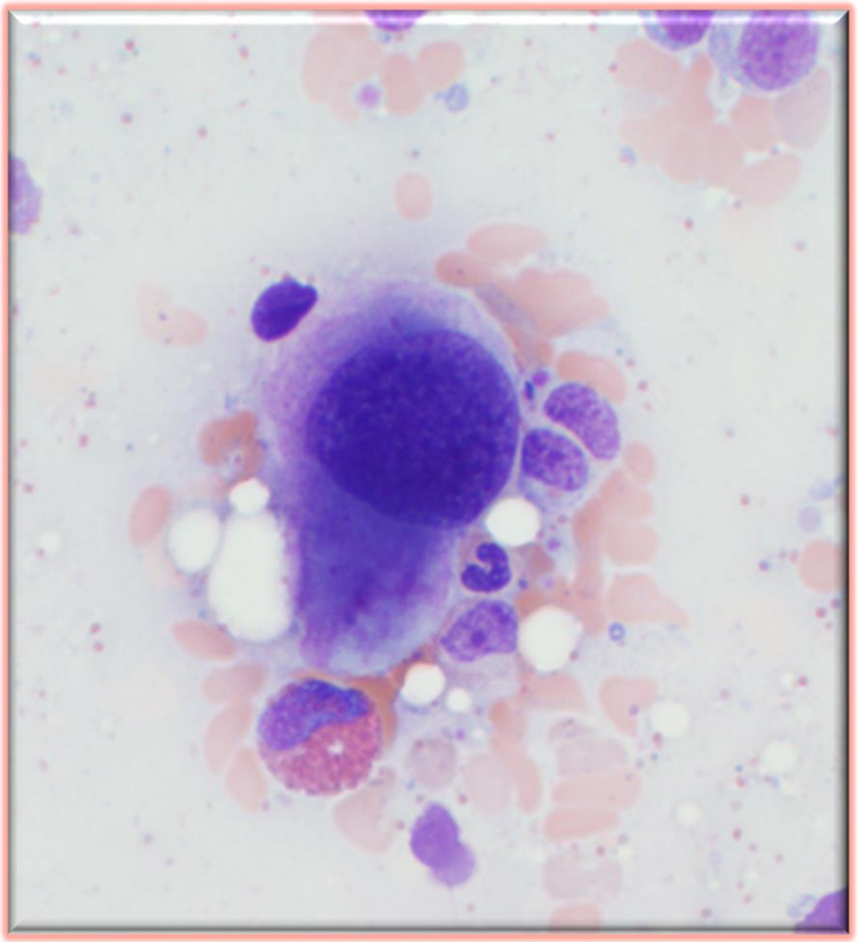


Case #1 – Bone Marrow Aspirate

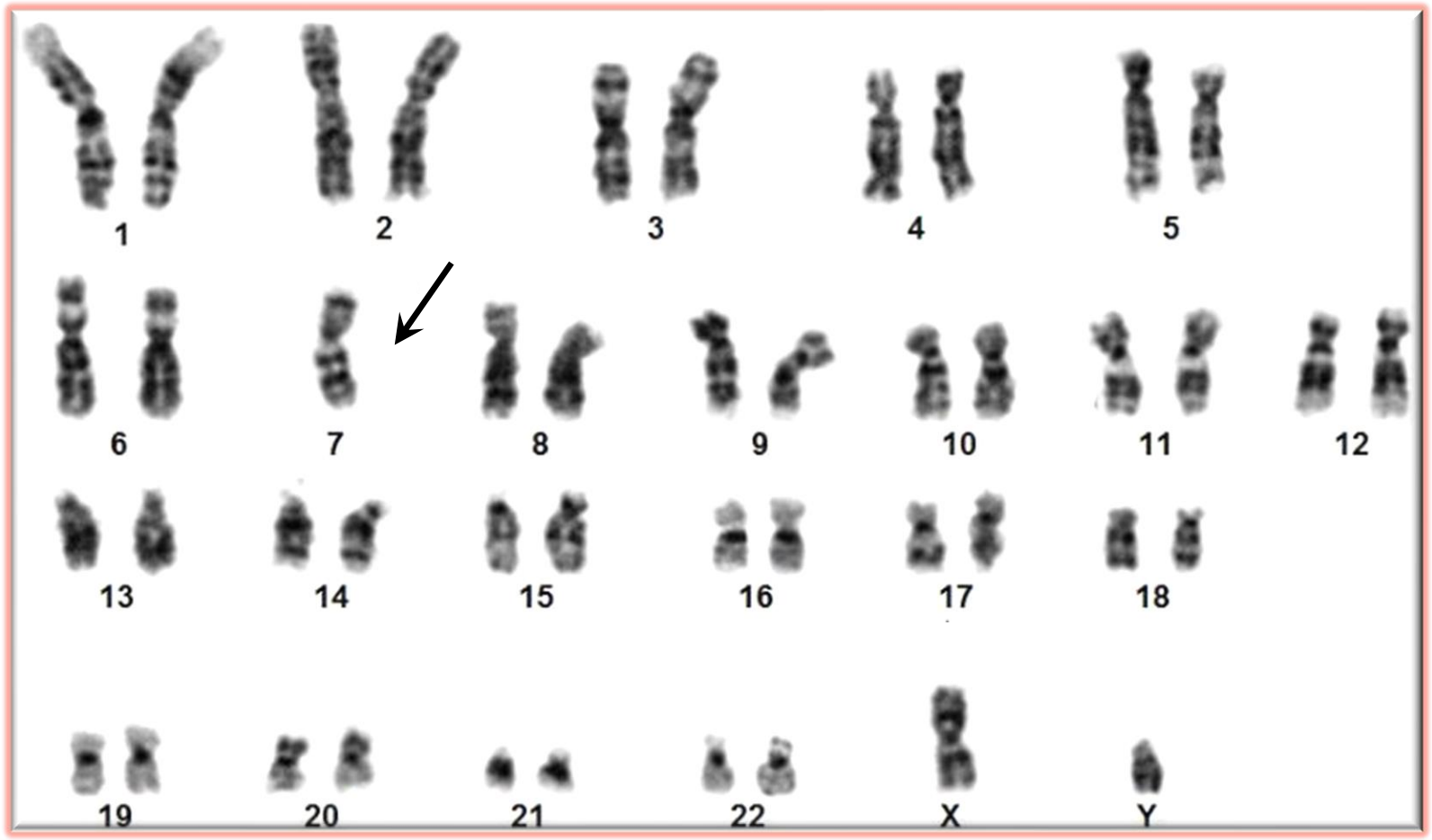








Case #1 – Cytogenetics



Case #1 – Diagnostic Impression

- Pediatric high-grade MDS (15% blasts by morphology)
- AML
- Other concerns:
  - Concern for familial MDS/AML:
    - A history of extensive warts
    - Maternal family history: significant for warts
  - Prognosis: worse prognosis with monosomy 7, any additional prognostic markers?

Hematologic Neoplasms with Germline Predisposition

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WHO 2016 and Fisher and Gramatges. Precision Molecular Pathology of Myeloid Neoplasm, 2017

Case #1 – Bone Marrow NGS Testing

- GATA2 c.1009C>T, p.Arg337X (VAF: 53%), confirmed by Sanger sequencing
- Germ line heterozygosity of GATA2 c.1009C>T, p.Arg337X , confirmed by skin biopsy
- Family member screening:
  - Mother: GATA2, c.1009C>T, p.Arg337X mutation
  - Siblings: no GATA2 mutation detected
- Additional variants indicating a poor prognosis
  - TP53 c.743G>A, p.R248Q (VAF: 12%), somatic mutation
  - ASXL1 c.2077C>T, p.R693X (VAF: 15%), somatic mutation

Case #1 – Final Diagnosis

- Myeloid neoplasms with germ line predisposition
- Germline GATA2 c.1009C>T, p.Arg337X (VAF: 53%) mutation detected

GATA2-Related MN in Children and Adolescents

MYELOID NEOPLASIA

CME Article

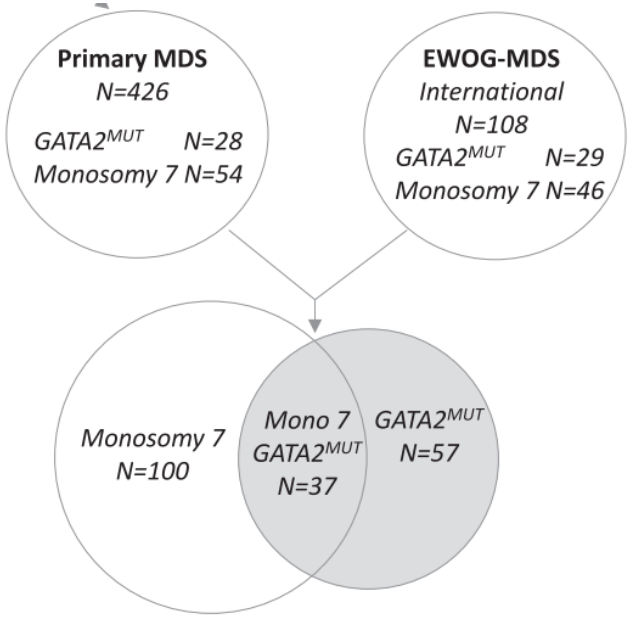
Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents

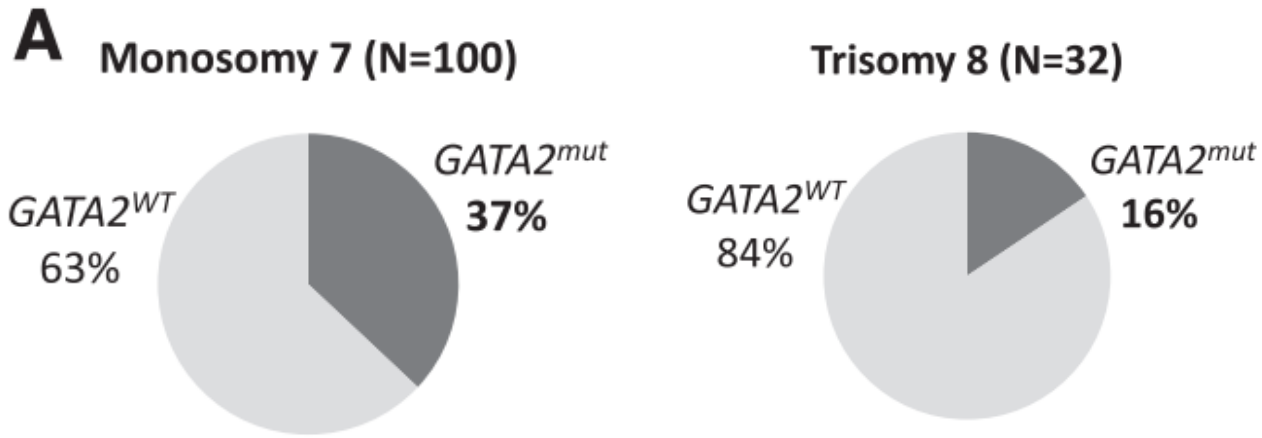
Marcin W. Wlodarski,[1,2] Shinsuke Hirabayashi,[1] Victor Pastor,[1] Jan Starý,[3] Henrik Hasle,[4] Riccardo Masetti,[5] Michael Dworzak,[6] Markus Schmugge,[7] Marry van den Heuvel-Eibrink,[8] Marek Ussowicz,[9] Barbara De Moerloose,[10] Albert Catala,[11] Owen P. Smith,[12] Petr Sedlacek,[3] Arjan C. Lankester,[13] Marco Zecca,[14] Victoria Bordon,[10] Susanne Matthes-Martin,[6] Jonas Abrahamsson,[15] Jörn Sven Kühl,[16] Karl-Walter Sykora,[17] Michael H. Albert,[18] Bartlomiej Przychodzien,[19] Jaroslaw P. Maciejewski,[19] Stephan Schwarz,[20] Gudrun Göhring,[21] Brigitte Schlegelberger,[21] Annámaria Cseh,[1] Peter Noellke,[1] Ayami Yoshimi,[1] Franco Locatelli,[22] Irith Baumann,[23] Brigitte Strahm,[1] and Charlotte M. Niemeyer,[1,2] for the EWOG-MDS

Wlodarski, Blood, 2016

GATA2-Related MN in Children and Adolescents

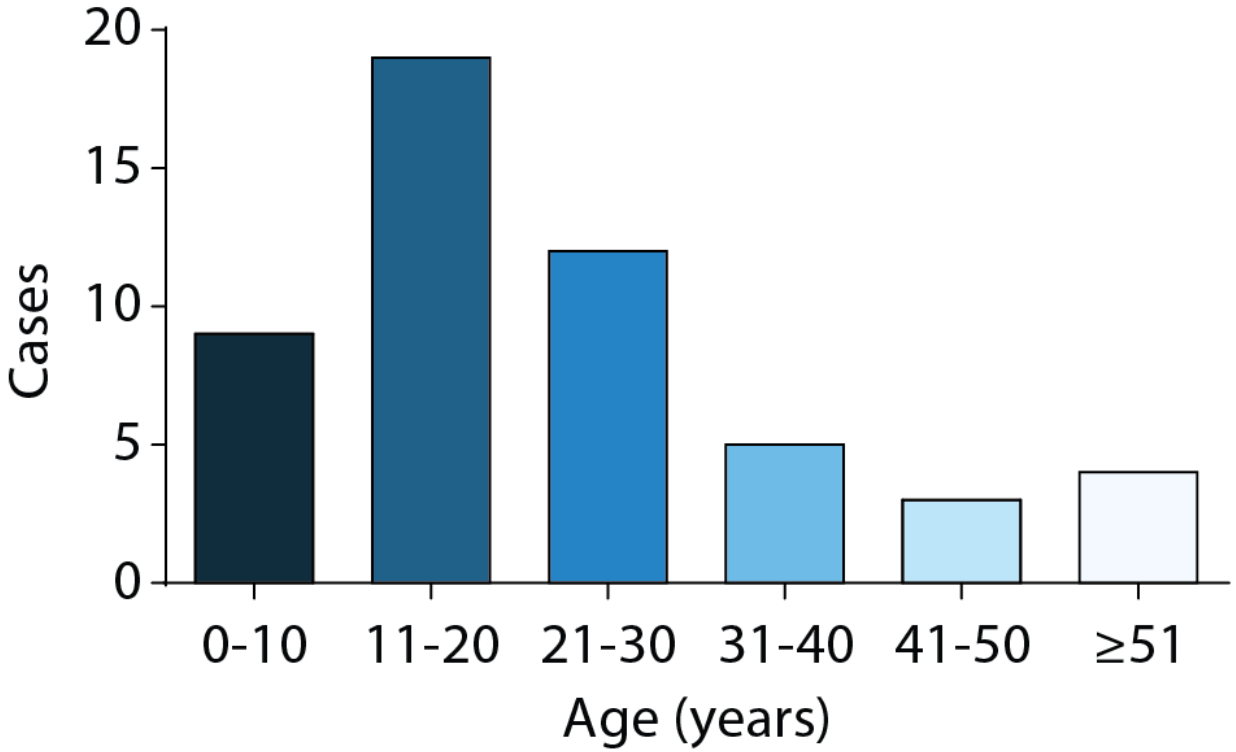
- Germline GATA2 mutations account for 15% of advanced and 7% of all primary pediatric MDS
- 72% of adolescents with MDS and monosomy 7 carry an underlying GATA2 deficiency
- Germline GATA2 mutations do not influence overall survival

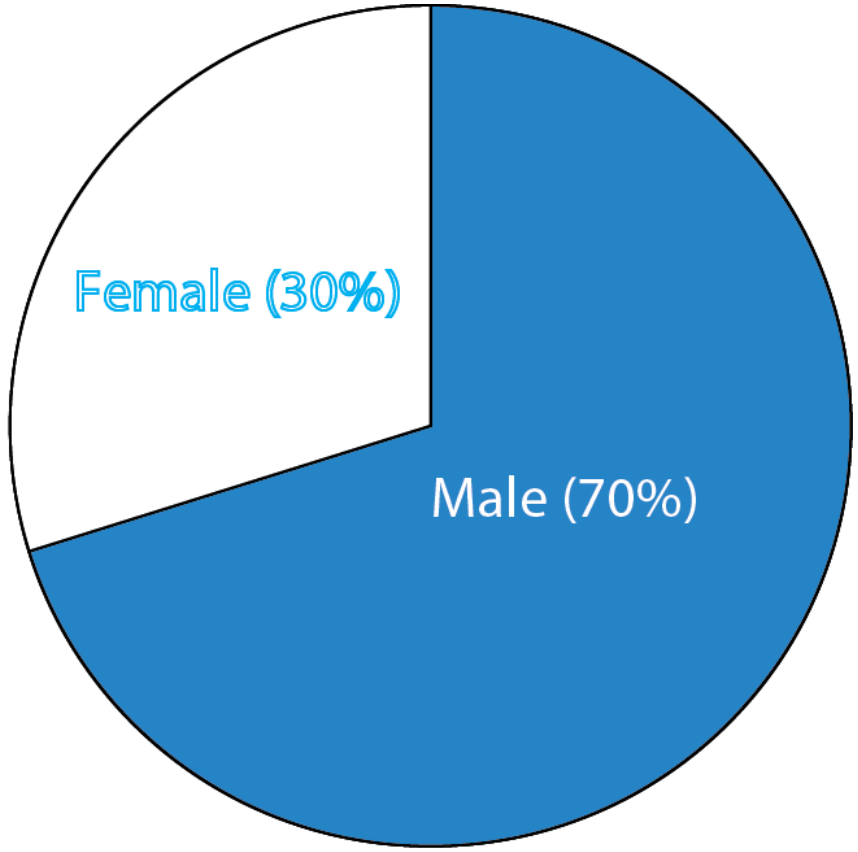




Wlodarski, Blood, 2016

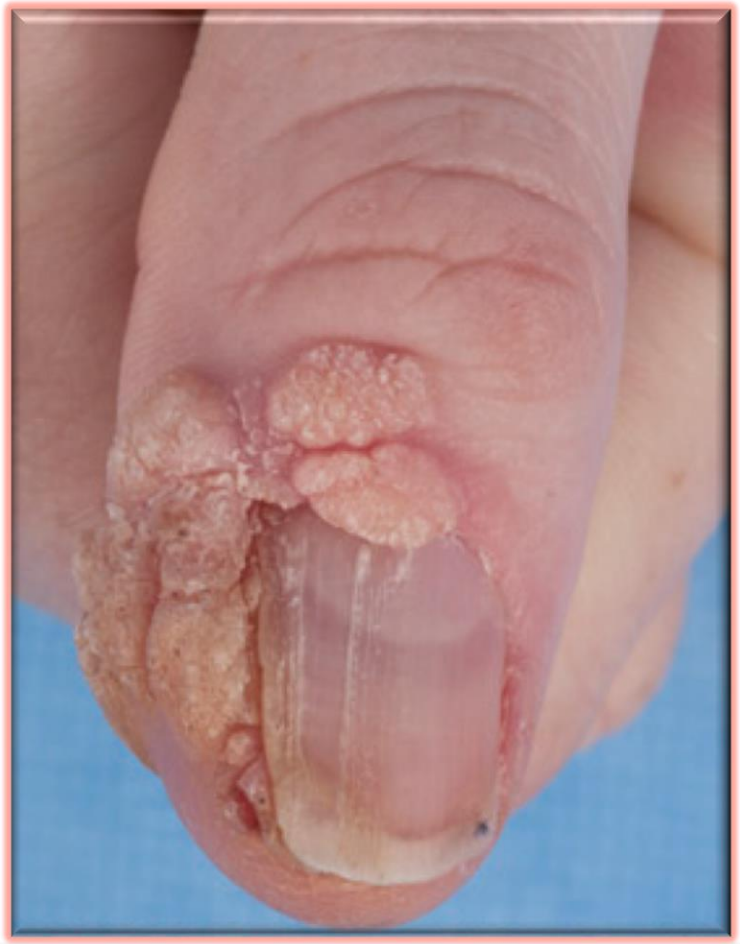
GATA2 Deficiency – Epidemiology

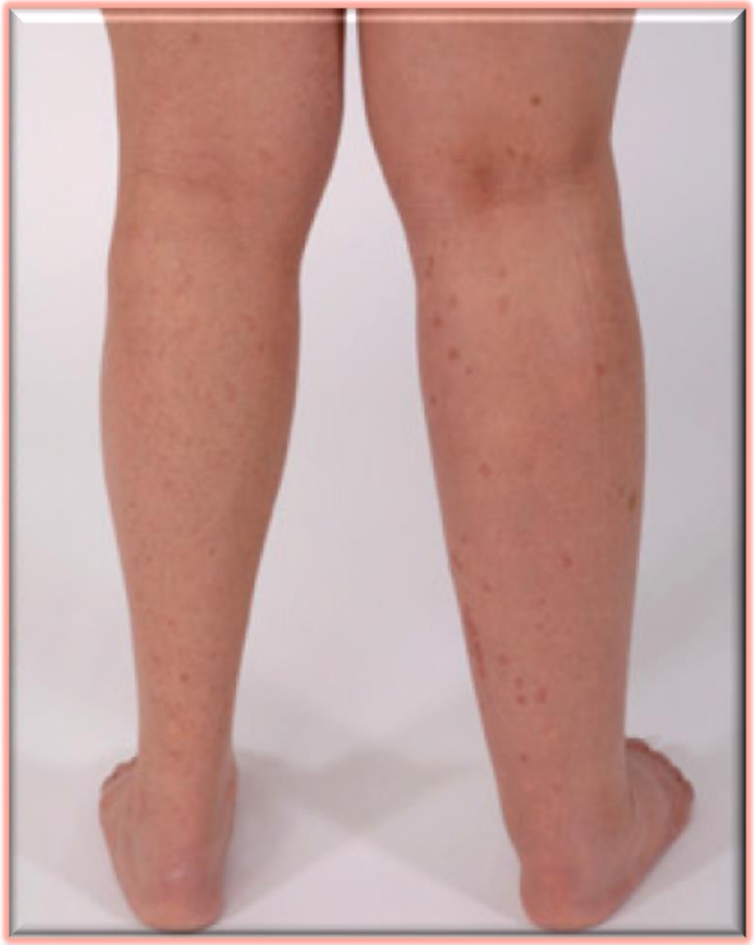


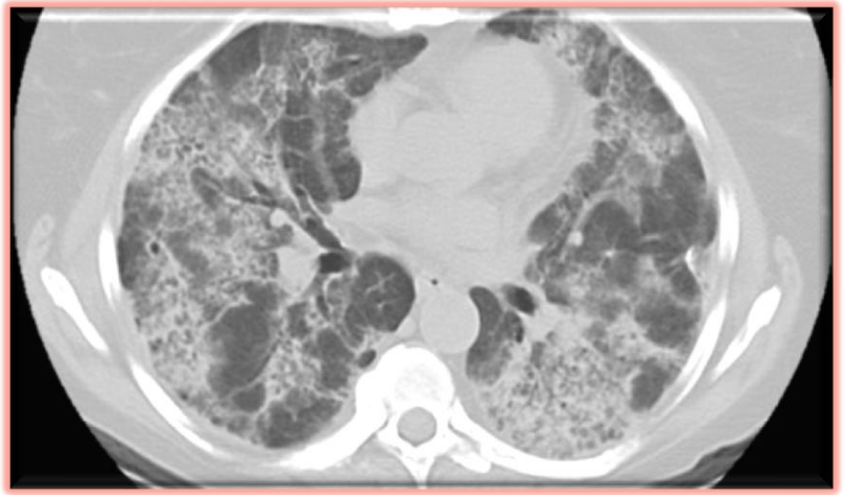


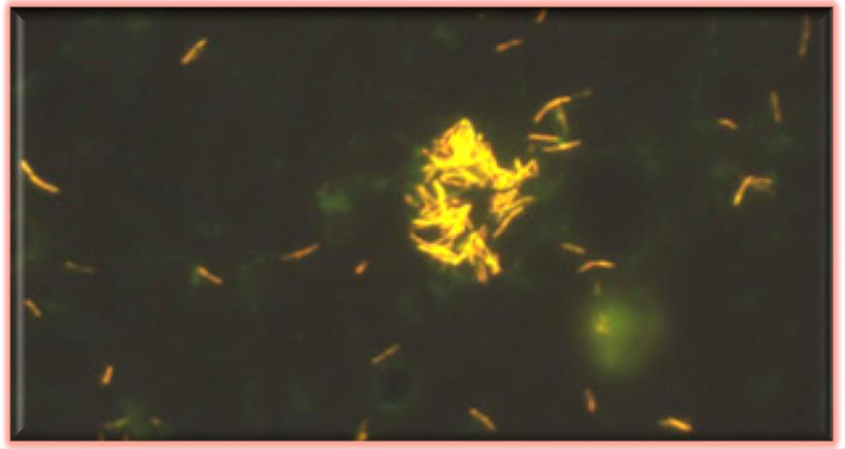
Spinner, Blood, 2014

GATA2 Deficiency – Clinical Hallmarks



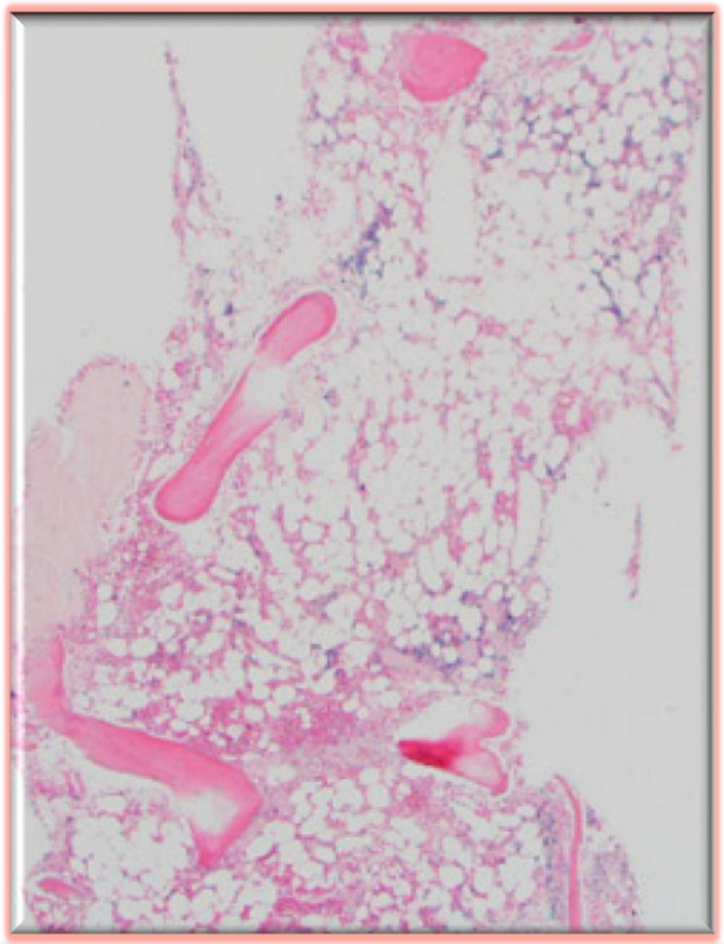


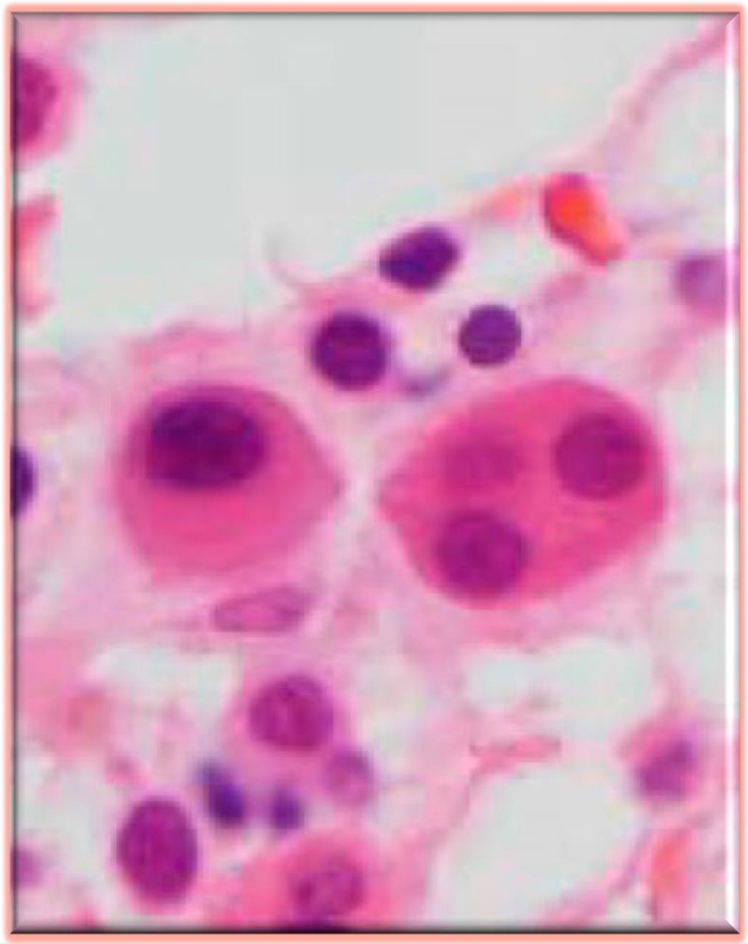


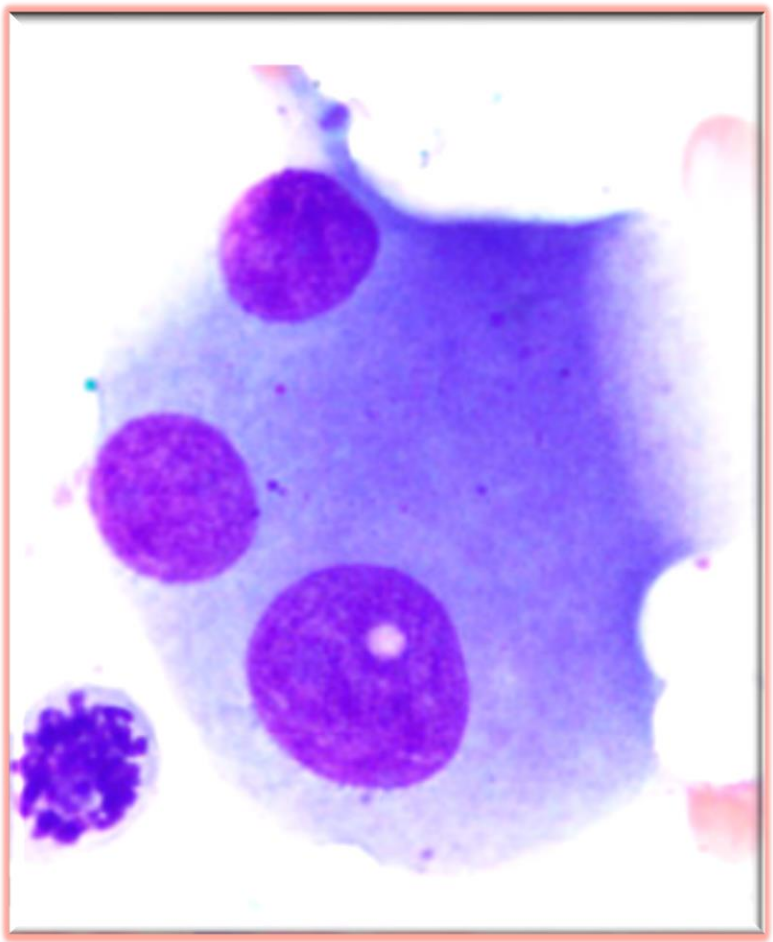


Spinner, Blood, 2014

GATA2 Deficiency – Marrow Hallmarks







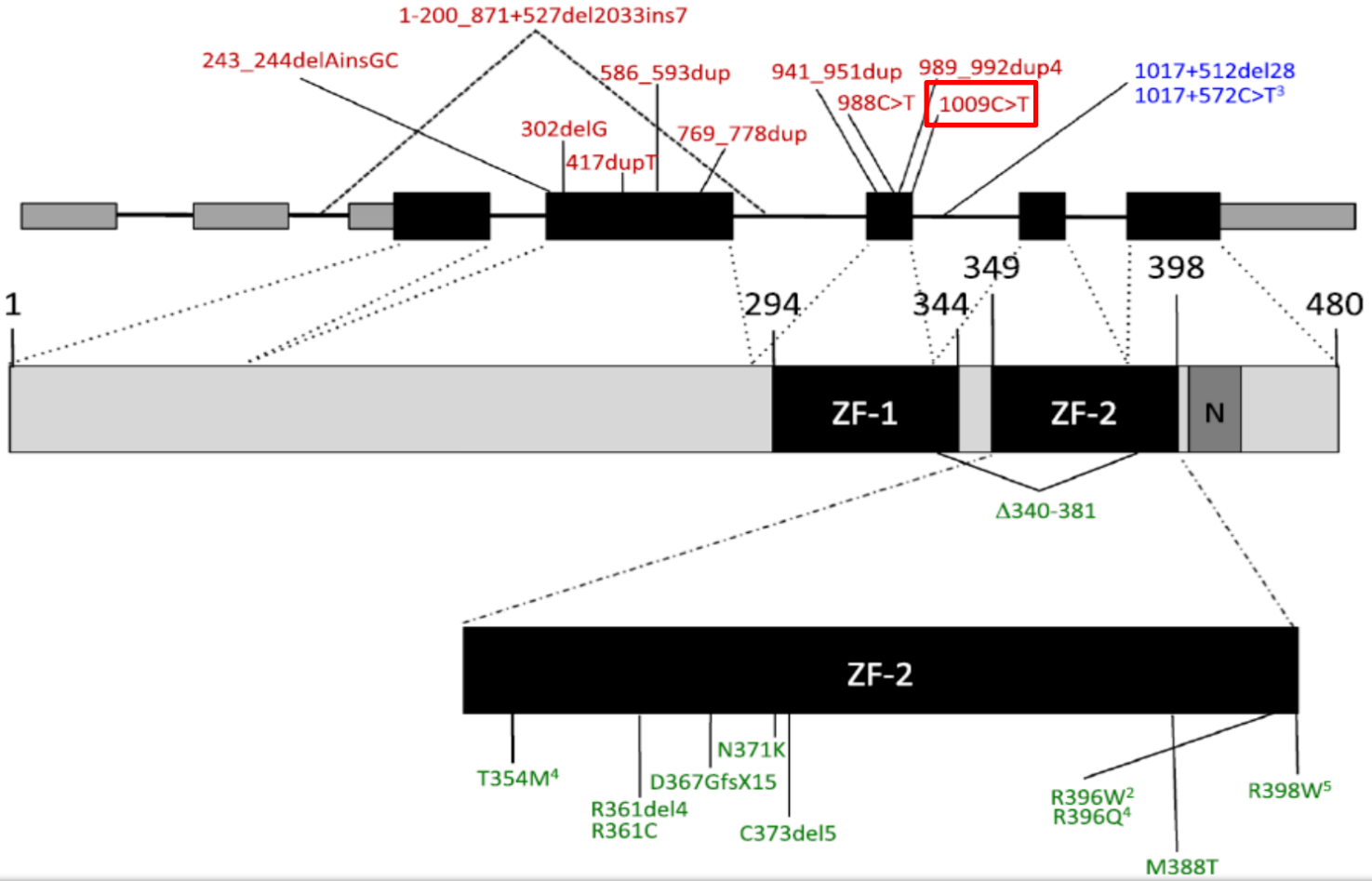
Spinner, Blood, 2014

GATA2 Mutations

Null allele
(LD, FS and NS)

Missense
(MS and IFD)

Regulatory
(Intronic)



Spinner, Blood, 2014

Other Prognostic Factors

Germ-line *GATA2* p.THR354MET mutation in familial myelodysplastic syndrome with acquired monosomy 7 and *ASXL1* mutation demonstrating rapid onset and poor survival

Csaba Bödör,[1,2] Aline Renneville,[3] Matthew Smith,[1] Aurélie Charazac,[1] Sameena Iqbal,[1] Pascaline Étancelin,[3] Jamie Cavenagh,[1] Michael J Barnett,[4] Karolina Kramarzová,[5] Biju Krishnan,[6] András Matolcsy,[2] Claude Preudhomme,[3] Jude Fitzgibbon,[1] and Carolyn Owen[7]

[1]Centre of Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, UK; [2]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary; [3]Centre de Biologie-Pathologie, Laboratoire d'Hématologie, CHRU de Lille, France; [4]Leukemia/BMT Program of British Columbia, British Columbia Cancer Agency and Vancouver General Hospital, and University of British Columbia, Vancouver, Canada; [5]Department of Pediatric Hematology and Oncology, 2nd School of Medicine, Charles University, Prague, Czech Republic; [6]Department of Haematology, Queens Hospital, Essex, UK; and [7]Division of Hematology & Hematological Malignancies, University of Calgary, Calgary, Canada

Bödör, haematologica, 2012

Case #1 – Follow Up

- High risk: Null allele, Monosomy 7, ASXL1 and TP53 mutations
- Original management plan: Bone marrow transplant
- Outcome: Rapidly progressed to AML and the patient deceased

Take Home Message – Case #1

- *GATA2* mutations predispose to MDS and AML
- Common in all primary pediatric MDS (7-15%) and enriched in adolescents (72%) or MDS with monosomy 7 (37%) and trisomy 8 (16%)
- Immunodeficiency
  - MonoMAC syndrome (atypical mycobacterial infection)
  - Dendric cell, monocyte, B and NK cell deficiency (viral infection)
- Emberger syndrome
  - Lymphoedema
  - Warts
  - High risk of MDS/AML

Case #2

- 31 year old male with easy bruising and fatigue for 3 months
- Found to have anemia and thrombocytopenia

Case #2 – CBC and Peripheral Blood

WBC: 17.7 × 10^9/L (5.0–14.5 × 10^9/L) ⇧

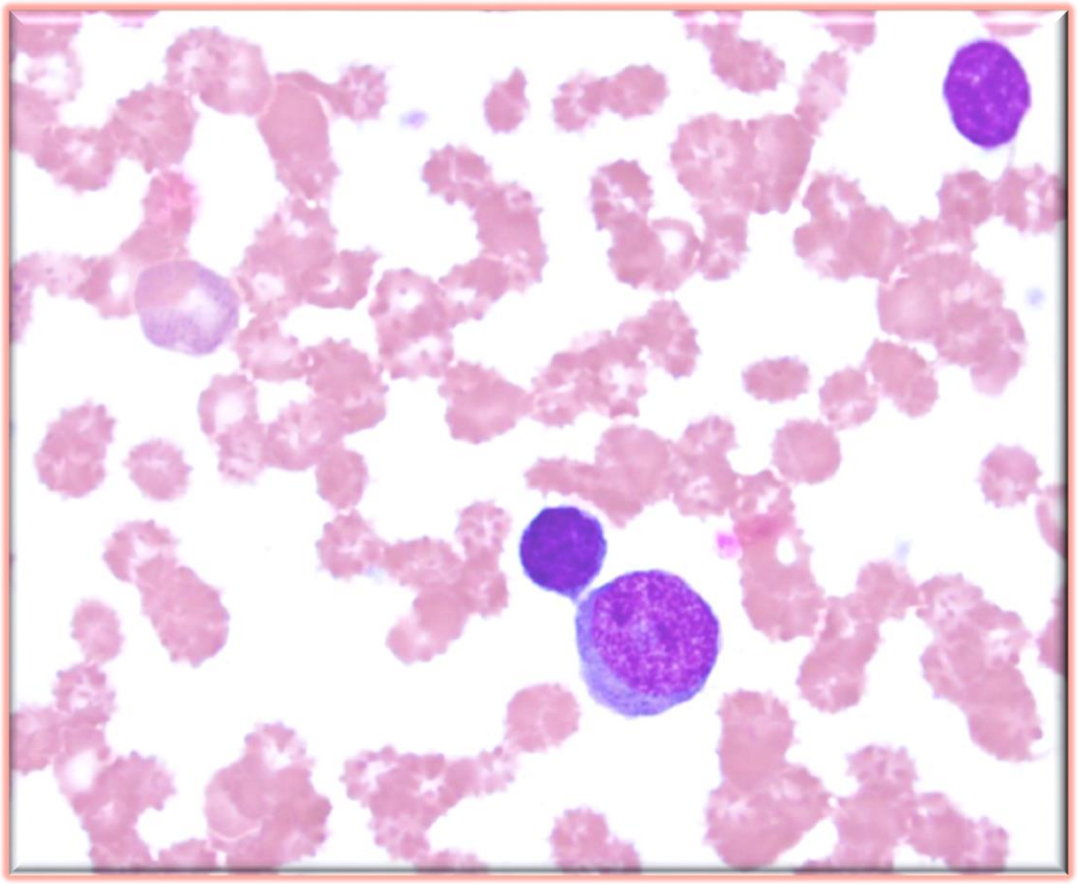
ANC: 1.2 × 10^9/L (1.5–8.0 × 10^9/L) ⇩

Other (blasts) 7.0 % ⇧

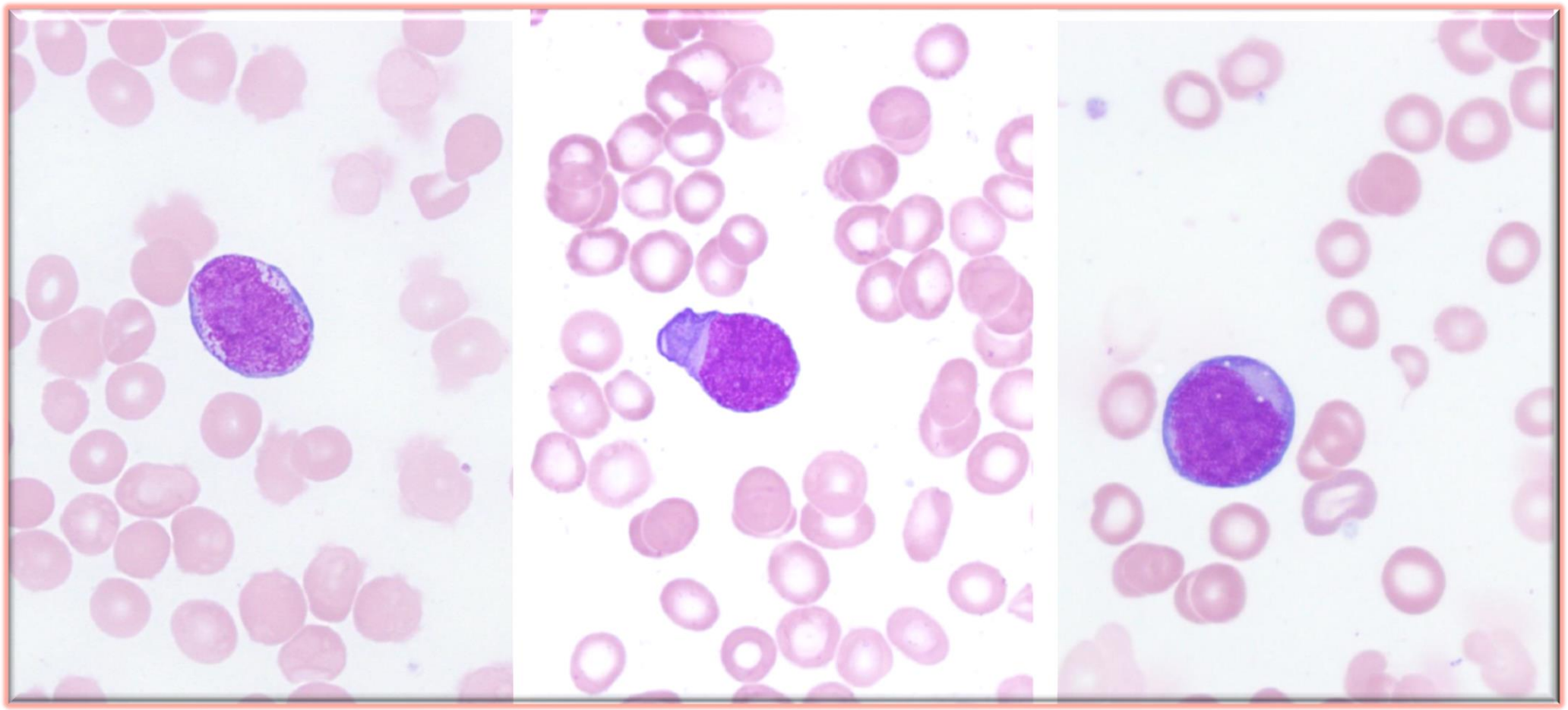
Hemoglobin: 7.4 g/L (131–169 g/L) ⇩

MCV 70.5 fl (76–90 fl)

Platelets: 5 × 10^9/L (150–450 × 10^9/L) ⇩



Bone Marrow Aspirate



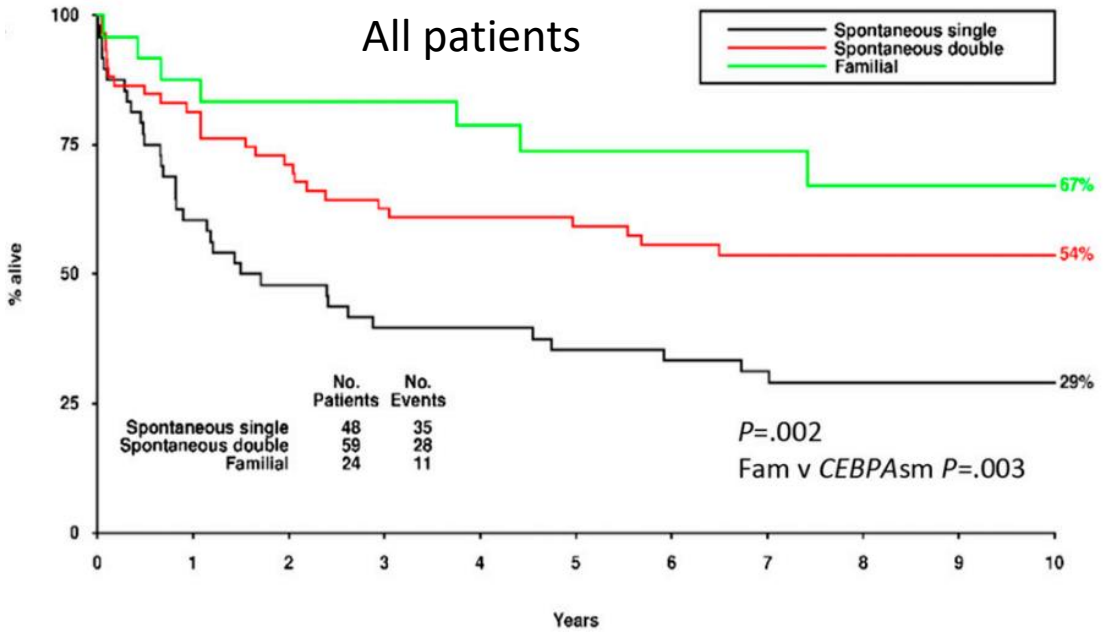
Final Diagnosis and Ancillary Testing

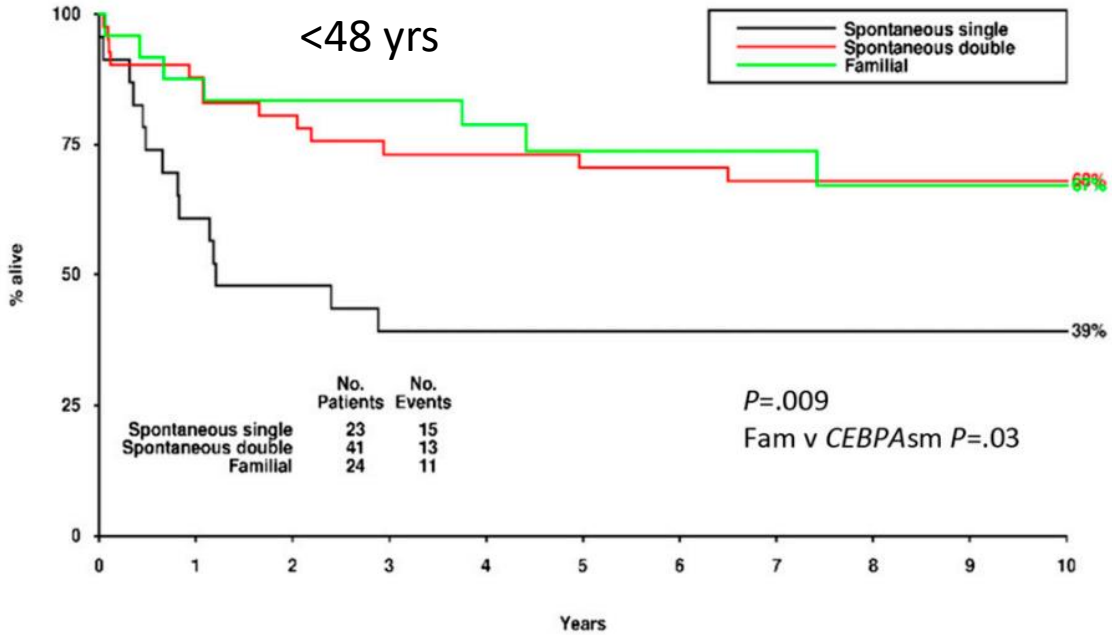
- Acute myeloid leukemia (45% blasts) with biallelic mutation of *CEBPA*
- M2 by flow cytometry
- Cytogenetics: 46,XY[20]

Mutations	Tiers	Initial diagnosis	Post induction
CEBPA c.287_311del, p.G96fs	1	45%	46%
CEBPA c.890G>C, p.R297P	1	42%	0%
GATA2 c.958Gdel, p.G320Sfs	1	6%	0%
KMT2A c.1975G>C, p.E659Q	2	46%	48%

AML with germline *CEBPA* mutations

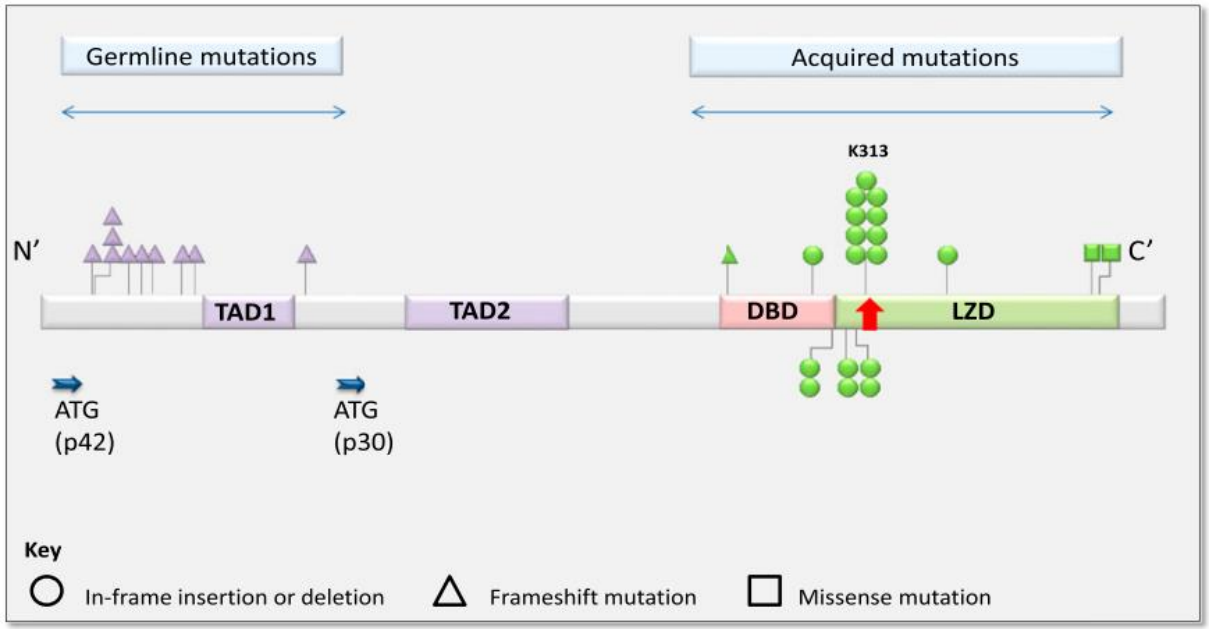
- High penetrance, 10% of all AML with biallelic *CEBPA* mutations
- Early-onset AML
- Favorable survival outcomes

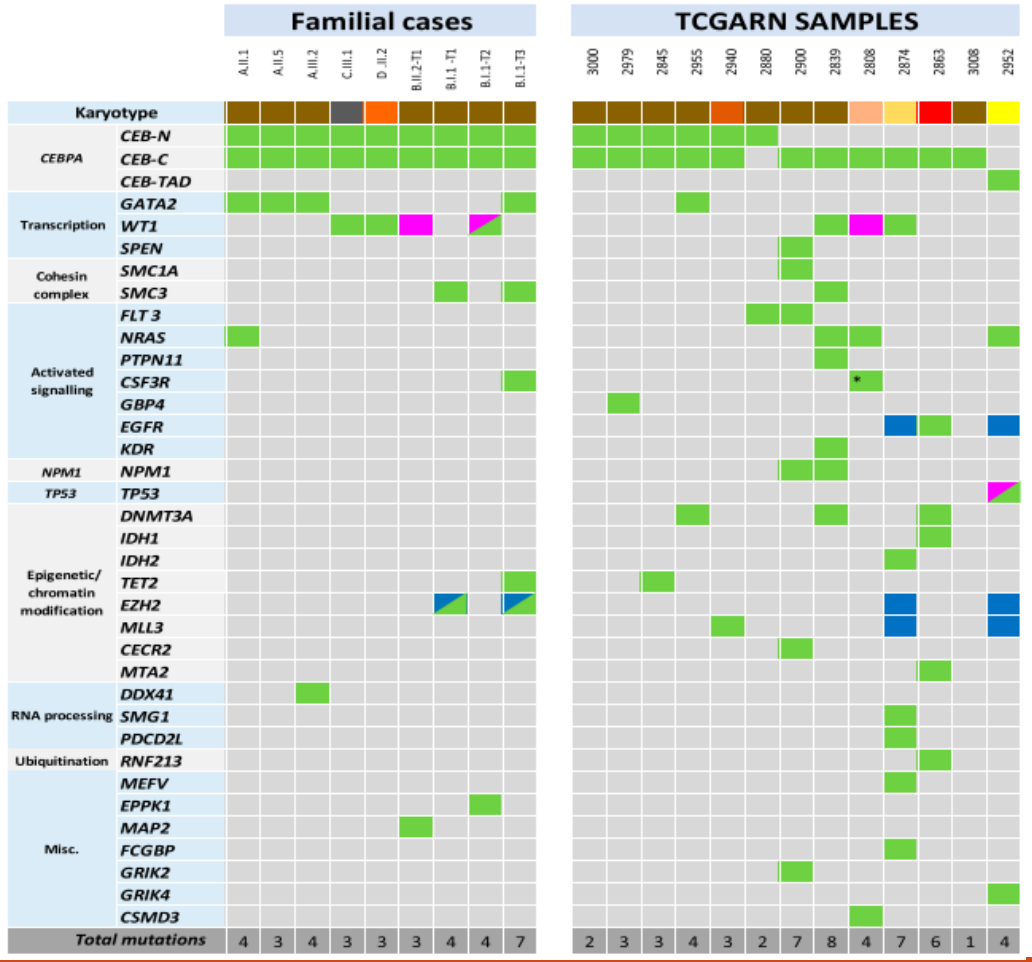




Tawana, Blood 2015

Genetic Profiles of AML with germline CEBPA Mutations

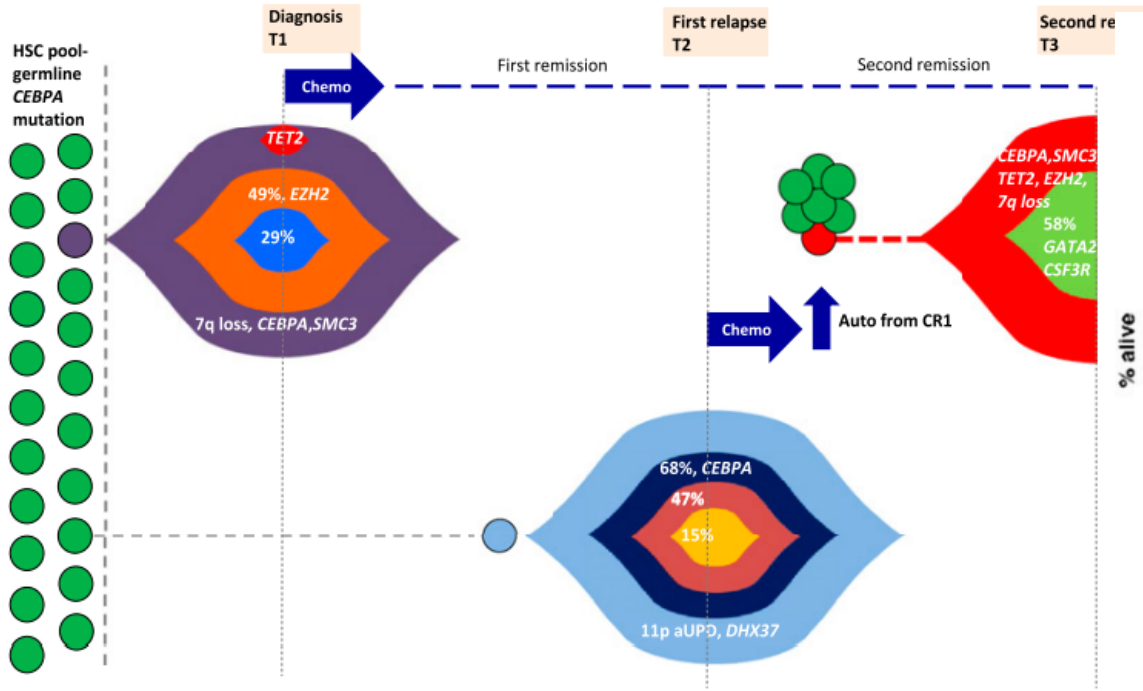


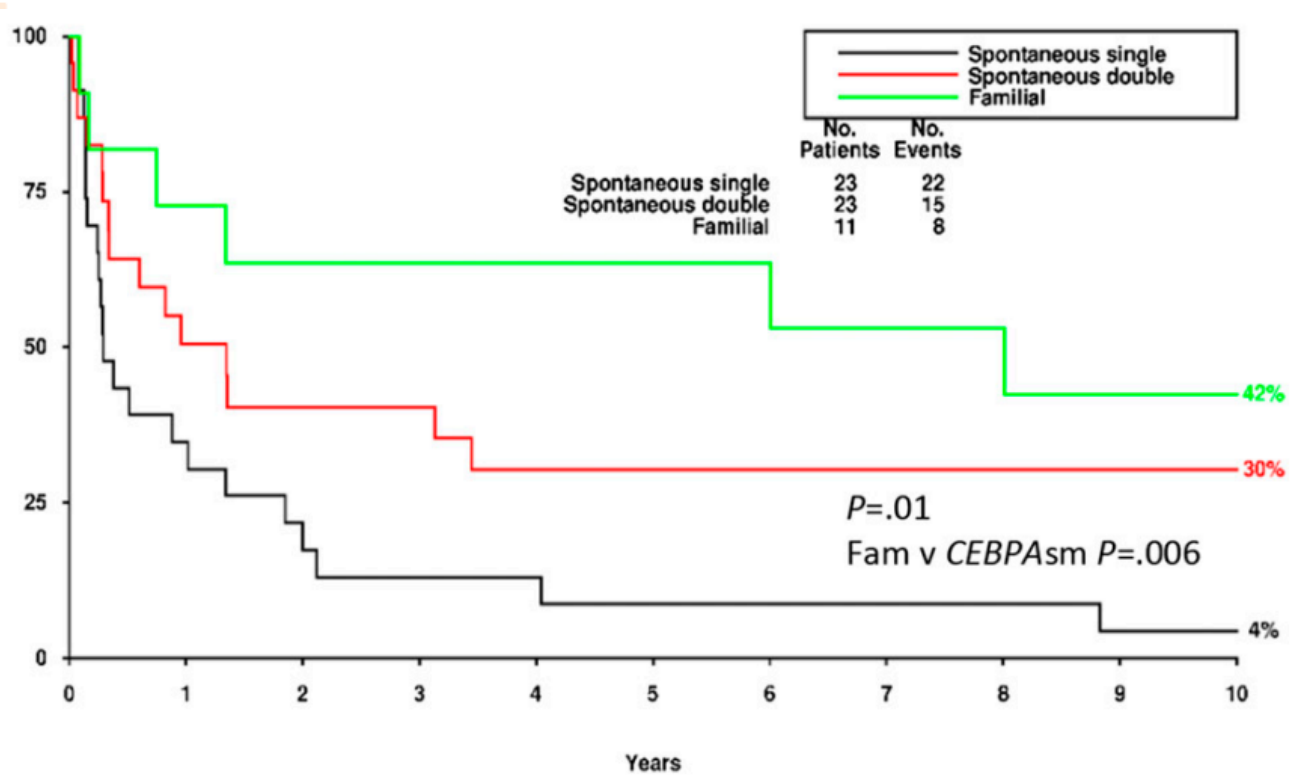


Tawana, Blood 2015

Unique Model of Disease Progression

Recurrence caused by novel, independent leukemic episodes.





Tawana, Blood 2015

Take Home Message – Case #2

- Germline *CEBPA* mutations predispose to AML
- Early onset
- 10% of all AML with biallelic CEBPA mutations
- Favorable survival outcomes
- Recurrence caused by novel, independent leukemic episodes with favorable survival outcomes

Acute Myeloid Leukemia Updates in WHO

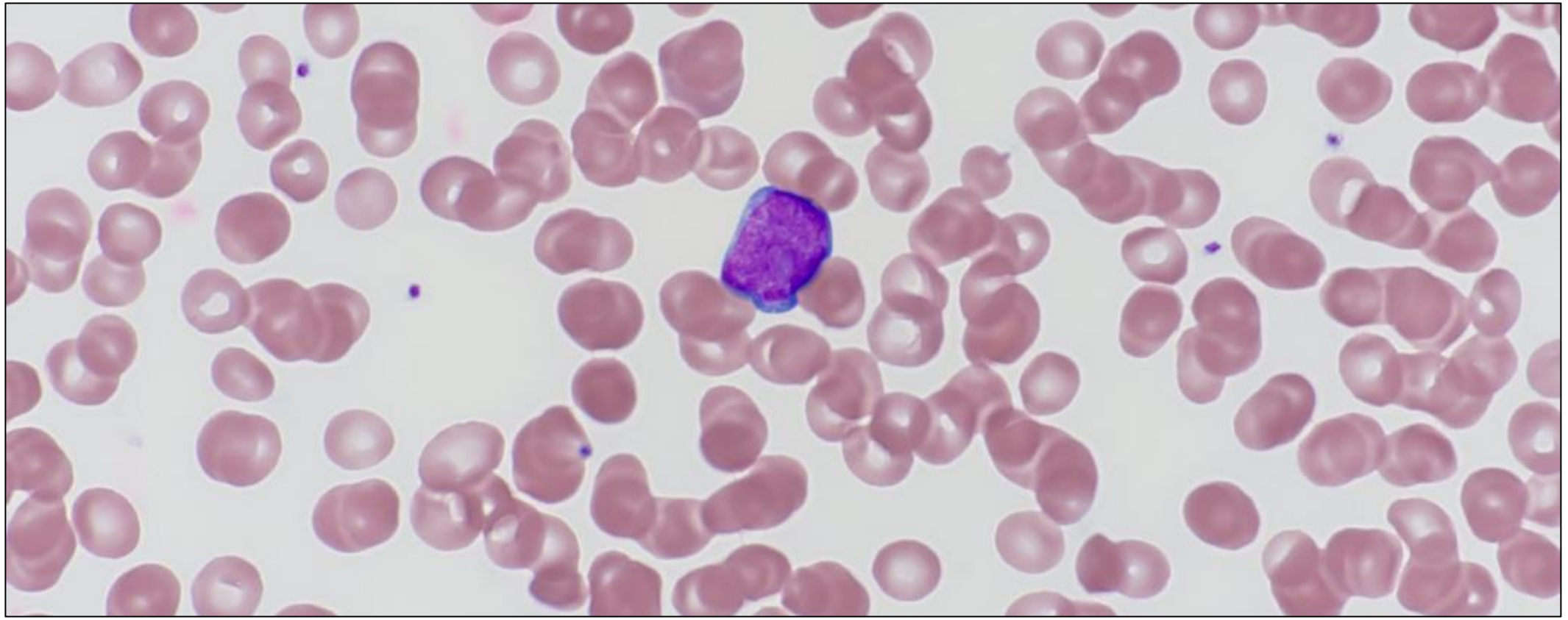
WHO Revised 4th Ed.	WHO 5th Ed.	ICC
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1	AML with RUNX1::RUNX1T1 fusion	AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 ≥10%
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	AML with CBFB::MYH11 fusion	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 ≥10%
APL with PML-RARA	Acute promyelocytic leukemia (APL) with PML::RARA fusion	APL with t(15;17)(q24.1;q21.2)/PML::RARA ≥10%
Not included	Currently mentioned in text	APL with other RARA rearrangements[1] ≥10%
AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3	Included in AML with KMT2A rearrangement	AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A ≥10%
Not included	AML with KMT2A rearrangement	AML with other KMT2A rearrangements[2] ≥10%
AML with t(6;9)(p23;q34.1); DEK-NUP214	AML with DEK::NUP214 fusion	AML with t(6;9)(p22.3;q34.1)/DEK::NUP214 ≥10%
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	Included in AML with MECOM rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1) ≥10%
Mentioned in text	AML with MECOM rearrangement	AML with other MECOM rearrangements[3] ≥10%
AML with t(1;22)(p13.3;q13.1); RBM15-MKL1	AML with RBM15::MRTFA fusion	Included in AML with other rare recurring translocations ≥10%
AML with BCR-ABL 1	AML with BCR::ABL1 fusion*	AML with t(9;22)(q34.1;q11.2)/BCR::ABL1 ≥20% blasts*
Not included	**AML with NUP98 rearrangement**	Included in AML with other rare recurring translocations ≥10%
Not included	**AML with other defined genetic alterations**	**AML with other rare recurring translocations**
AML with mutated NPM1	AML with NPM1 mutation	AML with mutated NPM1 ≥10%
AML with biallelic mutation of CEBPA	AML with **CEBPA mutation***	AML with **in-frame bZIP** CEBPA mutations ≥10%
AML with mutated RUNX1	**Not included**	**Not included**
Not included	Not included	**AML and MDS/AML with mutated TP53 10-19% (MDS/AML) and ≥ 20% (AML): at least one TP53 mutation with VAF >10%**

Case #3 Brief History

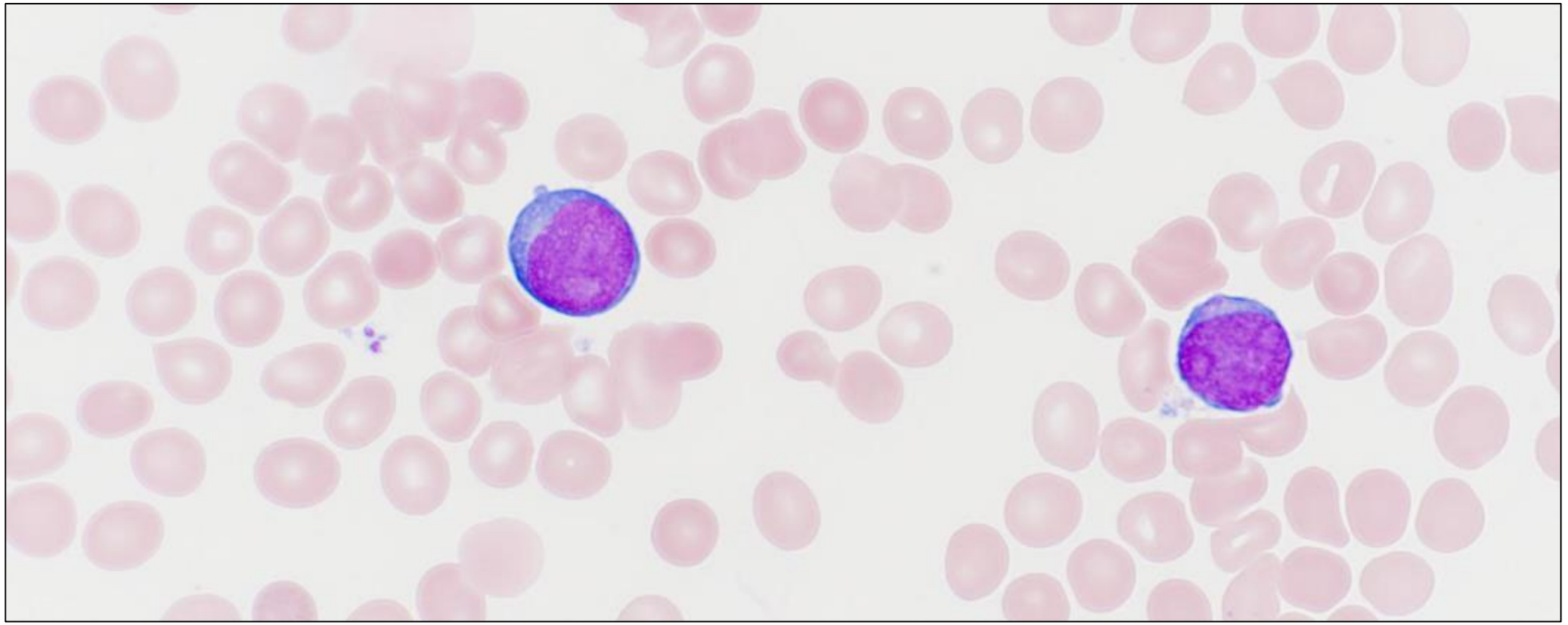
- 77 year old male with fatigue who was found to have pancytopenia for one year
- Bone marrow bx was performed

CBC (Reference)	Count
WBC (4.3 –11.3 x 10^9/L)	2.7 ⇩
Hemoglobin (14.8 – 17.8 g/dL)	10.9 ⇩
MCV (81.2 – 96.6 fL)	114 ⇧
Platelets (159 – 439 10^9/L)	77 ⇩
ANC (2.0 – 7.4 x 10^9/L)	1.6 ⇩

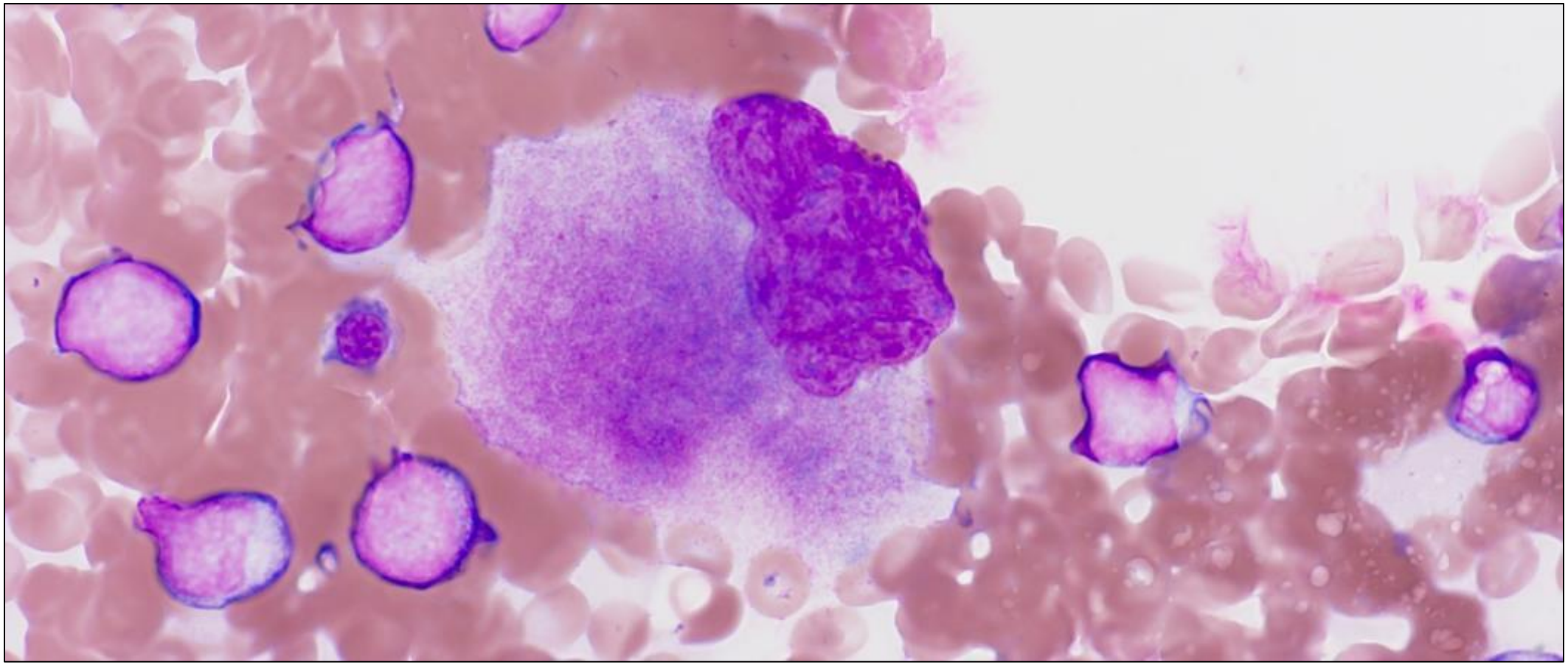
Peripheral Blood Findings



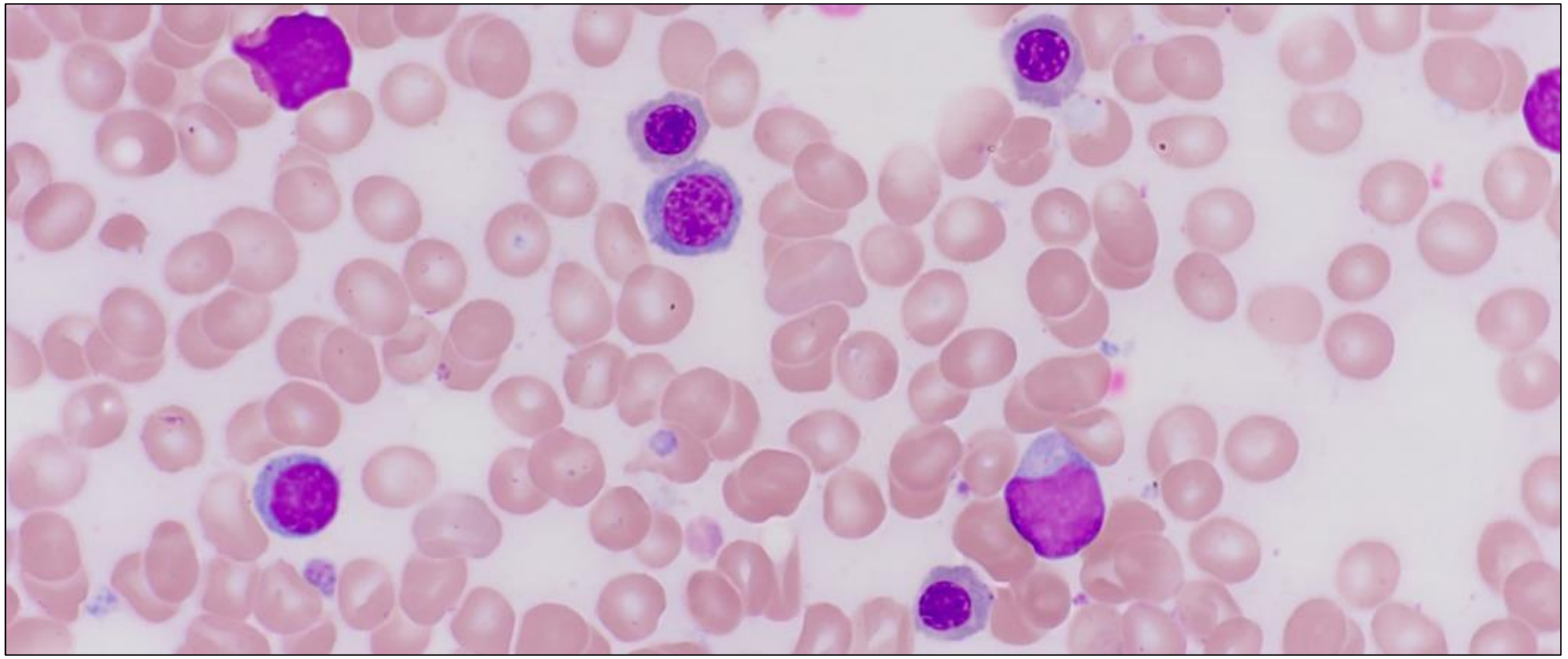
Bone Marrow Findings



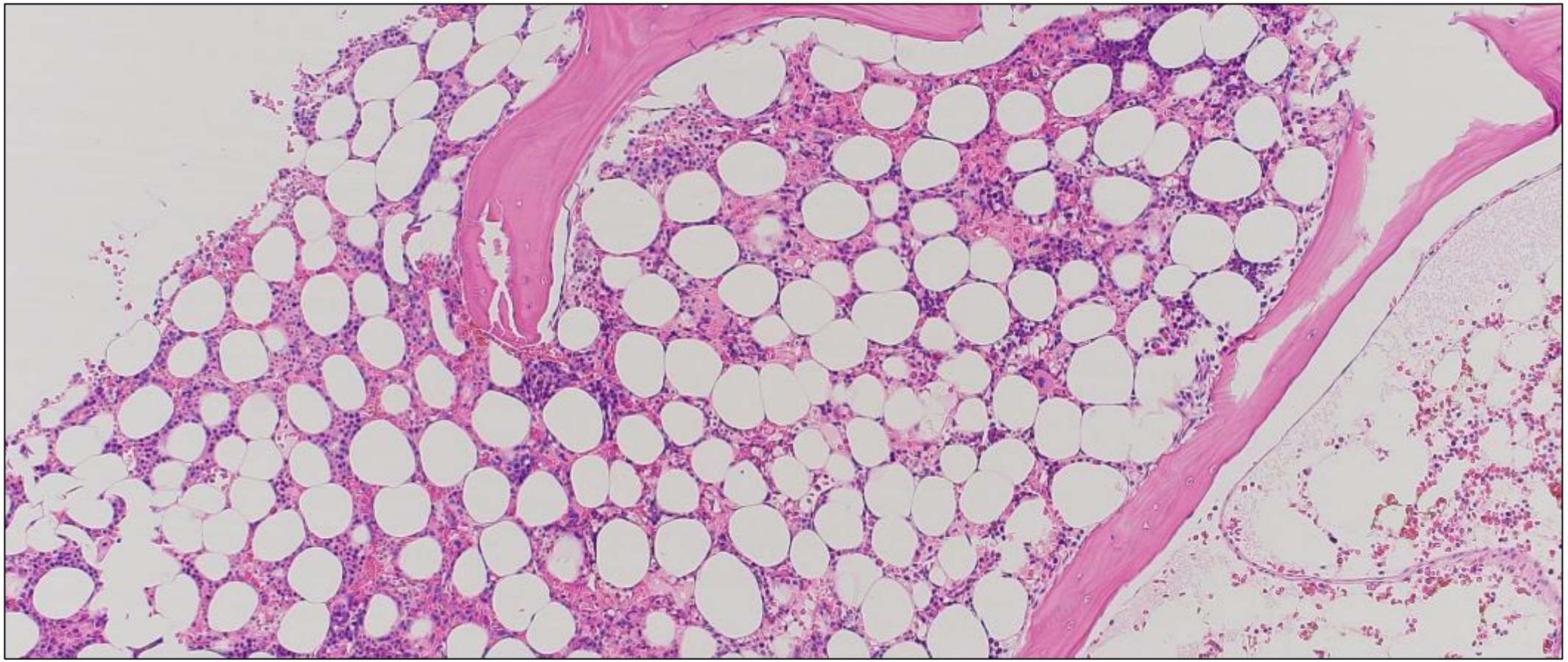
Bone Marrow Findings



Bone Marrow Findings

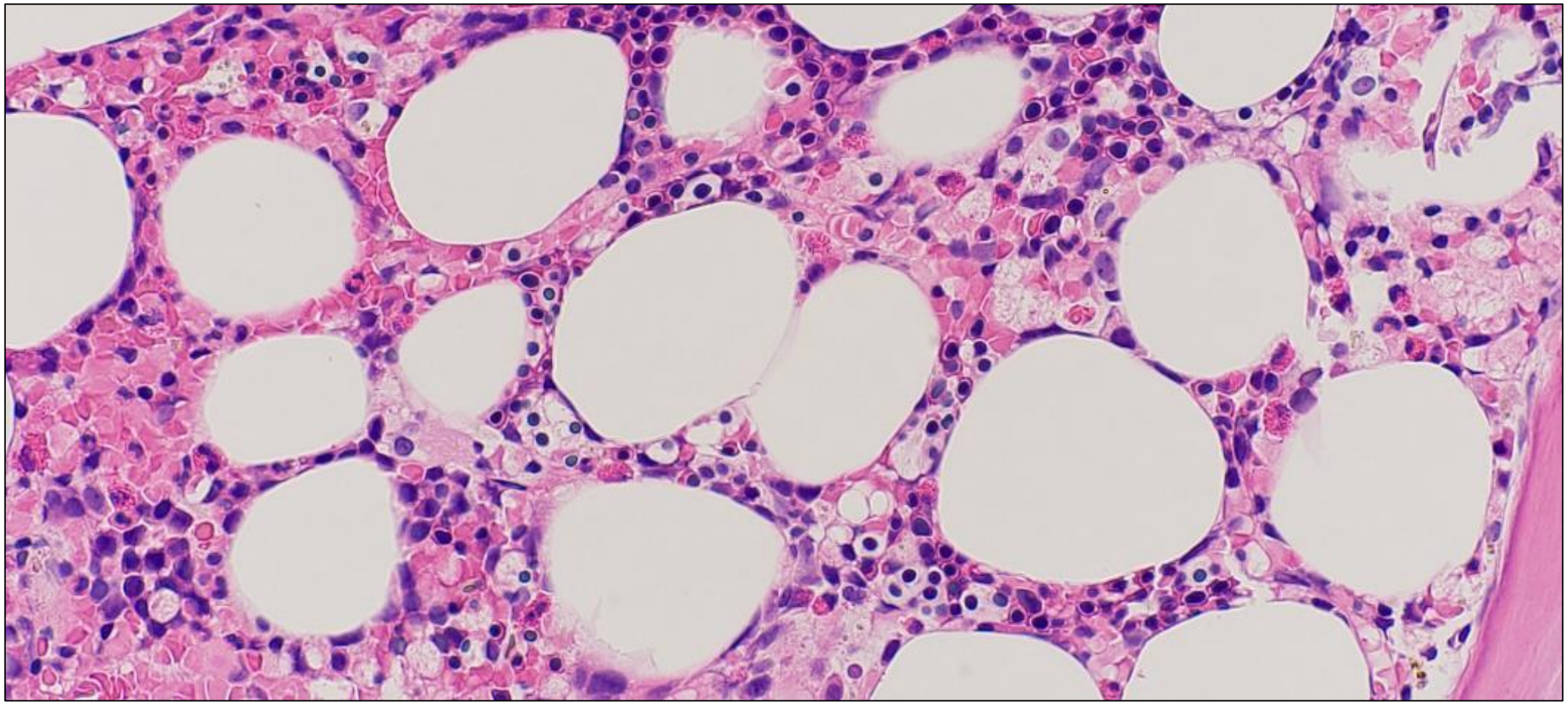


Bone Marrow Biopsy



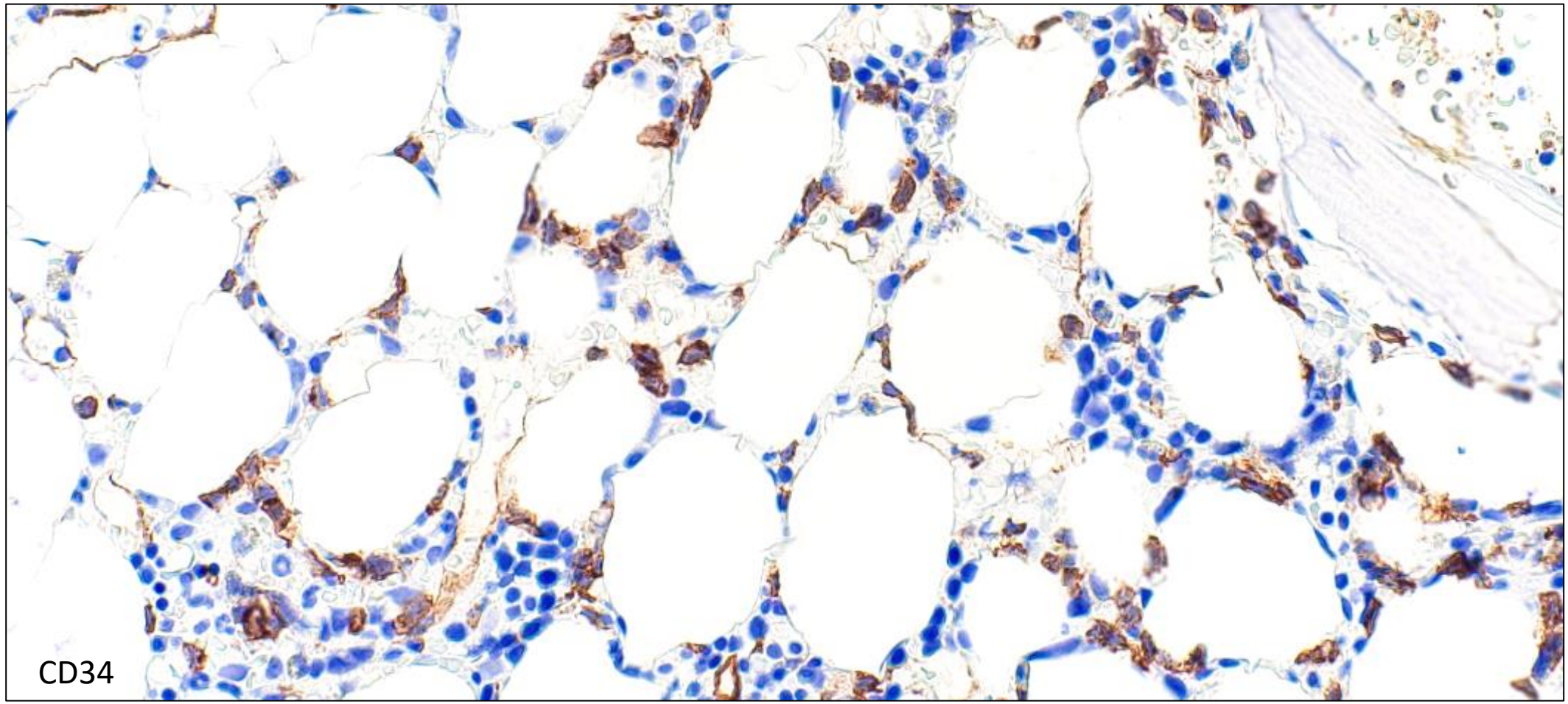
Li et al. Leukemia, 2021

Bone Marrow Biopsy



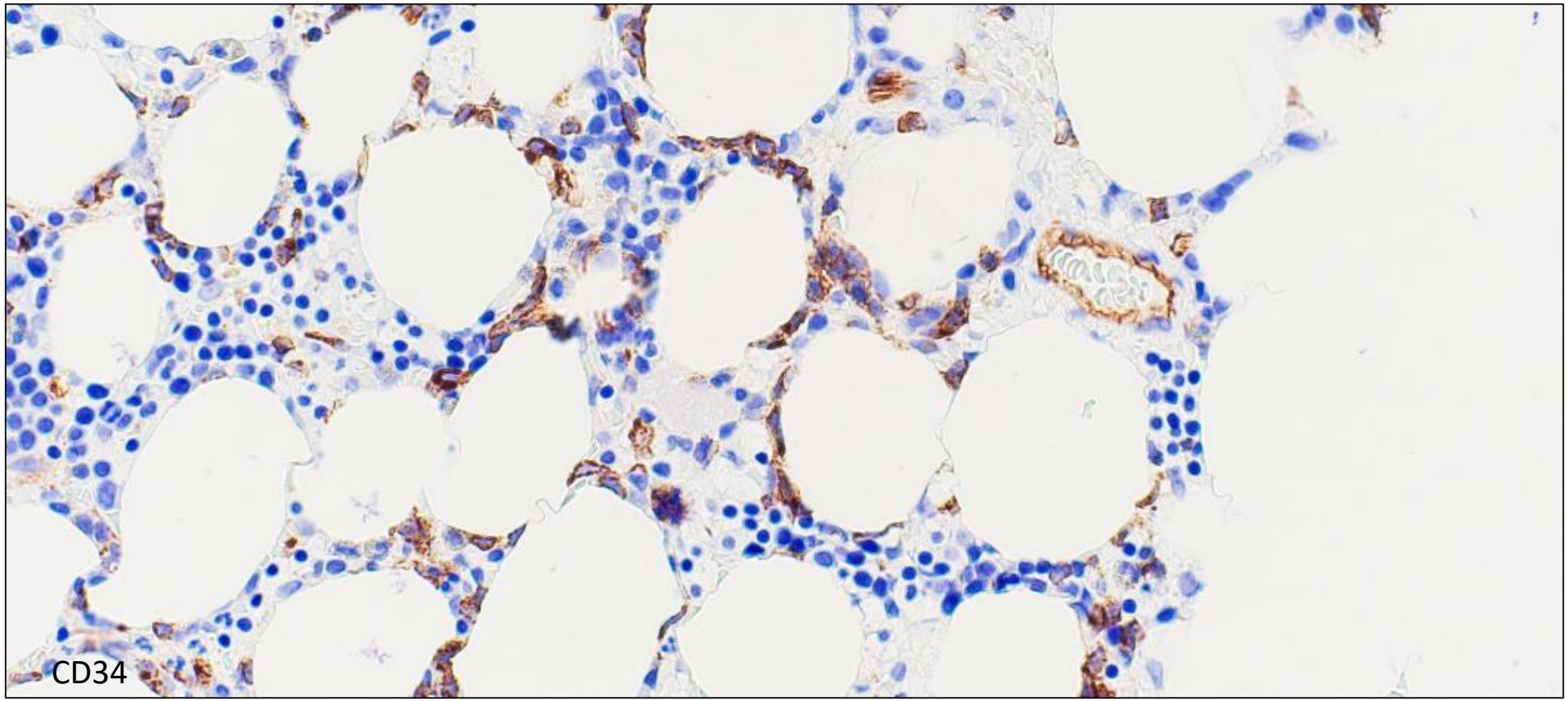
Li et al. Leukemia, 2021

Bone Marrow Biopsy



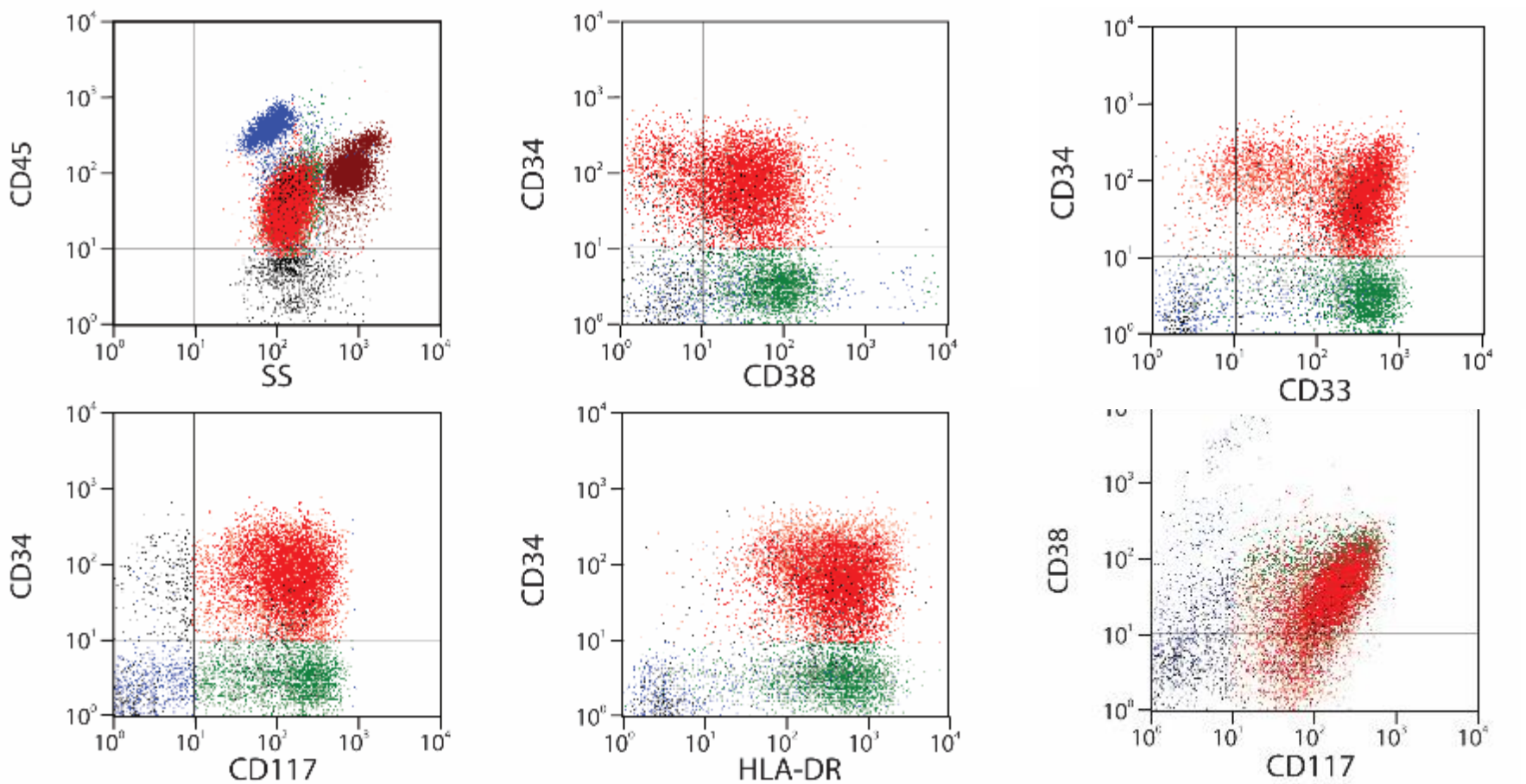
Li et al. Leukemia, 2021

Bone Marrow Biopsy



Li et al. Leukemia, 2021

Flow Cytometry



Li et al. Leukemia, 2021

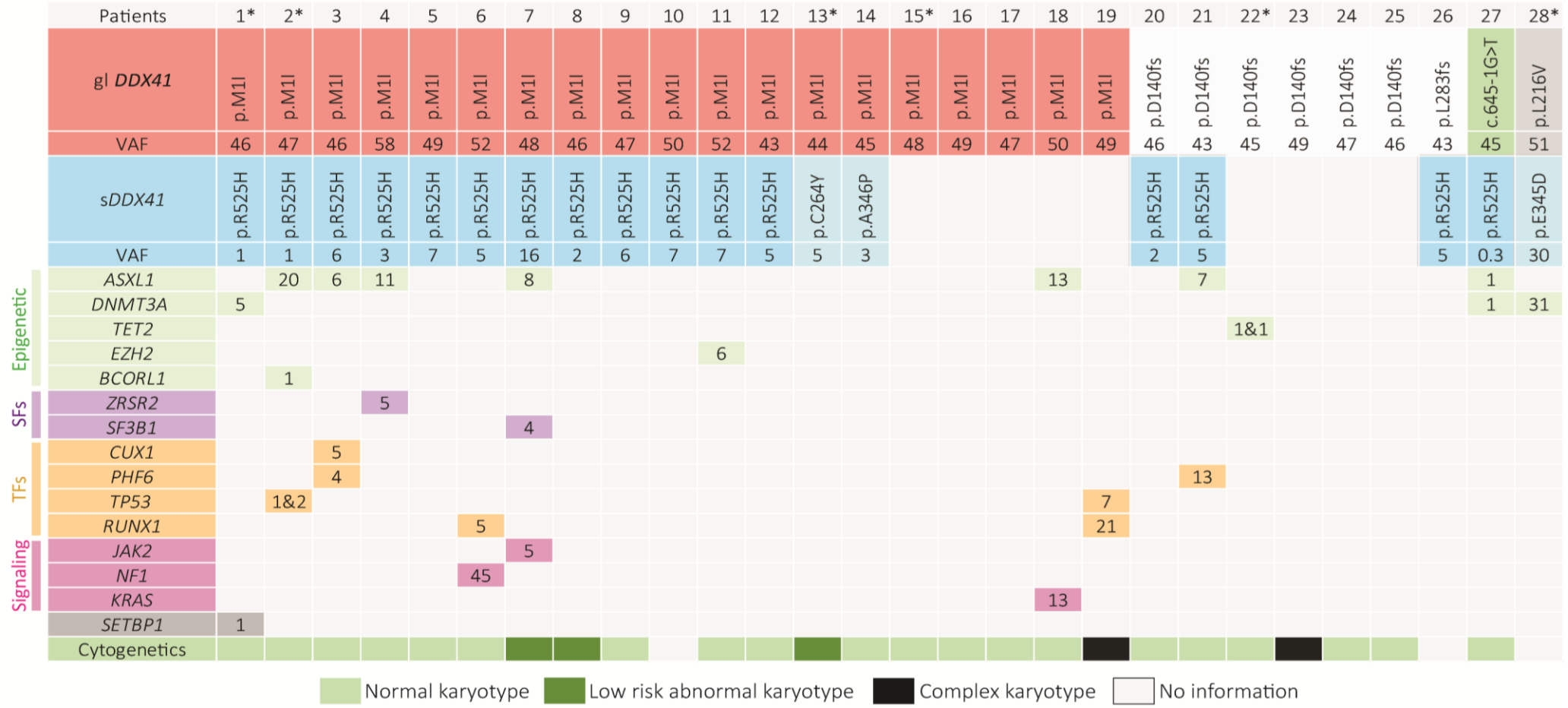
Ancillary Studies

- Iron stain: adequate storage iron and no ring sideroblasts
- Reticulin stain: MF-1
- Cytogenetics
  - 46,XY[20]

Summary

- Old patient with chronic pancytopenia
- Rare circulating blasts
- Normo/hypocellular marrow with borderline increase in blasts (approximately 20-30%)
- No ring sideroblasts or overt dysplasia
- Normal cytogenetics
- NGS findings

NGS findings



Li et al. Leukemia, 2021

Article

Cancer Cell

Inherited and Somatic Defects in *DDX41* in Myeloid Neoplasms

Highlights

- *DDX41* represents a class of tumor suppressor genes in myeloid neoplasms
- Somatic missense mutations in *DDX41* can be found in AML
- Germline *DDX41* mutations predispose to somatic *DDX41* mutations as a secondary hit
- *DDX41* expression is haploinsufficient in cases with del(5q) involving *DDX41* locus

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Prevalence of Germline DDX41 Mutation

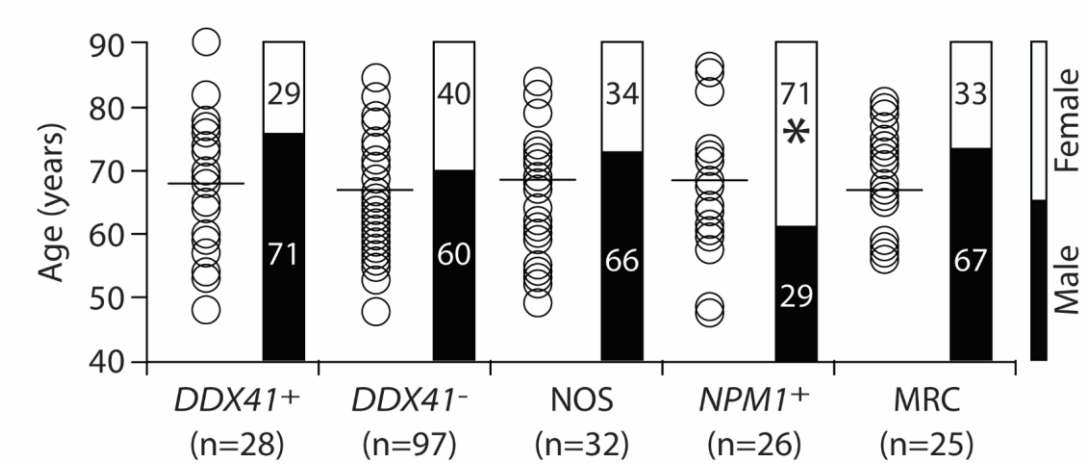
- Prevalence of familial MN with DDX41 mutation
  - Approximately 3% of index family with history, 5% of all newly diagnostic AML
- Prevalence of sporadic MN with DDX41 mutation
  - 3.0% (41/1406) of AML patients, 5% of adult AML and 7% of AML at age of 48 years and above
  - 1.4% (16/1125) of MDS patients
  - 2.0% (10/489) of MPN patients
- The prevalence of *DDX41*-related lymphoma is uncertain

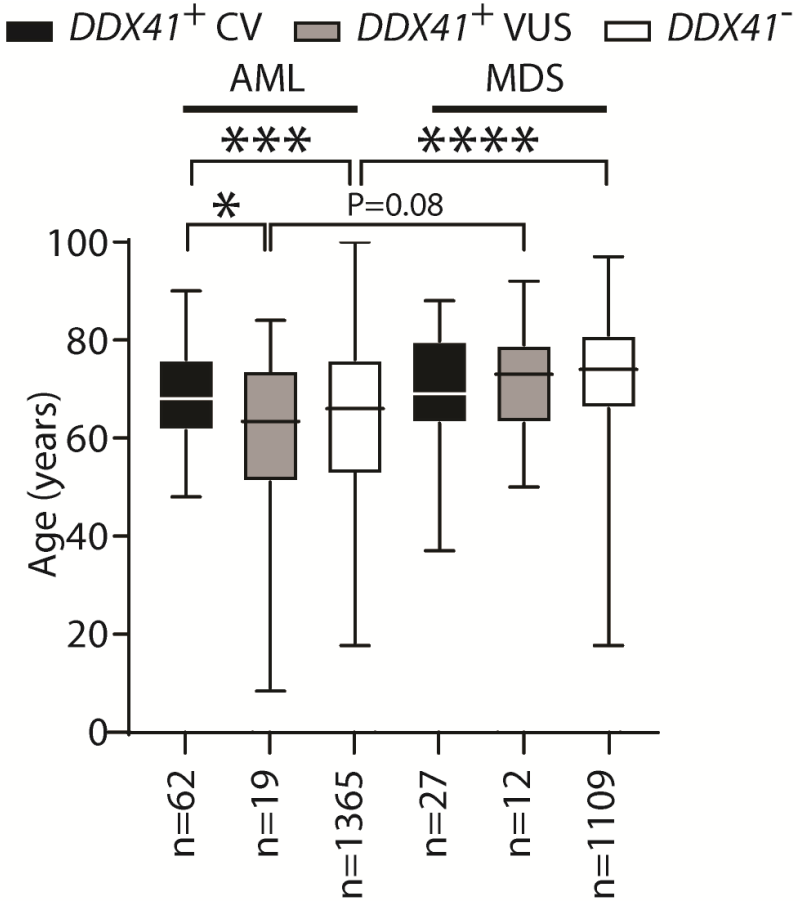
Sanders, Blood, 2019; Li, Blood, 2022

Patient's Gender and Age

- Marked male predominance (92%, Cleveland)
- Male predominance (76%, MD Anderson)

Parameter	Value
Men	26 (76%)
Women	8 (24%)





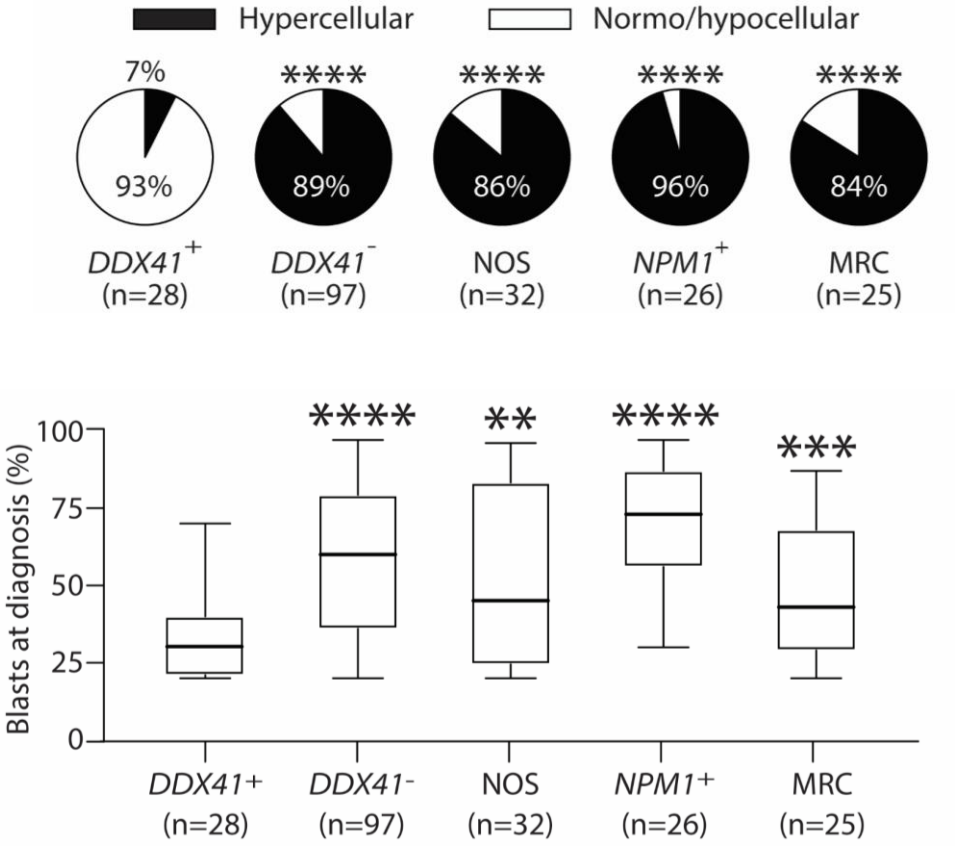
Li et al, Leukemia, 2021; Quesada et al, Am J Hematol 2019; Polprasert et al. Cancer Cell, 2015

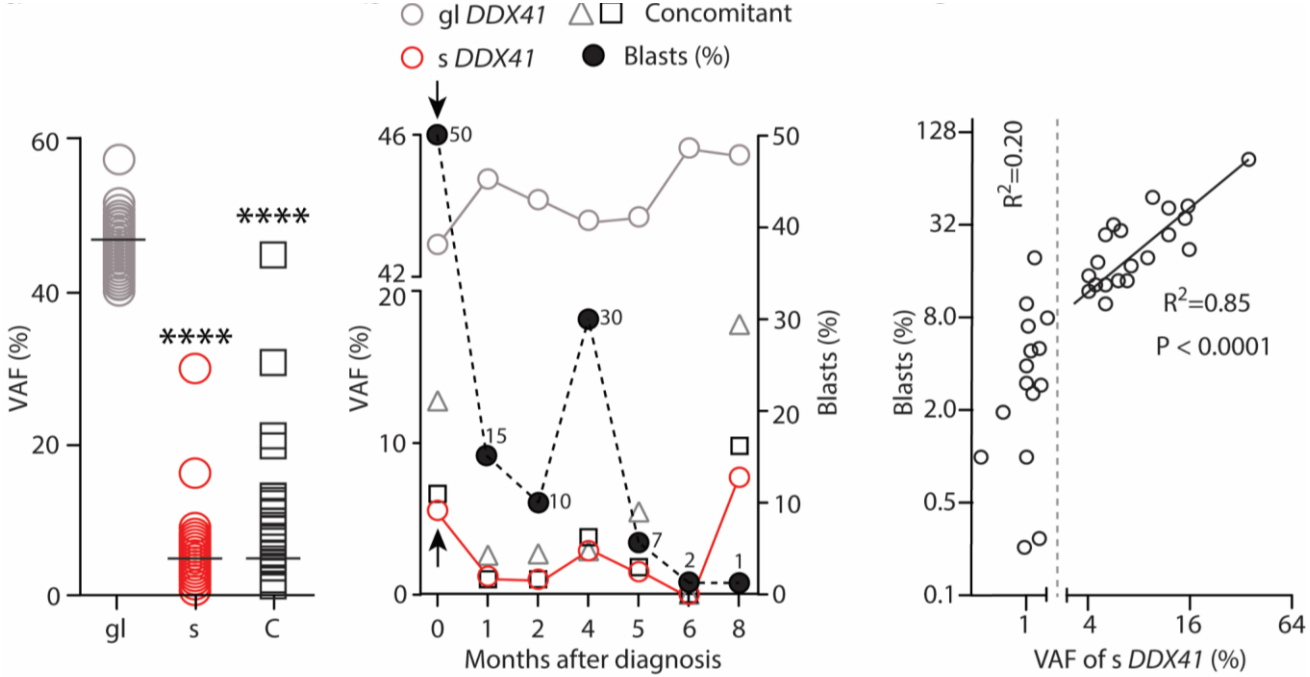
Clinical Manifestations of DDX41 Mutant AML/MDS

- Chronic cytopenia prior to initial AML diagnosis
- Manifest at an old age overlapping with sporadic AML/MDS
- No prior history or extramedullary manifestation
- Approximately 20% of all patients have family history of myeloid neoplasms

Quesada et al, Blood, 2019 Li, et al, Leukemia, 2022; Li, et al, Blood, 2022

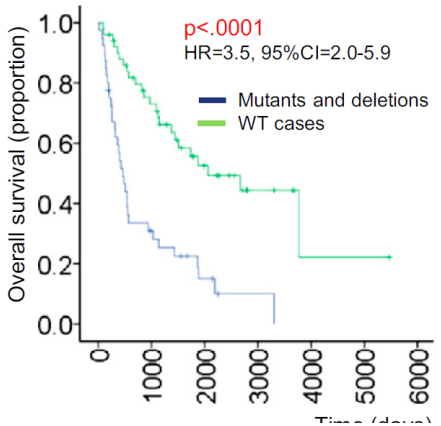
Pathologic Features

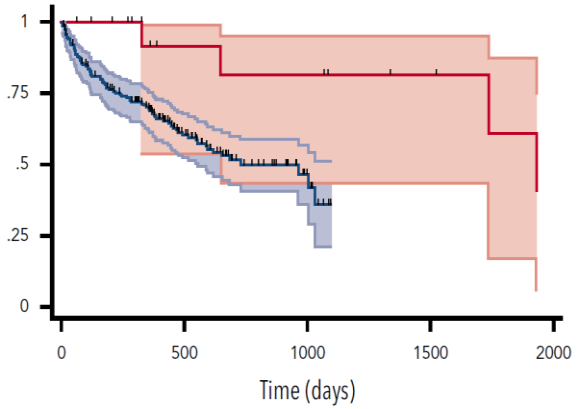


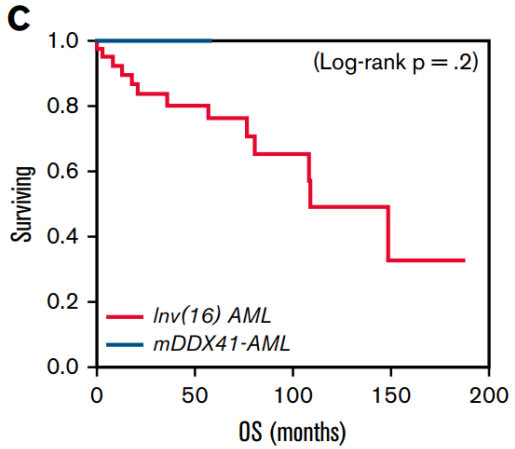


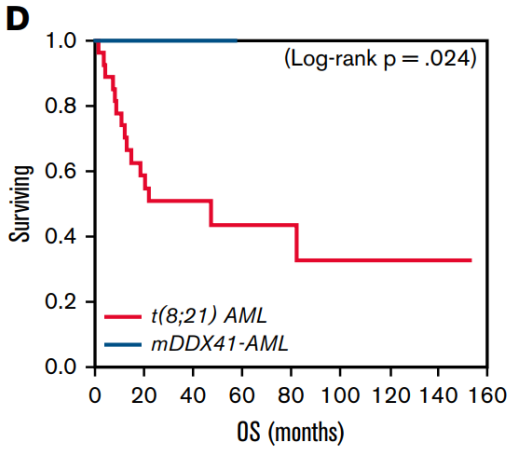
Li et al. Leukemia, 2021

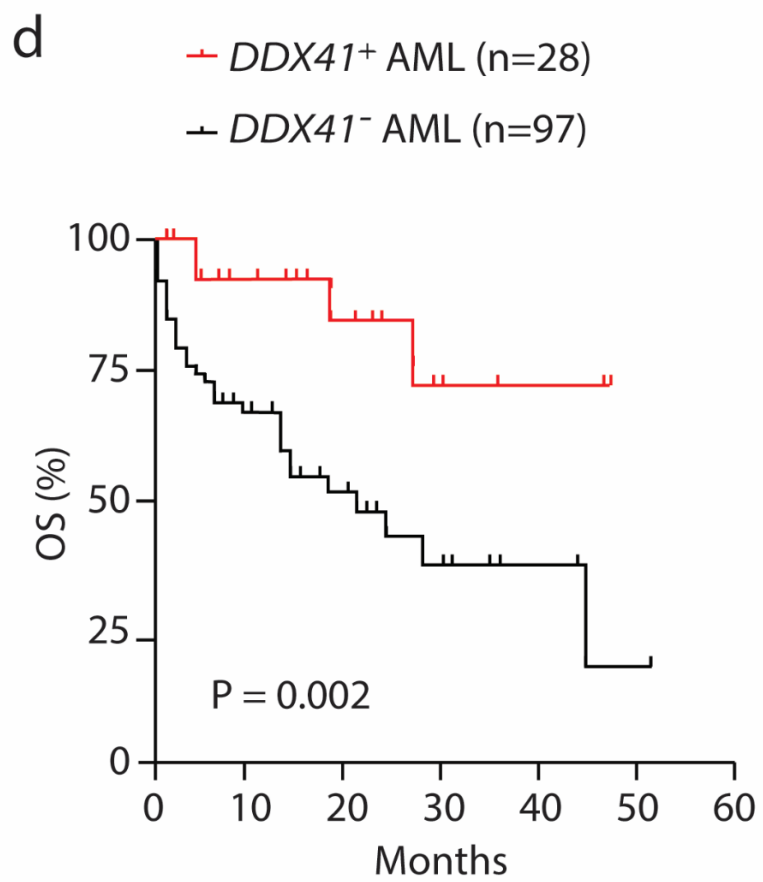
Overall Survival





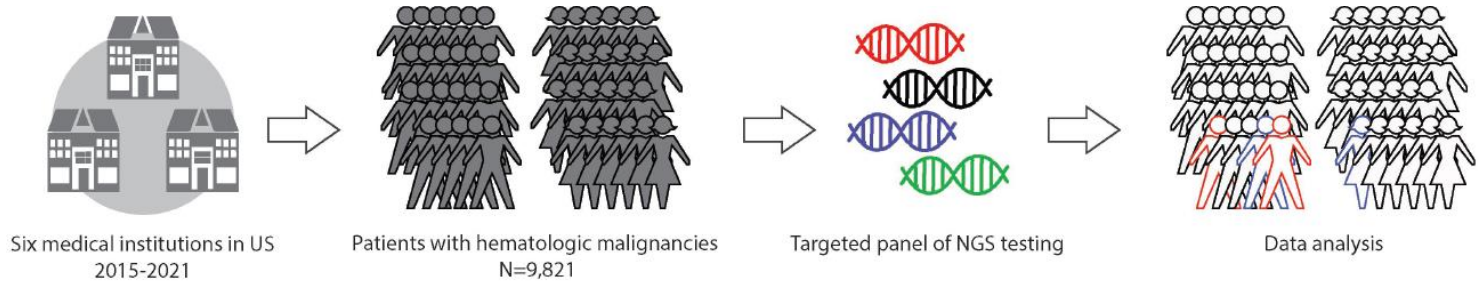


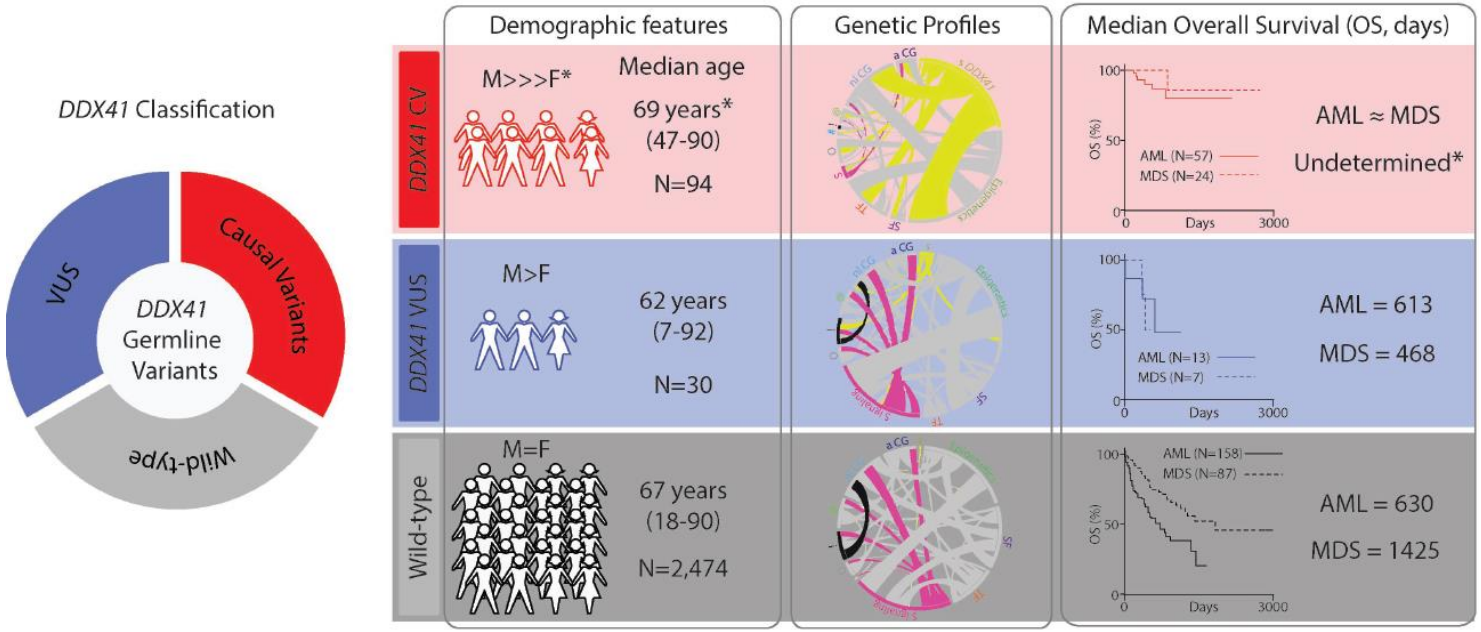




Polprasert et al. Cancer Cell, 2015; Quesada et al, Blood, 2019; Li et al. Leukemia, 2021; Alkhateeb et al. Blood Adv., 2021

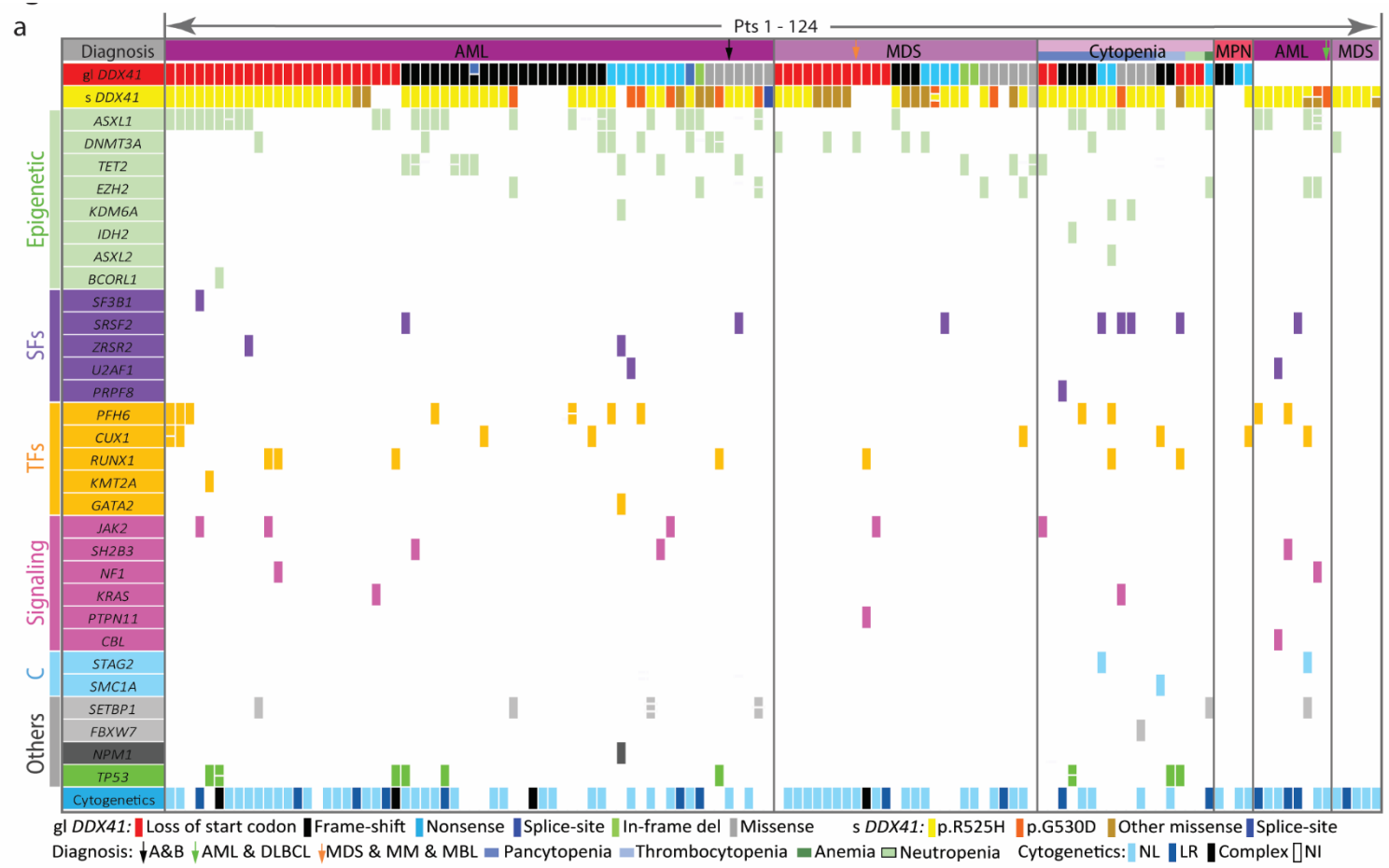
Landscape of Causal DDX41 Mutations

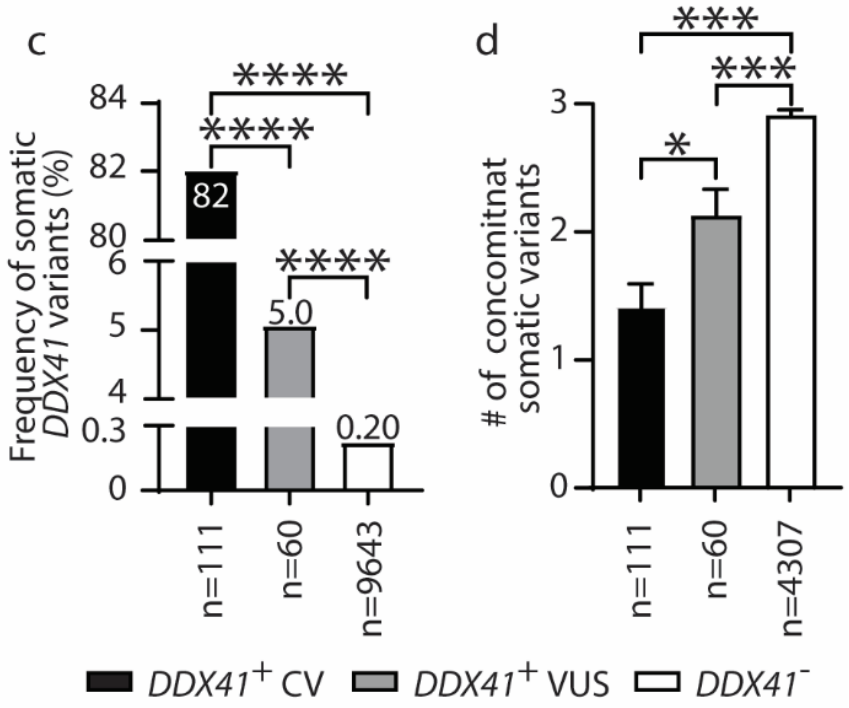




Li et al., Blood, 2022

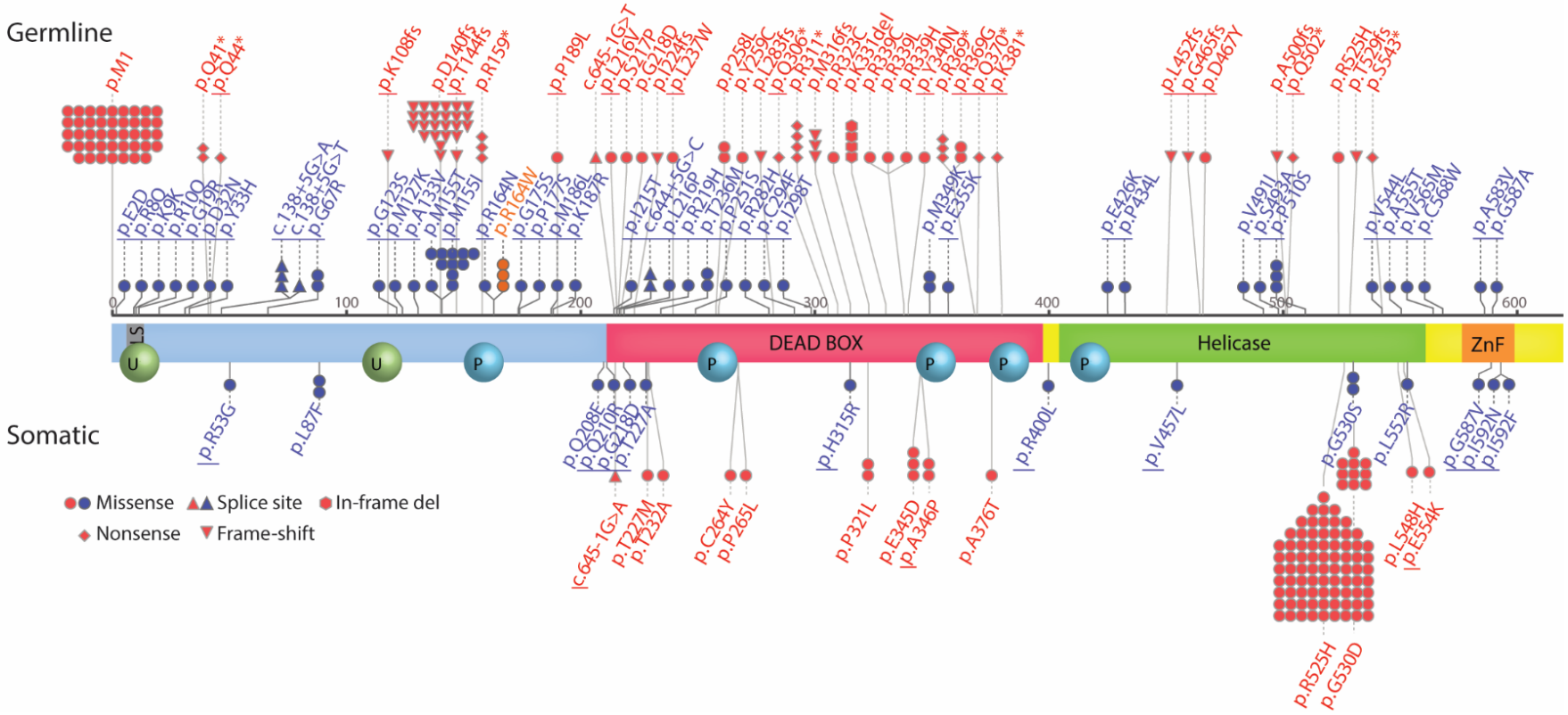
Landscape of Causal DDX41 Mutations

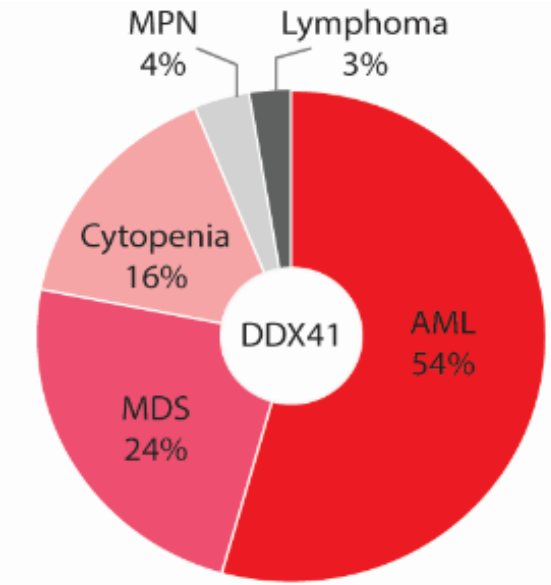




Li et al., Blood, 2022

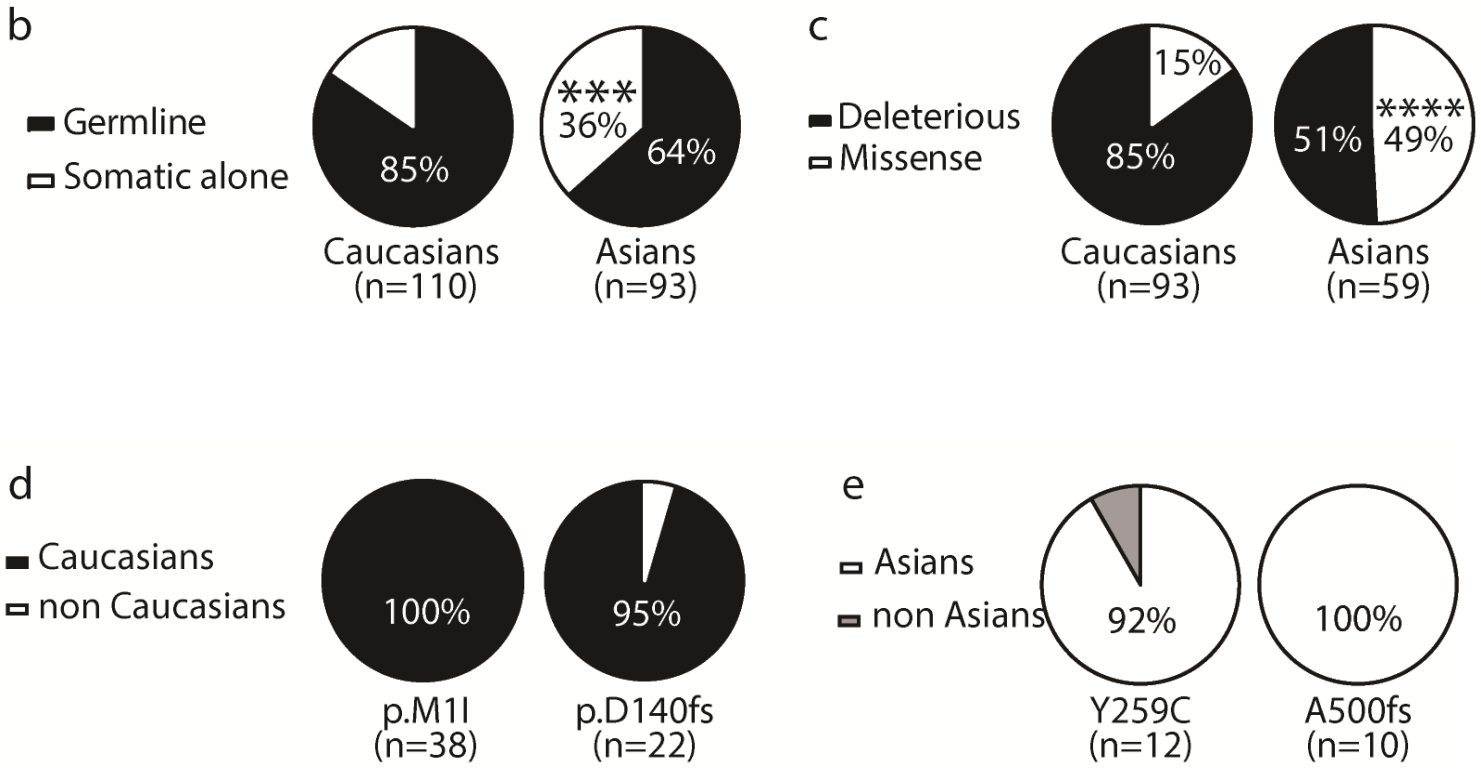
Landscape and Disease Spectrum





Li et al., Blood, 2022

Ethnic Difference



Li et al., Blood, 2022

Take Home Message – Case #3

- *DDX41* mutations predispose to myeloid and lymphoid neoplasms
- Most common gene mutation in hereditary myeloid neoplasms in adults
- A clinically distinct AML/MDS is the most common disease
  - Indolent course of cytopenia
  - Favorable overall survival
  - Most response to hypomethylation agents or 7+3 and achieve CR
  - Male predominance in the elderly
- Often lack of FH (20% with family history of MNs)
- Asymptomatic carrier and BMT donor selection

Li et al., Blood, 2022

Presentation Outline

- Clinical utilities of NGS testing
- Different types of NGS based testing for tumors
- Updates in common myeloid neoplasms with germline predisposition
- Challenges and future directions
- Take home message

Challenges and future directions

- Prevalence of each hematologic malignancy with germline predisposition
- Complete genetic landscape of causal variants of each gene (intronic variants)
- Complete disease spectrum
- Mechanisms of underlying pathogenesis (potential therapy)
- Gene-specific diagnostic and management guidelines

Take Home Message

- Rare disease is becoming more common
- Myeloid neoplasms with germline predisposition
  - *GATA2*
  - *CEBPA*
  - *DDX41*
- Gene-specific diagnostic and management guidelines