EHA 30 YEARS EUROPEAN HEMATOLOGY ASSOCIATION

UNIVERSITÄTS KLINIKUM FREIBURG
ZKJ ZENTRUM FÜR KINDER- UND JUGENDMEDIZIN

Pediatric versus Adult Myelodysplastic syndrome (MDS)

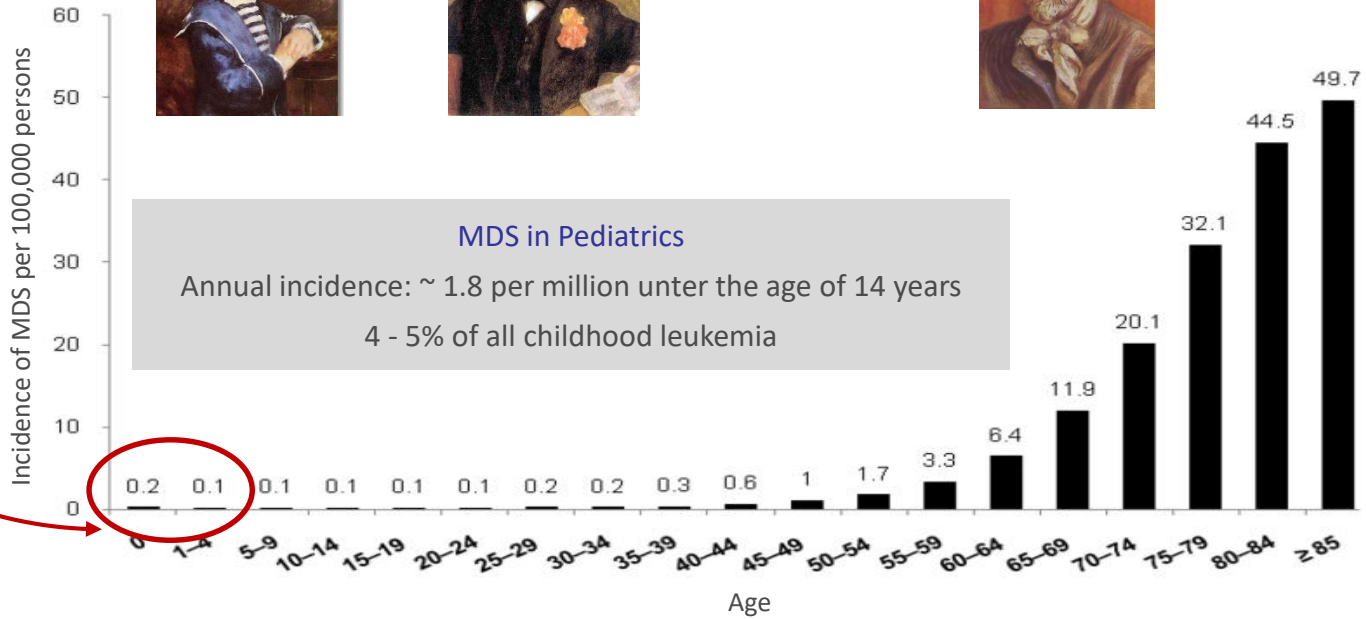
Charlotte Niemeyer MD
Klinik für Pädiatrische Hämatologie und Onkologie
Zentrum für Kinder- und Jugendmedizin
Universitätsklinikum Freiburg

Disclosure of Potential Conflicts of Interest
Charlotte M. Niemeyer

1. Employment / Leadership Position	none
2. Advisory Role	BMS, Novartis, Apriligen
3. Stock Ownership	none
4. Honoraria	none
5. Financing of Scientific Research	none
6. Expert Testimony	none
7. Other Financial Relationships	none

Incidence rate of MDS in different age groups

(adapted from NCI SEER*Stat Database for 2001 – 2008)



MDS in Pediatrics

Annual incidence: ~ 1.8 per million unter the age of 14 years

4 - 5% of all childhood leukemia

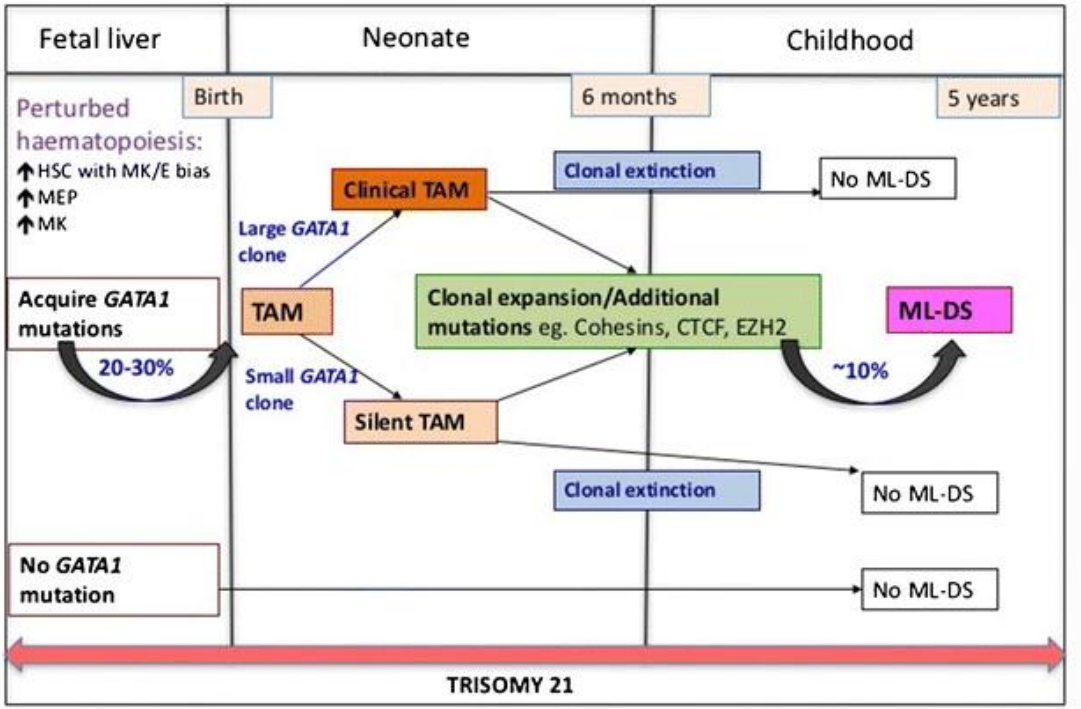
Xiaomei Ma: Epidemiology of Myelodysplastic Syndrome 2012. Am J Med:125 (7Suppl): S2-25

Pediatric versus adult myelodysplastic syndrome (MDS)

Pediatric	Adult
Nature of the disorder	
Germline predisposition	
Perturbed fetal hematopoiesis	Aging hematopoiesis
Perturbed postnatal hematopoiesis	
Nature of the host	
Young individual	Older individual
Plasticity of hematopoiesis	
Intensive Therapy - HSCT	Palliation

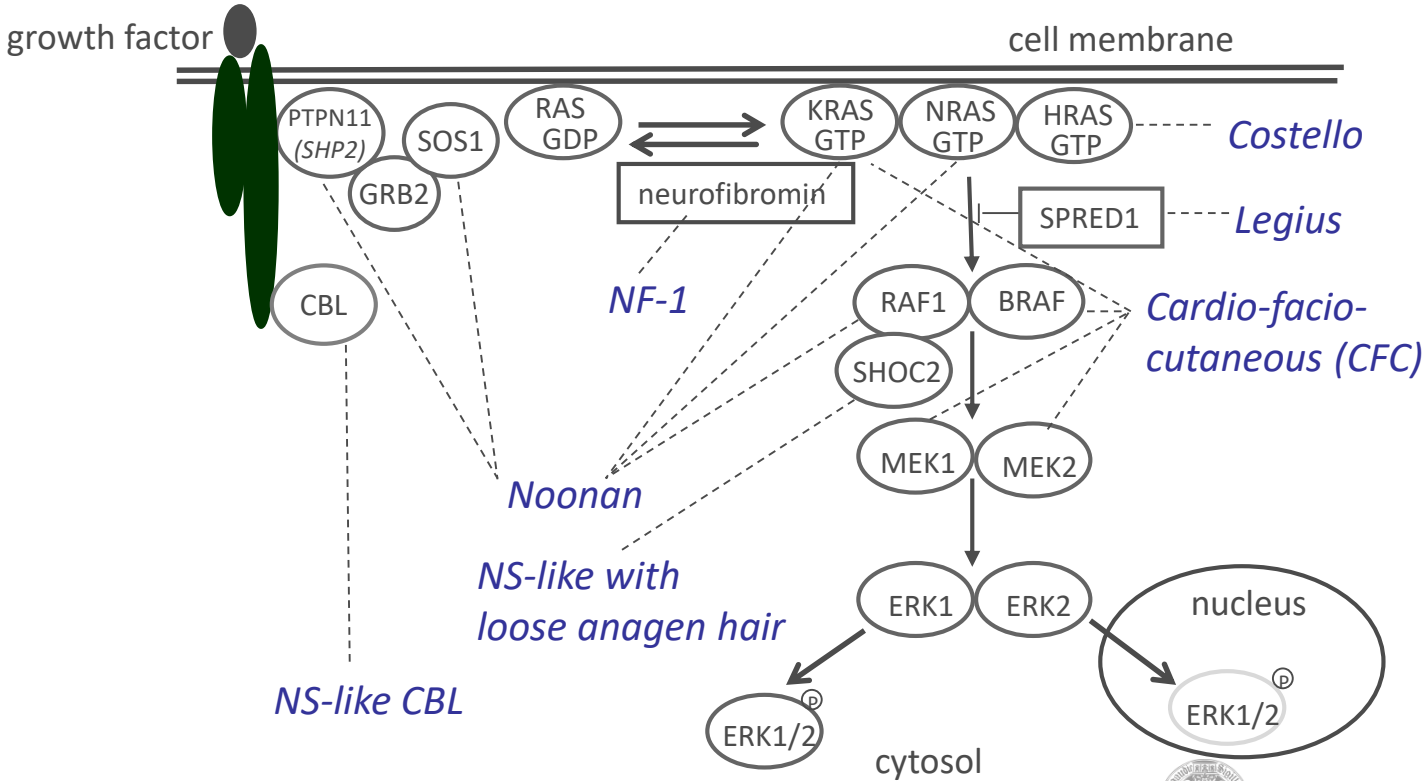
→ Classification

Natural history and pathogenesis of transient abnormal myelopoiesis (TAM) and myeloid leukemia of Down syndrome



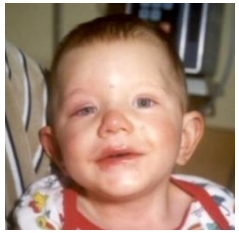
Bhatnagar N et al. Current Hematologic Malignancy Reports 11: 333–341. 2016

RASopathies are clinically overlapping dominant disorders with cancer susceptability



Adapted from Niemeyer C Hematologica 2014, 99: 653

Noonan syndrome-associated myeloprolif. disorder can clinically present like JMML



with permission

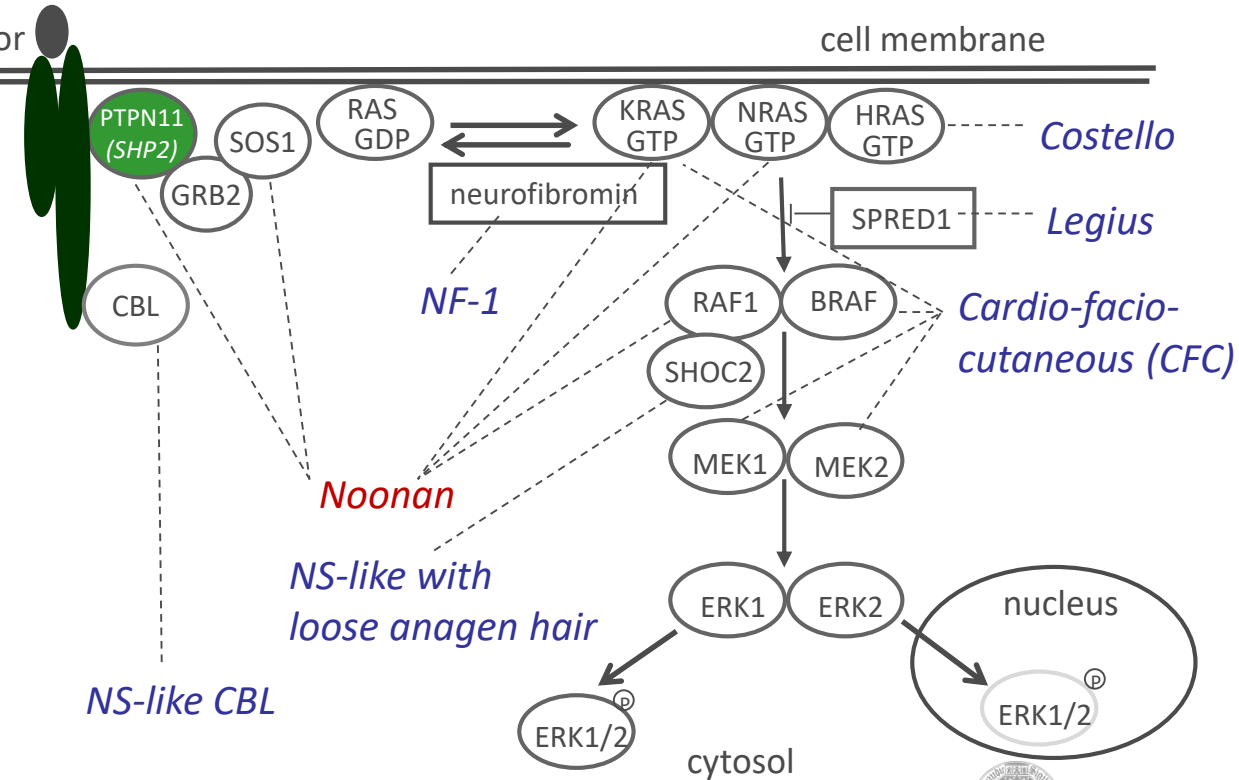
Noonan syndrome

Developmental disorder with:

- typical facial features
- short neck
- cardiac anomalies (pulmonic stenosis)
- chest deformity
- cryptorchism
- proportional short stature
- failure to thrive

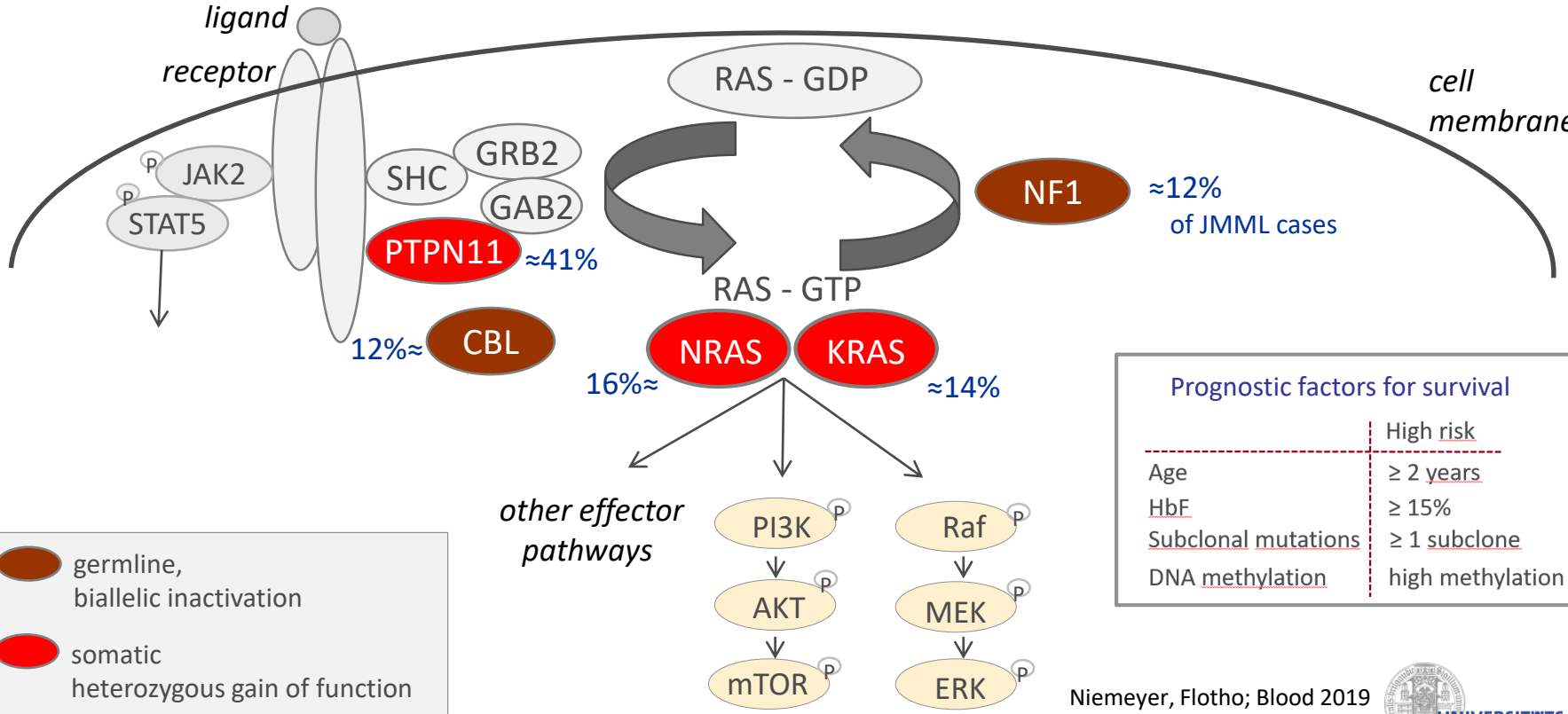
NS-associated myeloproliferation

- germline mutations in *PTPN11* (rarely *KRAS*, *NRAS* or *RIT*)
- polyclonal disease
- spontaneous resolution
- rare cases with monosomy 7



Kratz et al. 2005 Blood 106:2183; Strullu et al. 2014 J Med Genet 51:689

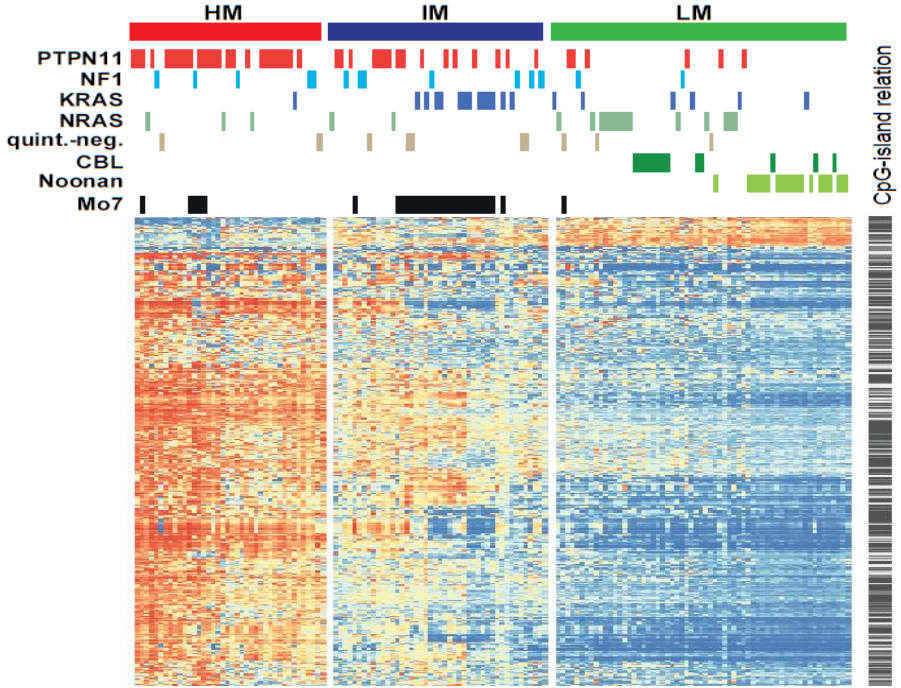
JMML is a unique MDS/MPD overlap disorder defined by canonical Ras pathway mutations

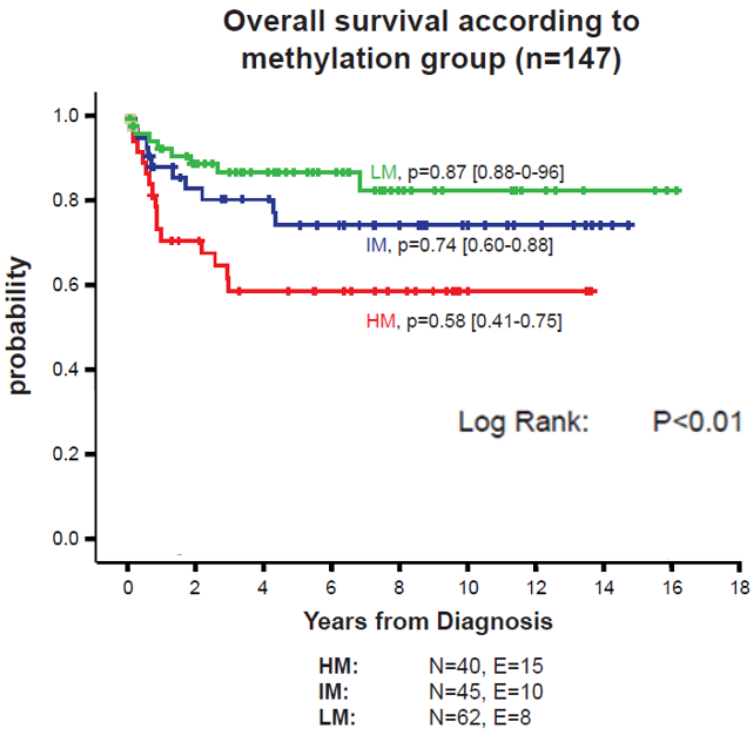


Prognostic factors for survival	High risk
Age	≥ 2 years
HbF	≥ 15%
Subclonal mutations	≥ 1 subclone
DNA methylation	high methylation

Niemeyer, Flotho; Blood 2019

RAS pathway mutation patterns define epigenetic subclasses with prognostic impact

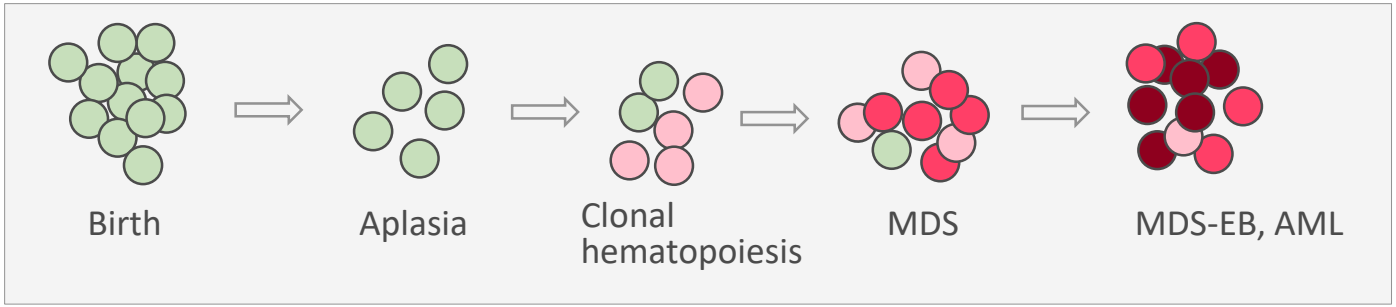




Lipka DB et al. Nat Comm 2017; 8:2126;

Also: Stieglitz et al. Nat Comm 2017; 8:2128; Murakami et al. Blood 2018; 131:1576; Schönung et al. Clin Cancer Res. 2021; 27:158.

Inherited disorders with BM failure and increased risk for myeloid neoplasia provided first clues for MDS pathobiology



Note:

- First acquired somatic events are often driven by somatic compensation
  - Fanconi anemia: unbalanced chromosomal translocation 1p+ : ↑MDM4 → ↓p53
  - Shwachman Diamond Syndrome: EIF6 haploinsufficiency (point mutations, del (20q)) improve ribosome function
- Somatic transformation may be the result of maladaptive compensation
  - Shwachman Diamond Syndrome: biallelic p53 mutations

Marie Sébert, …. Jean Soulier, ASH 2021; Alyssa L. Kennedy AL, ….. Akiko Shimamura, R. Coleman Lindsley. Nature Comm 2021

Traditional separation of primary from secondary pediatric MDS

Primary MDS

“Manifests as primary disease”

- Most are idiopathic (but reasonable to assume that most of these are in fact caused by yet unknown genetic predisposition)

- Germline predisposition:
  - **GATA2 (~7%)**
  - **SAMD9/9L (~8%)**
  - **RUNX1 (<1%)**

MDS with germline predisposition

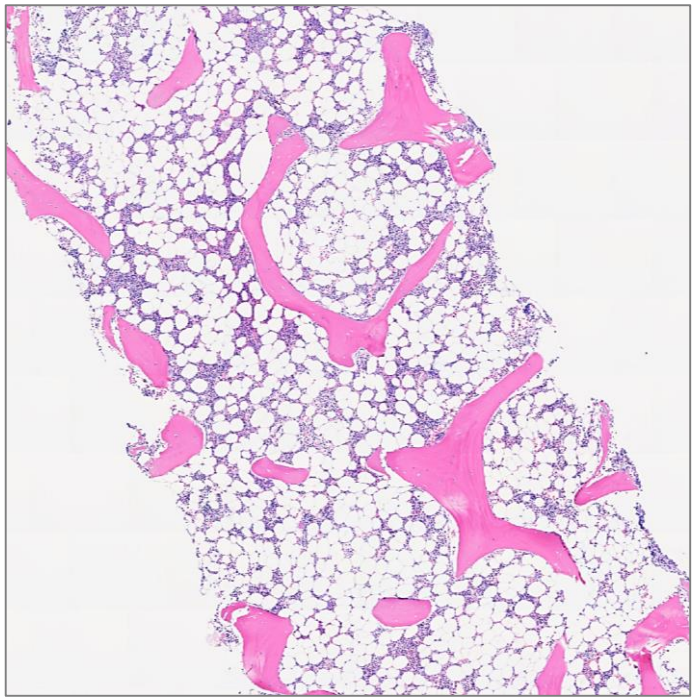
Secondary MDS

“After a preexisting problem”

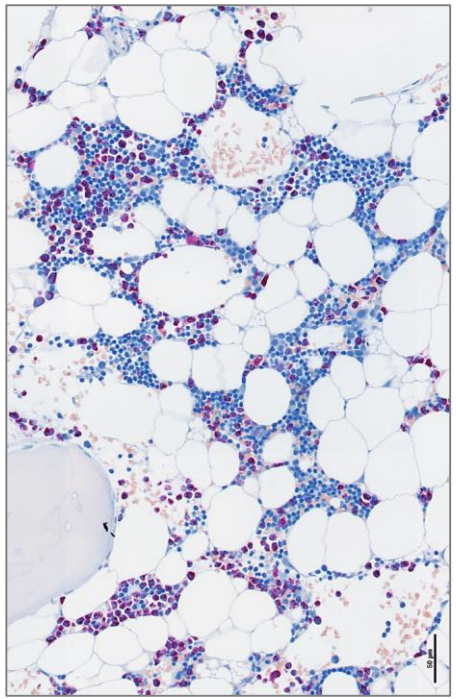
- Therapy-related (i.e. alkylating agents and topoisomerase inhibitors)
- Acquired aplastic anemia (<2% in pediatric SAA)
- Inherited bone marrow failure syndromes:
  - **Fanconi anemia**
  - **Shwachman-Diamond syndrome**
  - **Congenital neutropenia**
  - (Dyskeratosis congenita & DBA)

Histopathology of Refractory Cytopenia of Childhood (RCC)

- hypocellular bone marrow with marked decrease in granulopoiesis

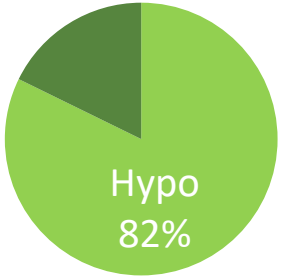


H&E staining



Chloracetatesterase staining:
reduced granulopoeisis in red

BM Cellularity in RCC



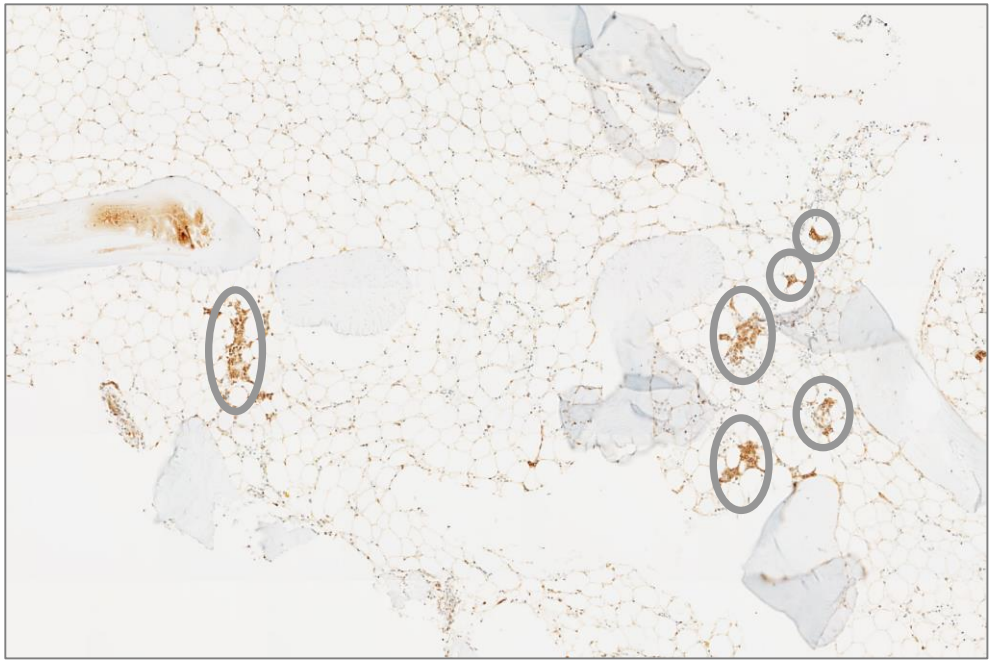
Yoshimi A et al. 2013 (N=445)

Baumann I et al. Histopathology 2012
WHO Classification 2017
Iwafuchi H, J Clin Exp Hematopathology 2018
IwaFuchi H, Ito M Histopathology 2019

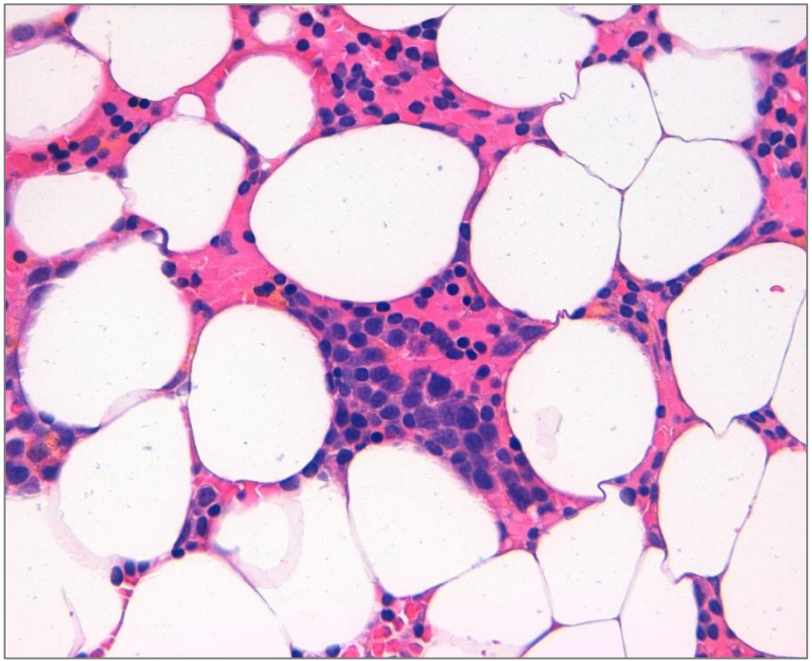
Courtesy of Martina Rudelius, Munich

Histopathology of Refractory Cytopenia of Childhood (RCC)

- patchy distribution of the erythropoeisis
- left shift, increased numbers of proerythroblasts and megaloblastoid changes



E-cadherin immunohistochemistry highlighting erythrones

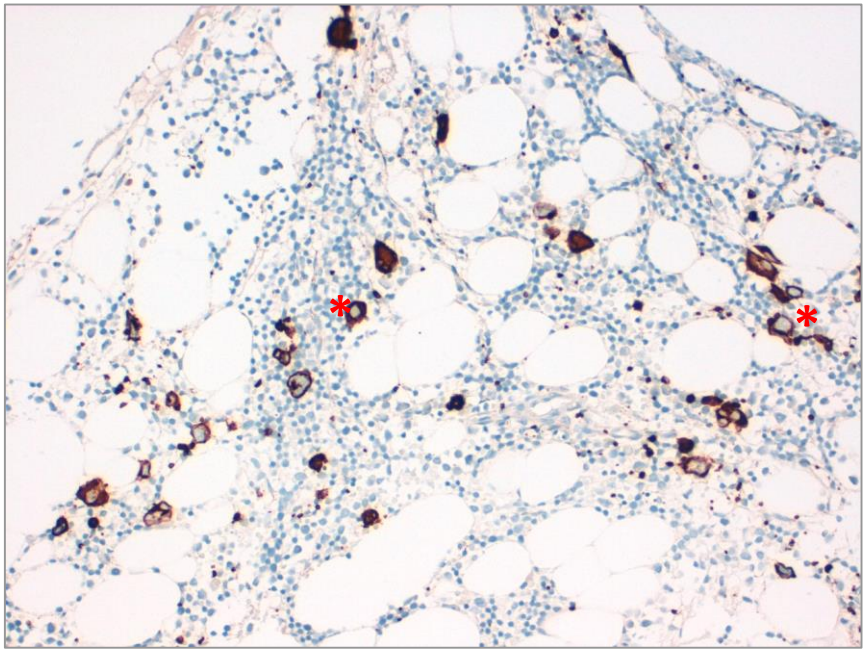


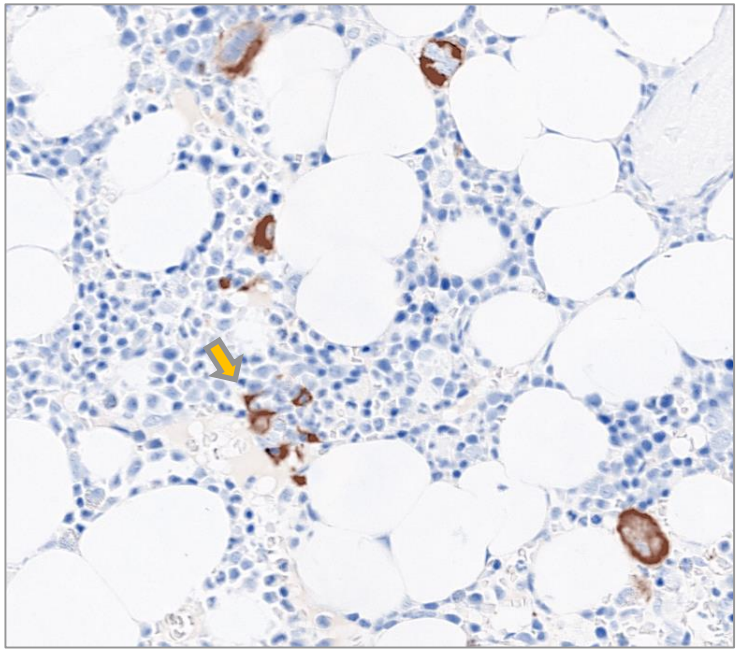
H&E staining

Courtesy of Martina Rudelius, Munich

Histopathology of Refractory Cytopenia of Childhood (RCC)

- marked decrease in the megakarypoeisis
- evt. micromegakarycytes, separated or round nuclei





CD42 immunohistochemistry: reduced megakaryopoiesis, round nuclei (*) and micromegakaryocytes ( )

Courtesy of Martina Rudelius, Munich

Histopathology of Refractory Cytopenia of Childhood (RCC)

- Persistent cytopenia, with < 5% blasts in BM and <2% blasts in PB
- Typical histopathological BM pattern
- Some dysplasia on cytology

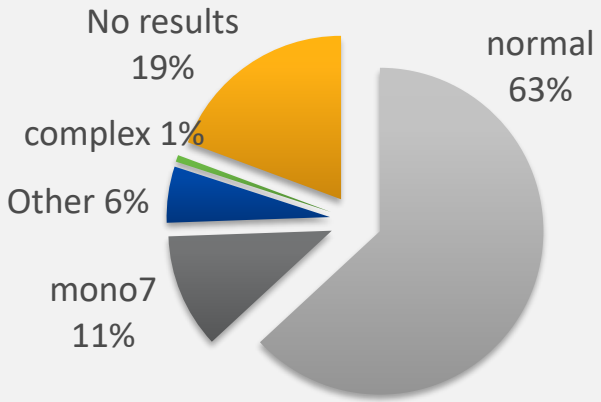
Table 6.07 Minimal diagnostic criteria for refractory cytopenia of childhood.
The criteria of dysplasia must be fulfilled in ≥ 10% of cells in ≥ 1 lineage; in some cases, lesser degrees of dysplasia are present in 2 or 3 lineages.

Specimen	Erythropoiesis	Granulopoiesis	Megakaryopoiesis
Bone marrow aspirate	Dysplastic changes[a] and/or megaloblastoid changes	Dysplastic changes[b] in granulocytic precursors and neutrophils; < 5% blasts	Unequivocal micromegakaryocytes; other dysplastic changes[c] in variable numbers
Bone marrow biopsy	A few clusters of ≥ 20 erythroid precursors Arrest in maturation, with increased number of proerythroblasts. Increased number of mitoses.	No minimal diagnostic criteria	Unequivocal micromegakaryocytes; immunohistochemistry is obligatory (CD61, CD41); other dysplastic changes[c] in variable numbers
Peripheral blood		Dysplastic changes[b] in neutrophils	

[a] Erythroid dysplasia: abnormal nuclear segmentation, multinucleated cells, nuclear bridges.
[b] Granulocytic dysplasia: pseudo–Pelger–Huët cells, hypogranularity or agranularity, giant bands (in cases with severe neutropenia, this criterion may not be fulfilled).
[c] Megakaryocytic dysplasia: variable size with separated nuclei or round nuclei; the absence of megakaryocytes does not rule out refractory cytopenia of childhood.

Karyotype

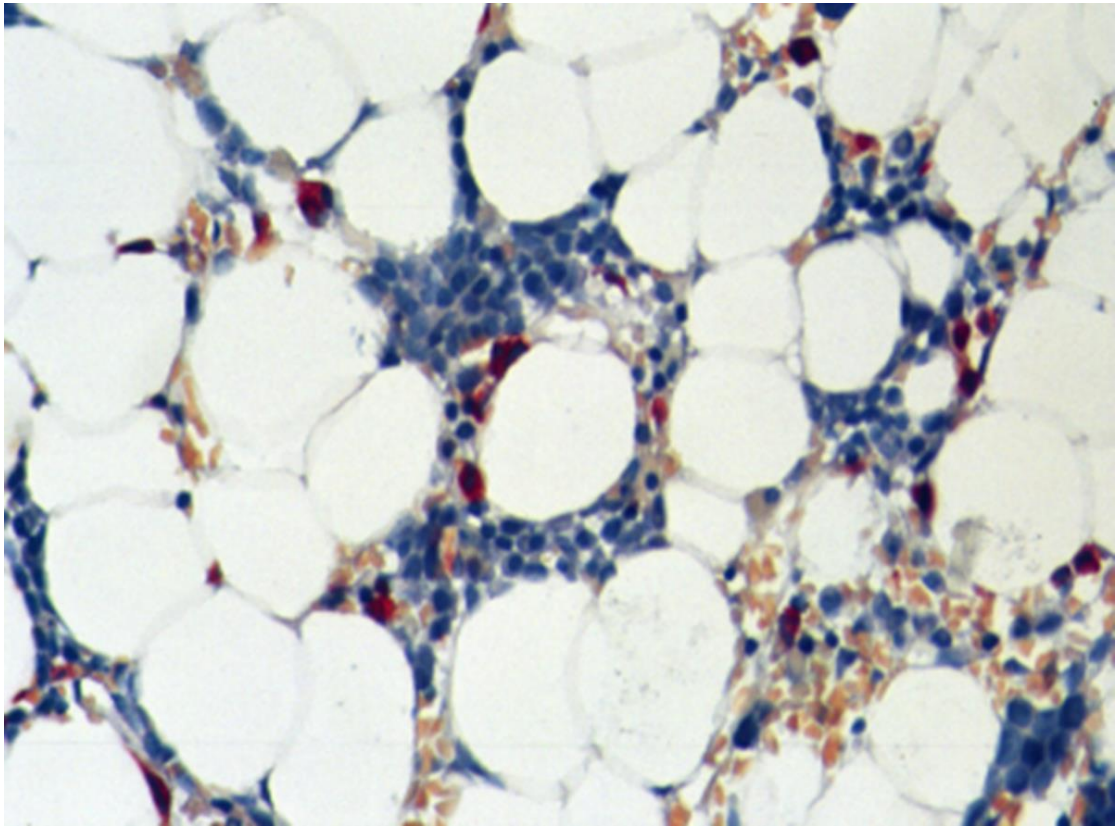
Metaphase Cytogenetics
(No result: neg. for -7, +8 FISH)



Yoshimi 2013 (N=445)

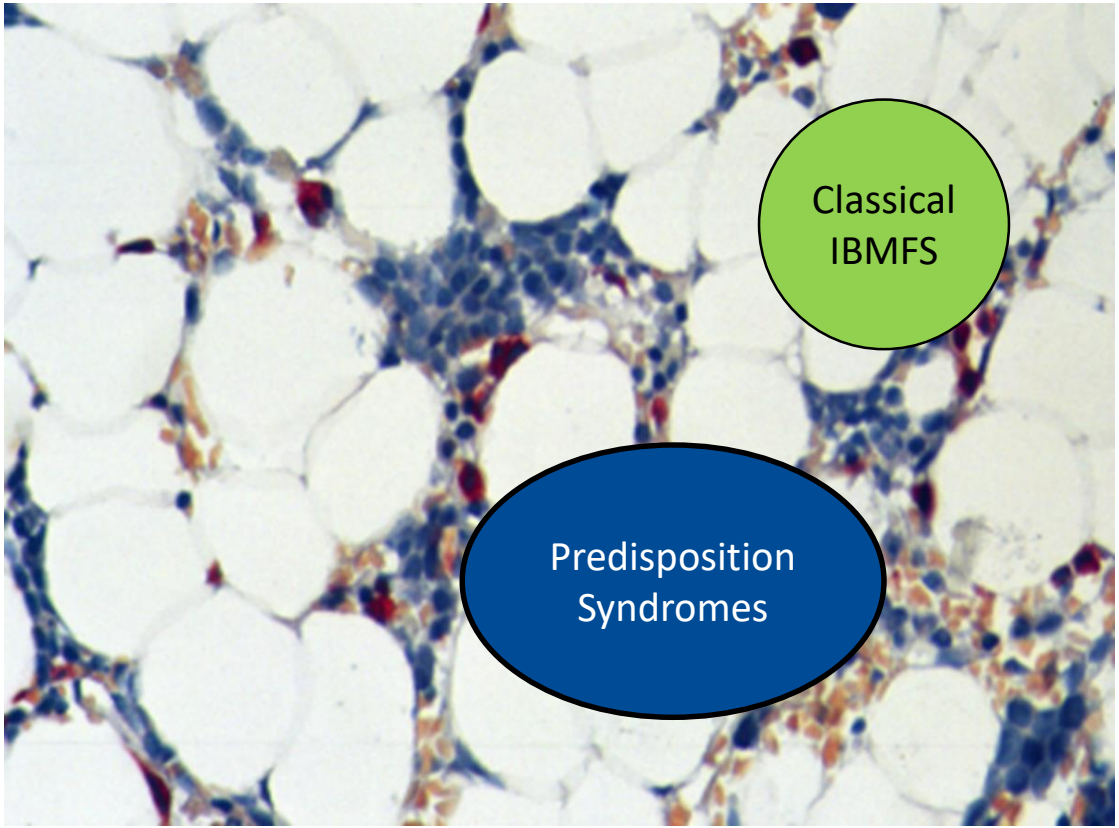
WHO 2016, Baumann et al. Histopathology 2012

Histopathological pattern of RCC: what it can do…..



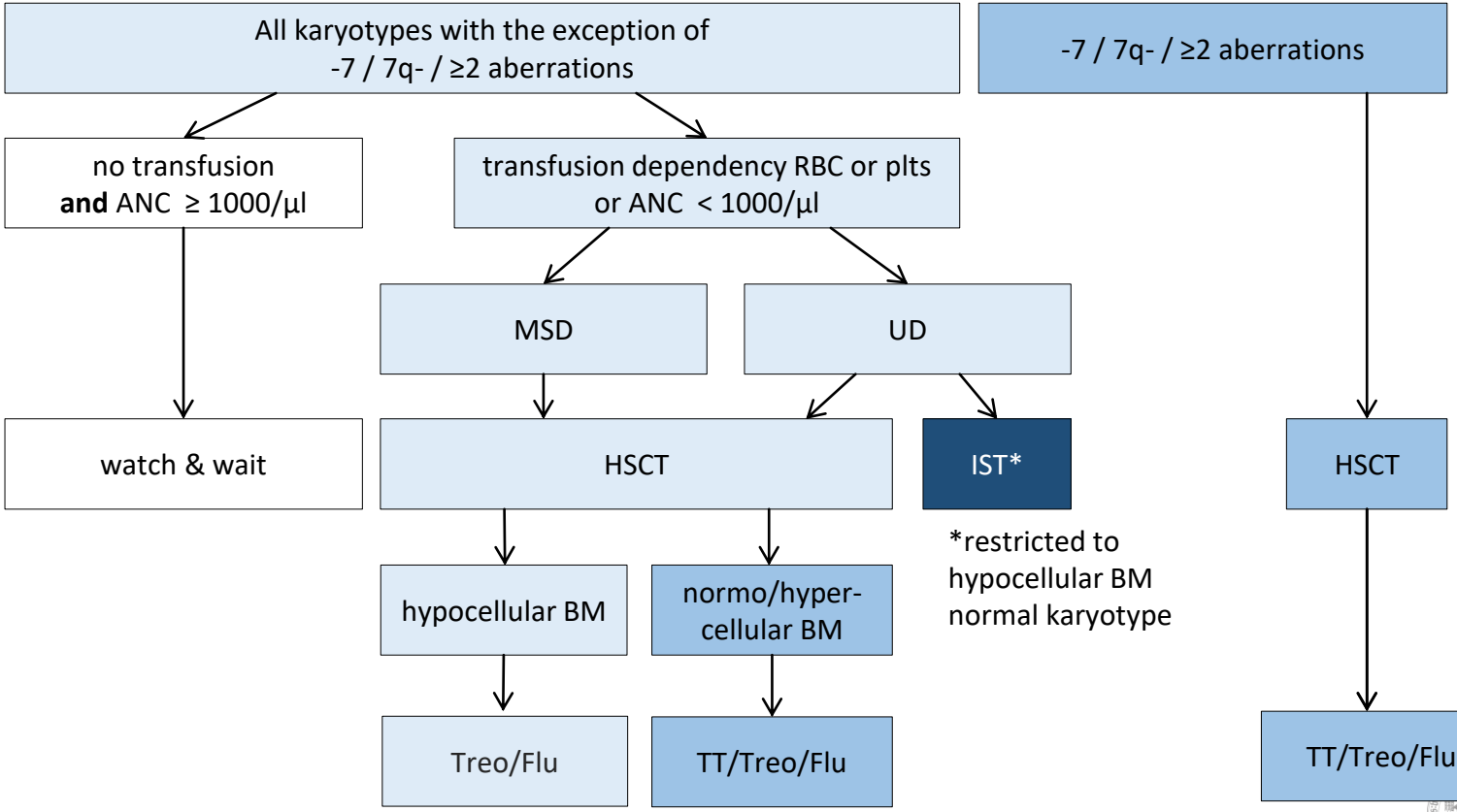
- Separates RCC from reactive changes
- Typical for intrinsic defects of hematopoiesis
- Separates RCC from SAA (at time of diagnosis)

Histopathological pattern of RCC: what it cannot do…..

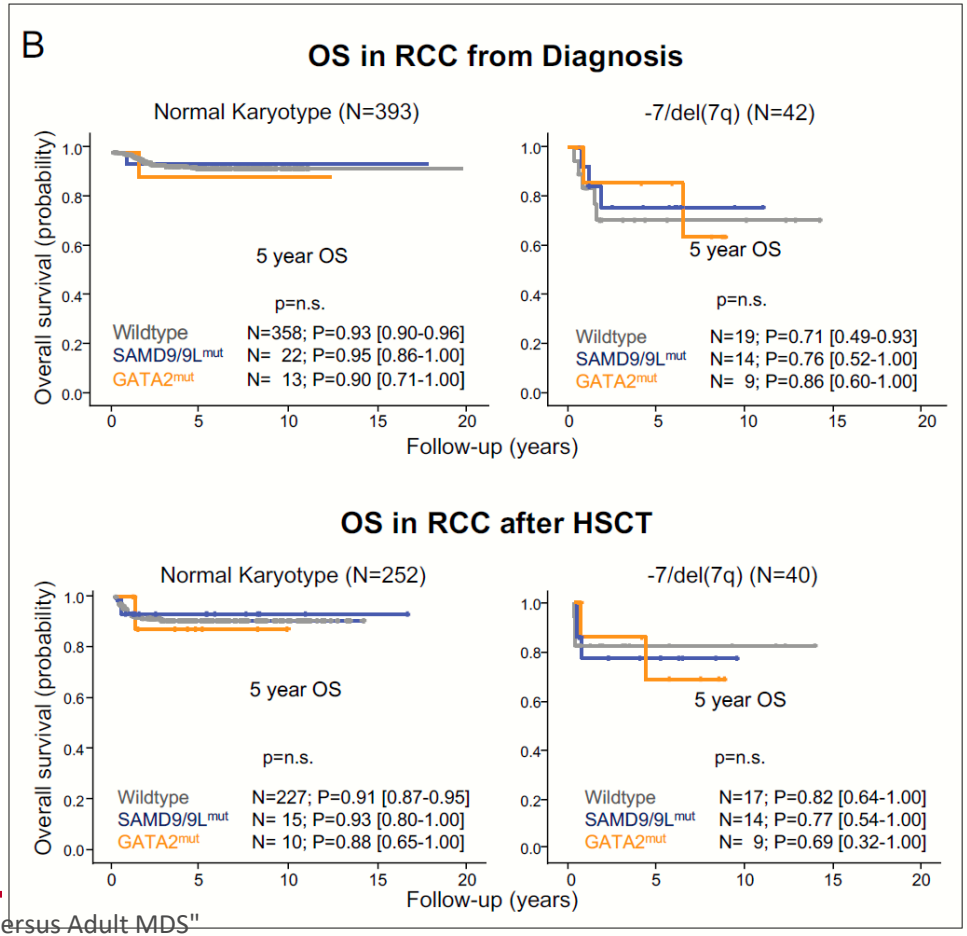


- ❑ Distinguish clonal from non-clonal disorders
- ❑ RCC pattern is present in classical IBMFS
- ❑ RCC represents a biological spectrum of disease stages reflecting the plasticity of the bone marrow in children
- ❑ Algorithm for management of patients with RCC (excluding classical IBMFS) is highly successful and still valid

Treatment algorithm of RCC according to karyotype and BM cellularity (EWOG-MDS)



Outcome of HSCT in RCC dependent on karyotype not predisposition



Sahoo et al, Nature Medicine 2021

Germline disorders predisposing to myeloid neoplasia

Disease / Gene	Risk for Heme Malign.	Age at onset, years range	Population at Risk	Reported Somatic Mutations	Reported Karyotypes	Cong. Anomalies
GATA2	Very High	0.4-78 **(~20)** **12 in children**	Children – Adults	SETBP1, ASXL1, RUNX1, PTPN11, NRAS, KRAS, CBL, EZH2, ETV6, STAG2, JAK3, IKZF1, CRLF2, IDH2, TP53	-7, der(1;7), +8, +21	++ Immuno deficiency
SAMD9, SAMD9L	Moderate	0.2–18 (**10**)	Children	SETBP1, ASXL1, RUNX1, PTPN11, KRAS, CBL, EZH2, ETV6, BRAF, RAD21 Somatic reversion (cis SAMD9/9L, UPD7q)	-7, del(7q)	++
RUNX1	High	6-77 (**~33**)	Children – Adults	RUNX1 (somatic), ASXL1, BCOR, DNMT3A, PHF6, WT1, GATA2, FLI1, JMJD5, KDM6B, CDC25C	+21, +8, -7	-
CEBPA	High (AML)	2-50 (**~25**)	Children – Adults	CEBPA (trans mutation at 3' end), GATA2, WT1, EZH2, TET2, SMC3, NRAS, DDX41, CSF3R		-
ETV6	Moderate (mostly ALL)	8-82	Children – Adults	BCOR, RUNX1, NRAS		-
DDX41	Moderate	6-93 (**~55**)	Adults	DDX41 (trans p.Arg525His mutation, p.Ala255Asp, p.Glu247Lys, p.Pro321Lys)	del(20q), del(7q), -7, +8	-
ANKRD26	Low	>30	Adults			-
ERCC6L2	High (AML M6)	14-65 (**38**)	Adults	TP53, IDH1	-7, +20, -18, del(5q)	-

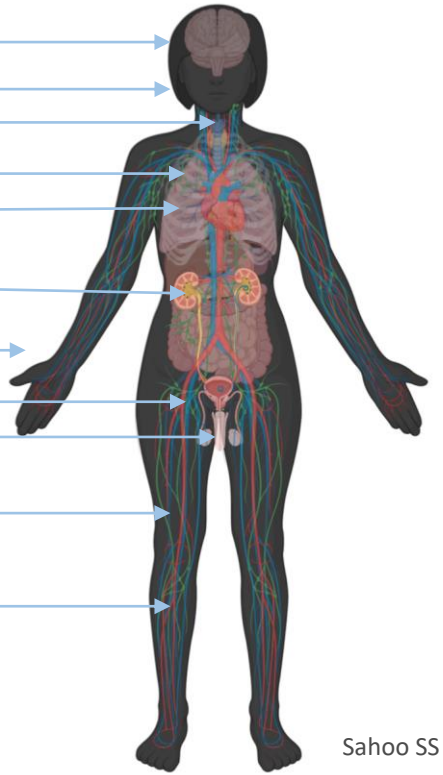
Mumbai Hematology Group "Pediatric versus Adult MDS"

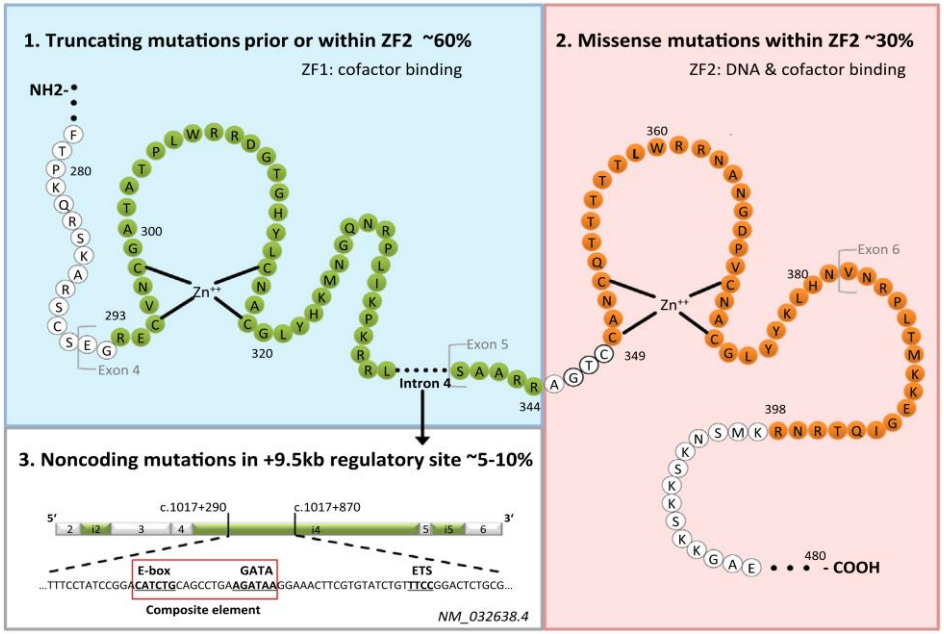
Courtesy of Marcin Wlodarski

GATA2 deficiency: phenotype defined by immunodeficiency and constitutional abnormalities, genetic bases by loss of function mutations

Autism/ADHD: 12%
Congenital deafness: 7%
Hypothyroidism
Pulmonary alveolar proteinosis
Interstitial lung disease
NTM, bact., viral, fungal infections
VUR, kidney anomalies: 12%
Warts
Miscarriages
Hydrocele , Hypospadia
Thrombosis
Lymphedema: 23%
Immunodeficiency: 39%

Any abnormality: 51%

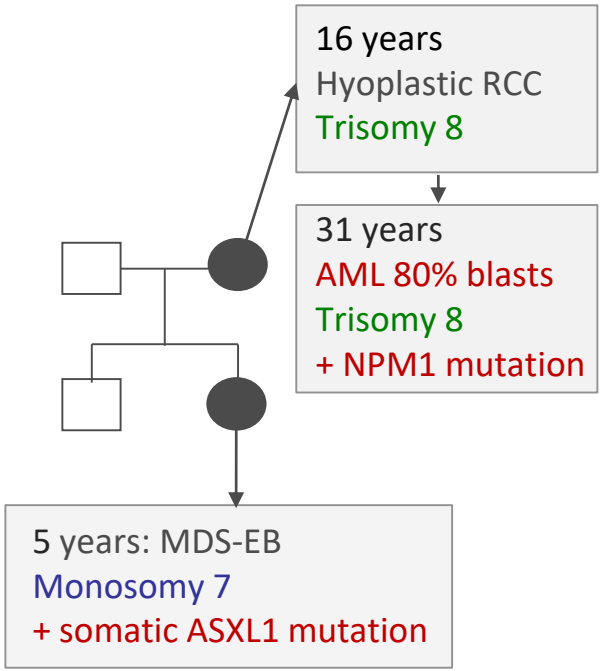




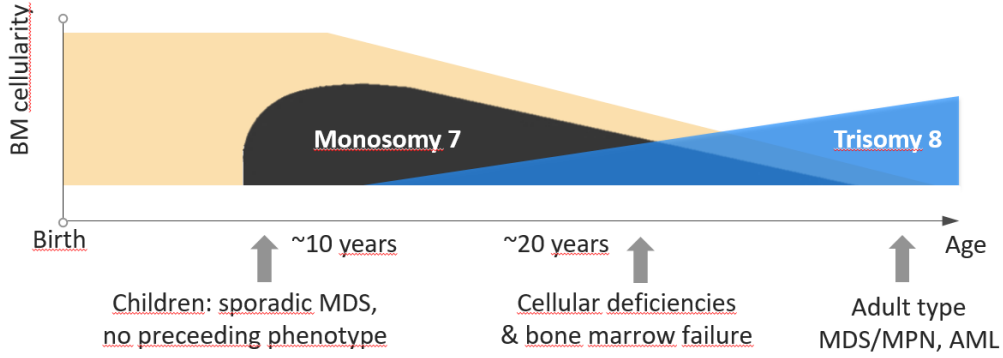
4. Gene deletions **5. Silent mutations**

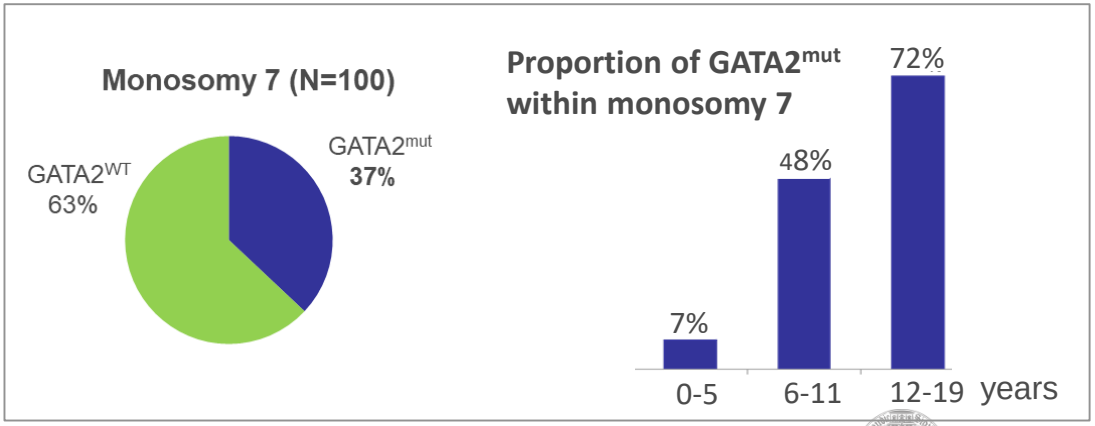
Sahoo SS et al. Best Pract Res Clin Haematol 2020 Wlodarski, Sem Hematol, 2017

GATA2 deficiency: hematological phenotype may differ among age groups



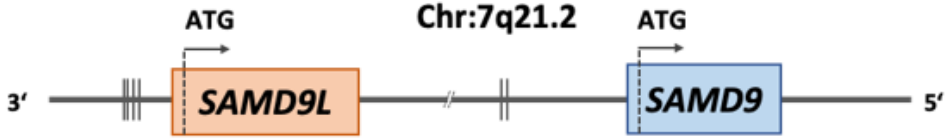
Germline GATA2 ZF2: c.1113C>A, p.N371K



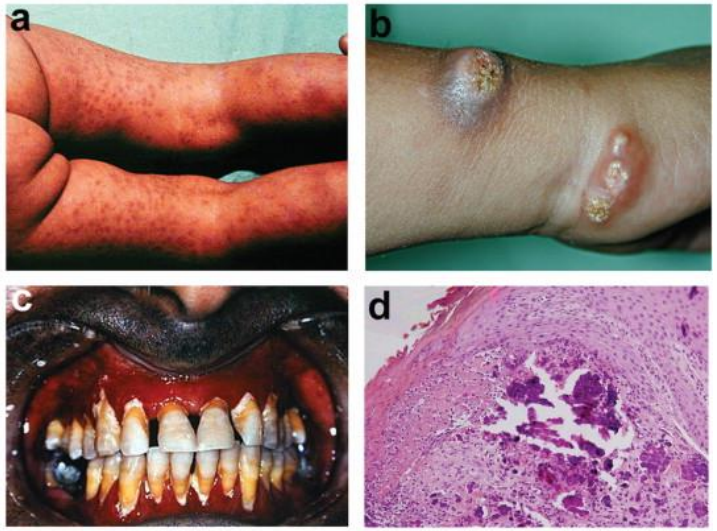


Wlodarski MW et al. Blood 2016

Sterile alpha motif domain-containing protein 9 (SAMD9) and SAMD9-like (SAMD9L) are bona fide tumor suppressors



- Paralogue genes on 7q, high sequence identity
- Terminate signaling downstream of growth factors (e.g. EGF), anti-proliferative
- Involved in IFN-response and anti-viral immunity
- *SAMD9L*$^{+/-}$ and *SAMD9L*$^{-/-}$ mice develop myeloid malignancies



A Deleterious Mutation in *SAMD9* Causes Normophosphatemic Familial Tumoral Calcinosis

Orit Topaz, Margarita Indelman, Ilana Chefetz, Dan Geiger, Aryeh Metzker, Yoram Altschuler, Mordechai Choder, Dani Bercovich, Jouni Uitto, Reuven Bergman, Gabriele Richard, and Eli Sprecher

The American Journal of Human Genetics Volume 79 October 2006

Germline disorders with gain of function mutations in *SAMD9* and *SAMD9L* share a hematological phenotype as common denominator

MIRAGE syndrome (SAMD9):

- Adrenal hypoplasia / dysfunction
- Genital phenotypes
- Growth restriction / SGA

Ataxia-pancytopenia syndrome (SAMD9L):

- Cerebellar and hippocampal hypoplasia
- Neurodegeneration (loss of Purkinje cells)
- Other malformations

Both:

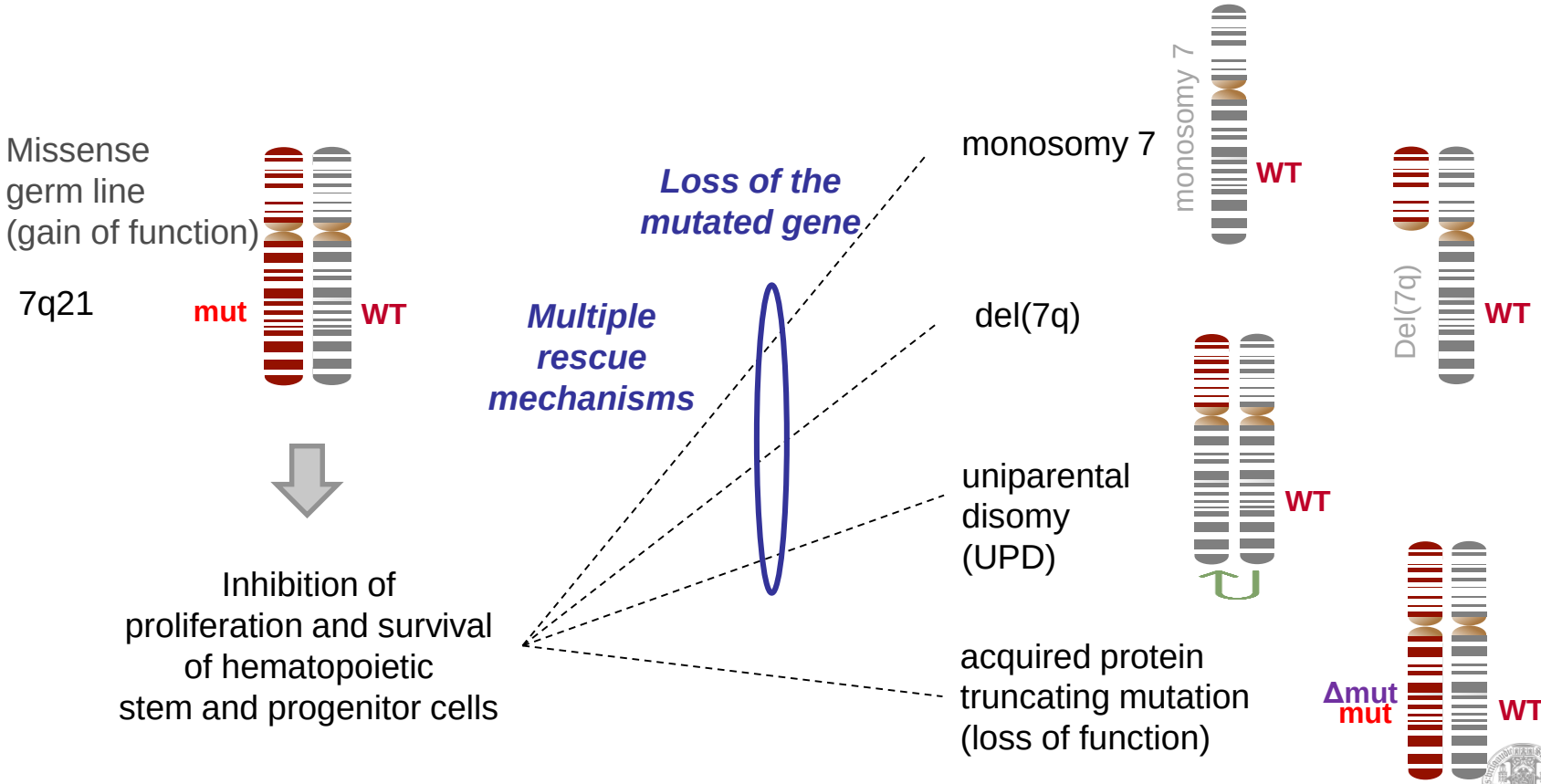
Hematopoietic failure

Risk of MDS

Chromosomal 7 aberrations frequent …can be transient!

Narumi et al. Nat.Genet, 2016; Buonocore F et al. JCI, 2017; Chen et al. AJHG, 2016

SAMD9/SAMD9L syndrome: how to get rid of a „toxic“ gene

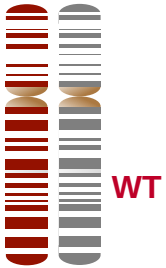


Courtesy of Miriam Erlacher, EWOG-MDS

SAMD9/SAMD9L syndrome: how to get rid of a „toxic“ gene

Missense
germ line
(gain of function)

7q21



Inhibition of
proliferation and survival
of hematopoietic
stem and progenitor cells

Loss of the mutated gene

Multiple rescue mechanisms

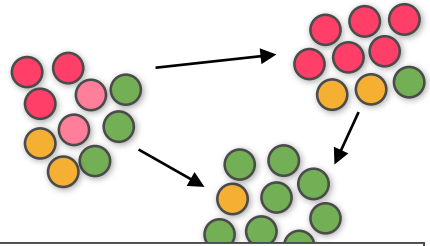
monosomy 7

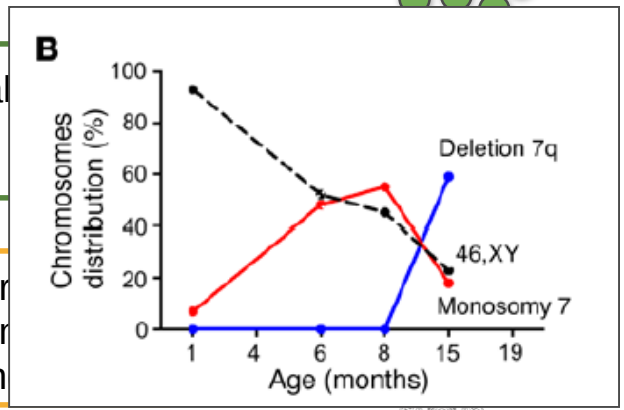
del(7q)

uniparental
disomy
(UPD)

acquired pr
truncating r
(loss of fun

Oncogenic event





[Buonocore F et al, JCI, 2017]

SAMD9/9L syndrome in pediatric MDS

EWOG-MDS

nature medicine

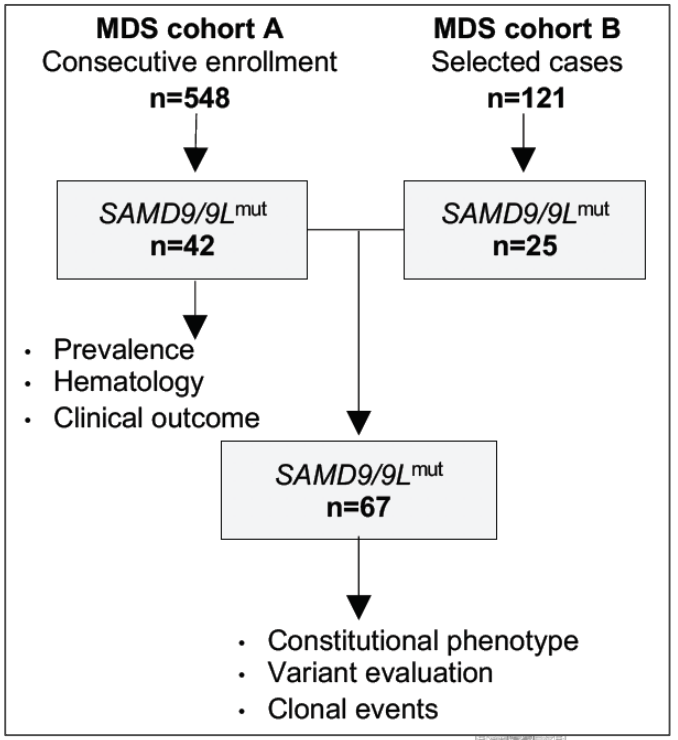
Explore content ∨ About the journal ∨ Publish with us ∨

nature > nature medicine > articles > article

Article | Published: 07 October 2021

Clinical evolution, genetic landscape and trajectories of clonal hematopoiesis in SAMD9/SAMD9L syndromes

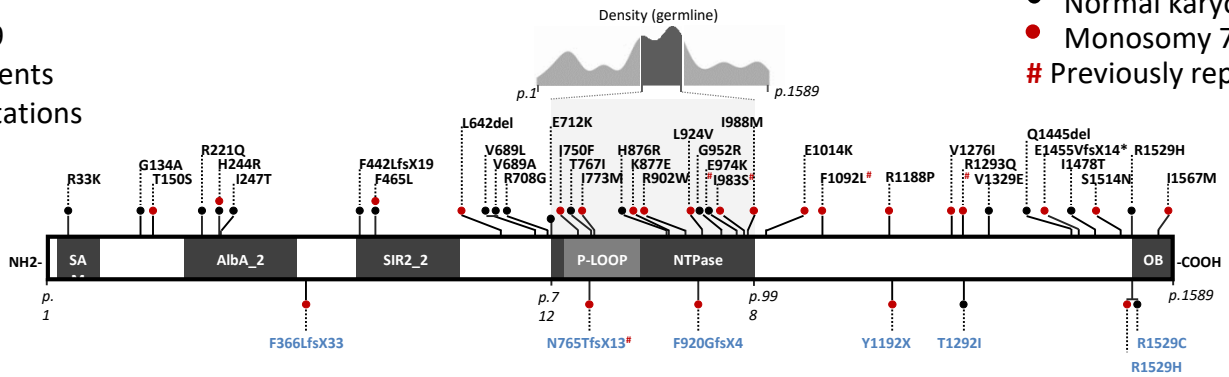
Sushree S. Sahoo, Victor B. Pastor, [...] Marcin W. Wlodarski



SAMD9/9L mutations cluster in the middle region

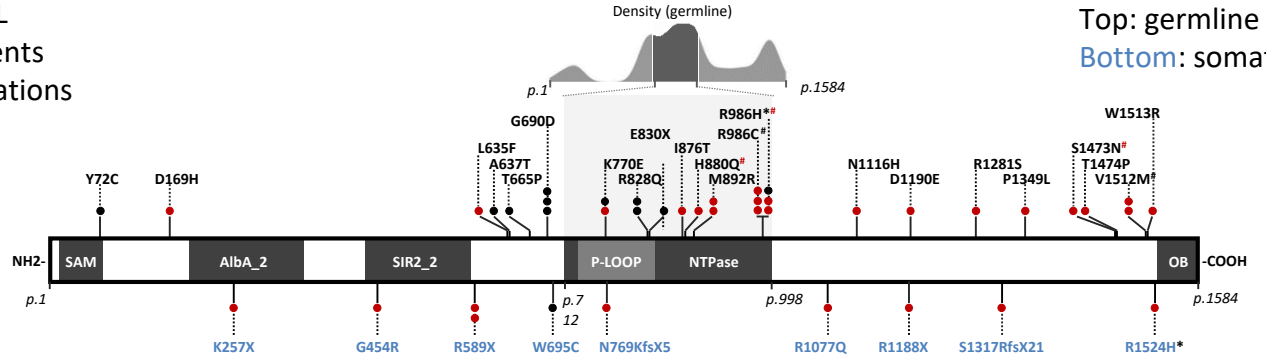
Prediction of pathogenicity of SAMD9/9L is challenging

SAMD9
37 Patients
44 Mutations



- Normal karyotype
- Monosomy 7
- # Previously reported

SAMD9L
30 Patients
43 Mutations

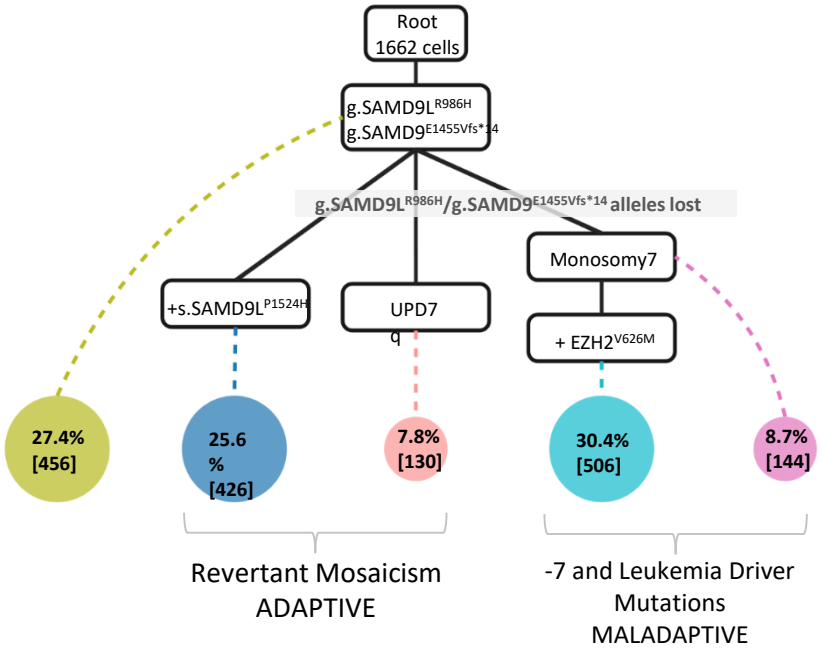


Top: germline
Bottom: somatic

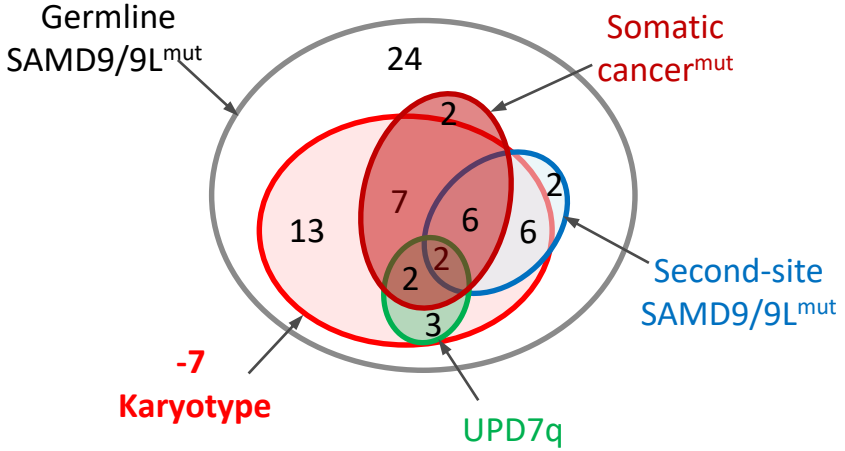
Sahoo et al. Nature Medicine 2021

Somatic genetic rescue: coexisting hematopoietic clones with multiple layers of functional redundancy

Single-cell DNA sequencing assay

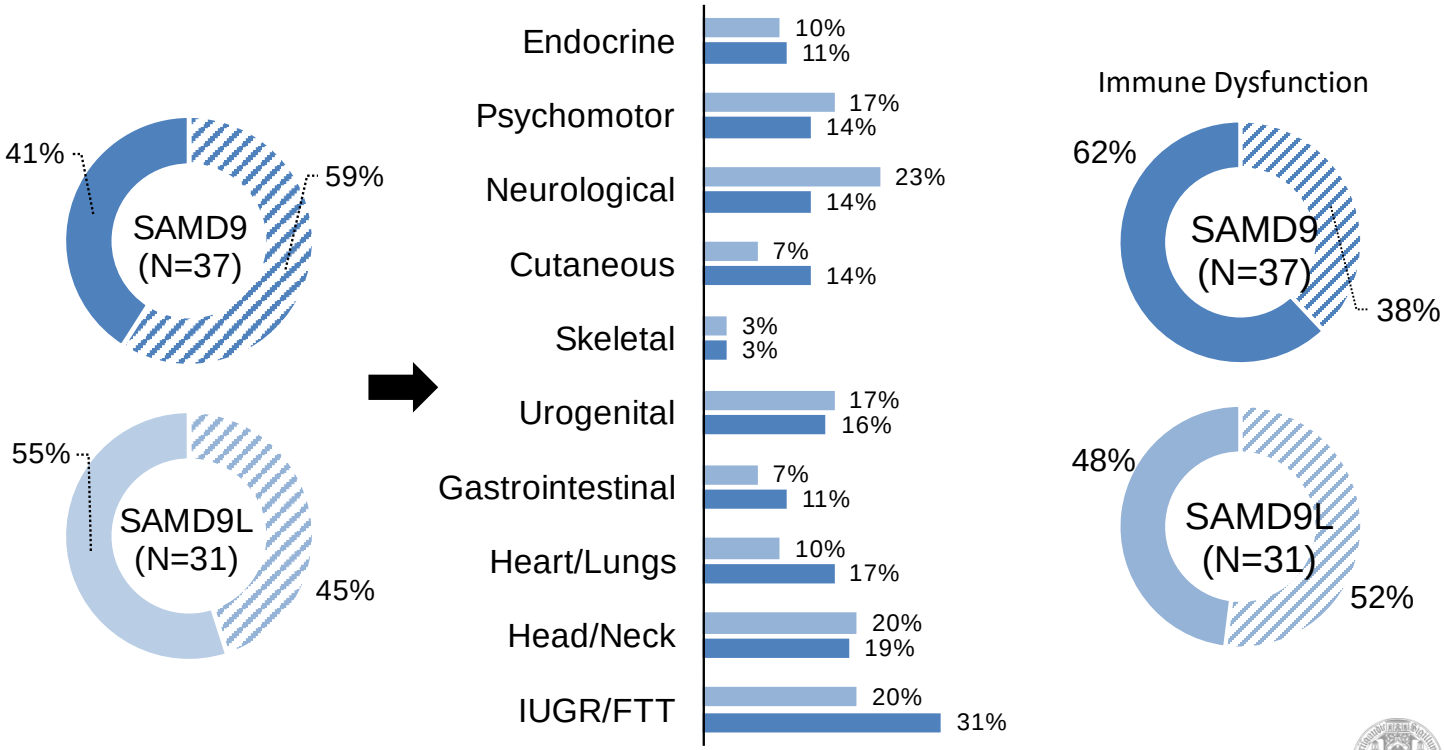


Acquired events in 64% of SAMD9/9L patients



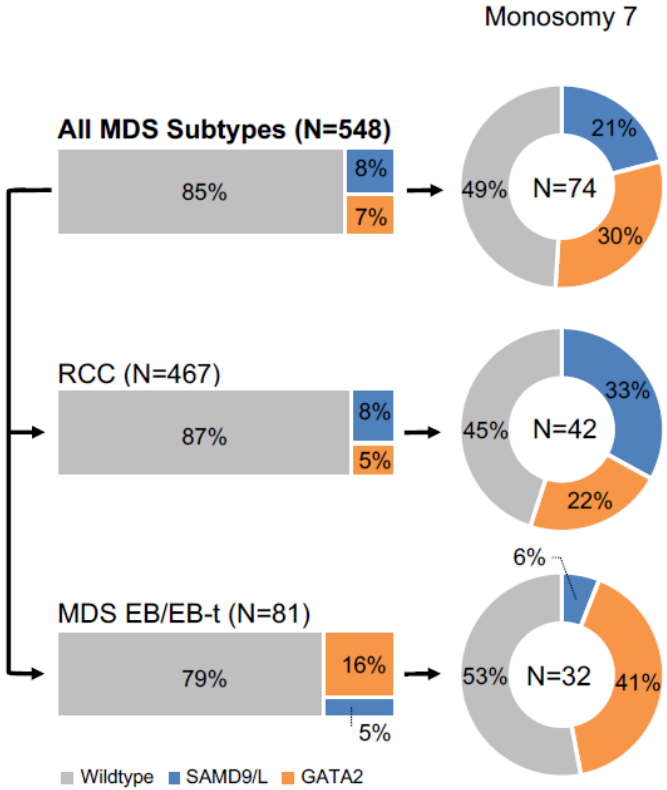
Sahoo et al. Nature Medicine 2021

Constitutional phenotypes and immune dysfunction in pediatric MDS with germline SAMD9 and SAMD9L disorders are similar



Sahoo et al. Nature Medicine 2021

SAMD9/L and GATA2 germline disease account for half of pediatric MDS with -7



Sahoo et al. Nature Medicine 2021

Leukemia Pastor et al. 2017, 31: 728 – 760

Mutational landscape in children with myelodysplastic syndromes is distinct from adults: specific somatic drivers and novel germline variants

blood Plenary Paper

RED CELLS, IRON, AND ERYTHROPOIESIS

CME Article

A landscape of germ line mutations in a cohort of inhe bone marrow failure patients

Olivier Bluteau,[1-3,*] Marie Sebert,[2,3,*] Thierry Leblanc,[4] Régis Peffault de Jean-Hugues Dalle,[2,4] Flore Sicre de Fontbrune,[6] Etienne Lengline,[9] Raj Nadia Vasquez,[1] Mélanie Da Costa,[1] Julien Masliah-Planchon,[3] Wendy C Pierre Fenaux,[2,9] Sébastien Maury,[10] Claudine Schmitt,[11,12] Marc Muller,[Isabelle Pellier,[16,17] Mathilde Hunault,[16,17] Stéphane Blanche,[18,19] Arnauc André Baruchel,[2,4,5] Gérard Socié,[2,6,7] and Jean Soulier[1-3]

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-01590-5 OPEN

The genomic landscape of pediatric myelodysplastic syndromes

Jason R. Schwartz[1], Jing Ma[2], Tamara Lamprecht[2], Michael Walsh[2], Shuoguo Wang[3], Victoria Bryant[2], Guangchun Song[2], Gang Wu[3], John Easton[3], Chimene Kesserwan[1], Kim E. Nichols[1], Charles G. Mullighan[2], Raul C. Ribeiro[1] & Jeffery M. Klco[2]

Bone Marrow Failure

Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients

Siobán B. Keel,[1]* Angela Scott,[2,3,4]* Marilyn Sanchez-Bonilla,[5] Phoenix A. Ho,[2,3,4] Suleyman Gulsuner,[6] Colin C. Pritchard,[7] Janis L. Abkowitz,[1] Mary-Claire King,[6] Tom Walsh,[6]** and Akiko Shimamura[5]**

UNIVERSITÄTS KLINIKUM FREIBURG
ZKJ ZENTRUM FÜR KINDER- UND JUGENDMEDIZIN

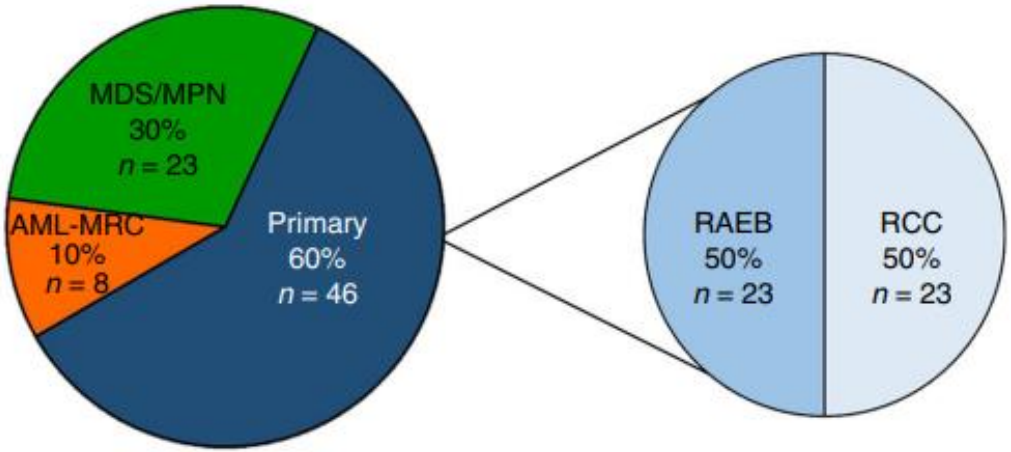
nature COMMUNICATIONS 2017, 8:1557

ARTICLE

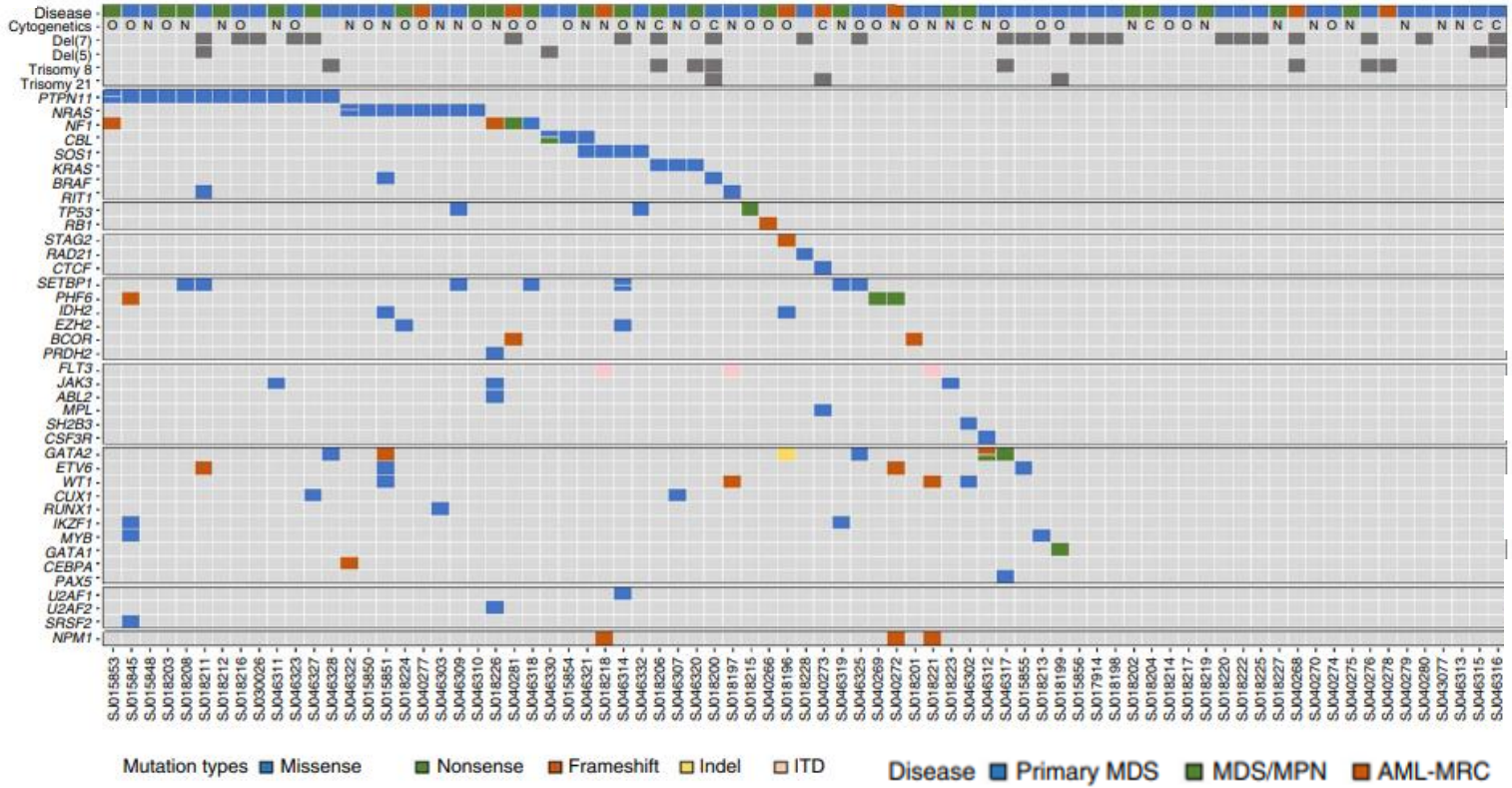
DOI: 10.1038/s41467-017-01590-5 OPEN

The genomic landscape of pediatric myelodysplastic syndromes

Jason R. Schwartz[1], Jing Ma[2], Tamara Lamprecht[2], Michael Walsh[2], Shuoguo Wang[3], Victoria Bryant[2], Guangchun Song[2], Gang Wu[3], John Easton[3], Chimene Kesserwan[1], Kim E. Nichols[1], Charles G. Mullighan[2], Raul C. Ribeiro[1] & Jeffery M. Klco[2]



Genomic Landscape of Pediatric MDS and related disorders



RAS/MAPK

Cell Cycle

Cohesin

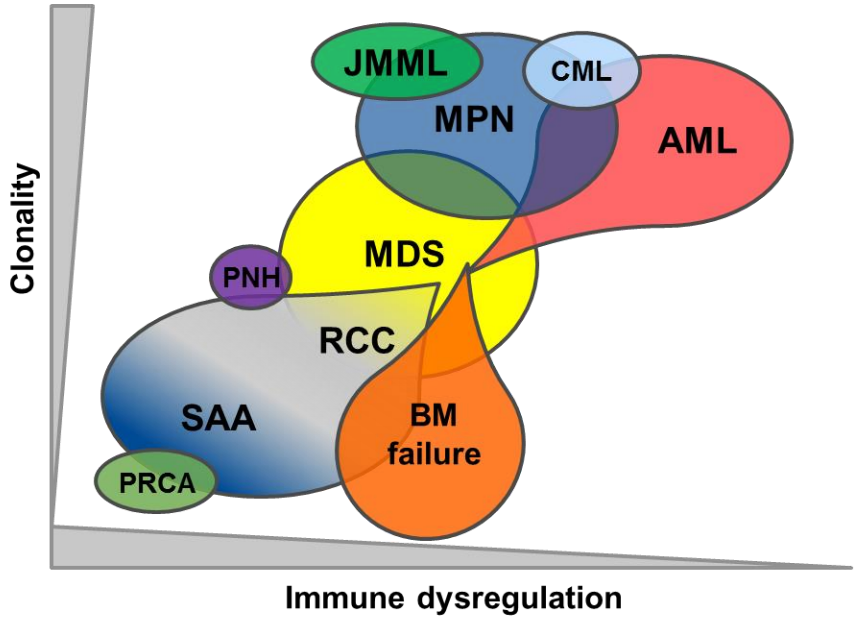
Epigenetic modifiers

Other signaling

Transciption factors

Splicing/RNA Processing, NPM1

Myelodysplastic syndromes (MDS)



modified: Gerds et al. Cambridge University Press, 2016

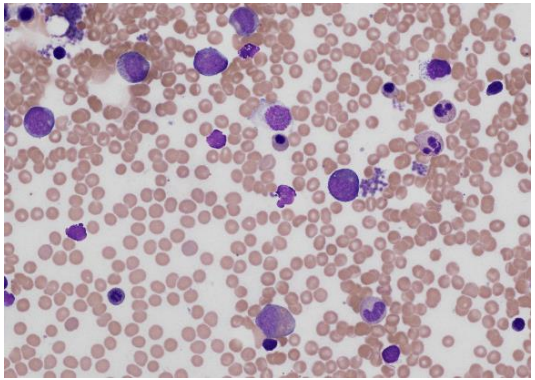
"Classification systems optimally identify diseases that….. retain the core ontogeny of their original presentation."

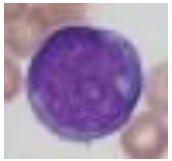
Hasserjan et al. ASCO Educational Book 2021

The separation of MDS from AML is crucial for young individuals

Patient 1 (10 years, m):

- 23% blasts in a normocellular bone marrow
- M2 morphology
- some Auer rods
- orbital choloroma
- translocation t(8;21), RUNX1-RUNX1T1
- rapidly progressing blast percentage

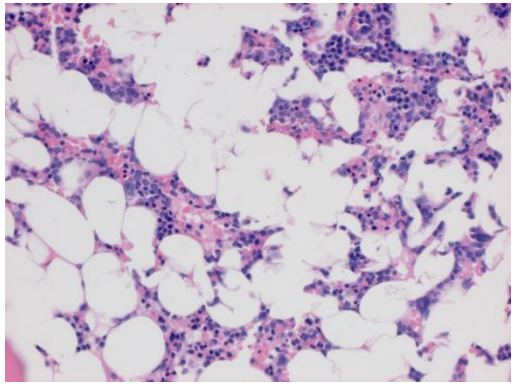


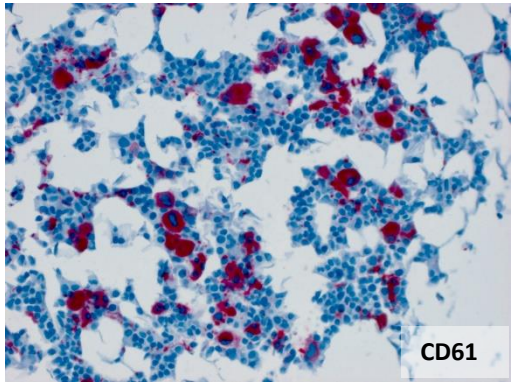


AML M2
→ in remission after AML-BFM 2019

Patient 2 (5 years, f):

- 16% blasts in a hypocellular bone marrow
- dysplastic signs such as micromegakaryocytes
- monosomy 7
- mutations: GATA2 (germline); ASXL1 (somatic)
- familial disease
- stable blast percentage for 4 months





MDS-EB in GATA2 deficiency
→ in remission after HSCT

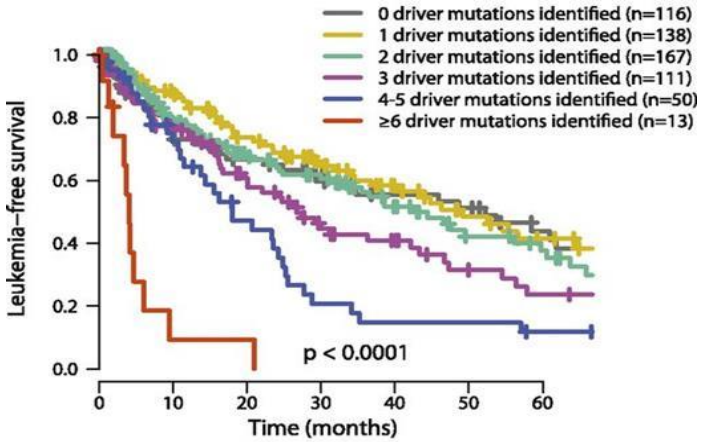
Courtesy of Stephan Schwarz-Furlan / Ayami Yoshimi

The separation of MDS from AML may not matter for MDS in older adults

Is MDS different from AML?

Although the peripheral cytopaenias become progressively worse as the disease persists, most cases of MDS are characterized by a cellular bone marrow with active cell turnover and cell division. As the disease progresses, the percentage of blasts in the bone marrow increases, and cytogenetic abnormalities arise. When faced with an elderly person with anaemia and a bone marrow that is cellular but not replaced with blasts, a haematologist might wonder whether the diagnosis is AML or a MDS that has progressed to AML. For such a patient and his physician, this dilemma is inconsequential: the prognosis is grim. For the oncologist, MDS present a fascinating enigma of stem-cell biology and neoplastic transformation.

Corey SJ et al. Nature Reviews Cancer, 2007



Papaemmanuil E et al. Blood, 2013

…defining patients with 10-30% blasts (“AML/MDS”) as eligible for either AML or MDS studies would …. allow patients access to more therapies, and potentially simplify the regulatory approval process.

Estey et al. Blood 2021

Some myeloid neoplasia with a blast percentage of 20%-30% blasts may behave more like MDS than AML

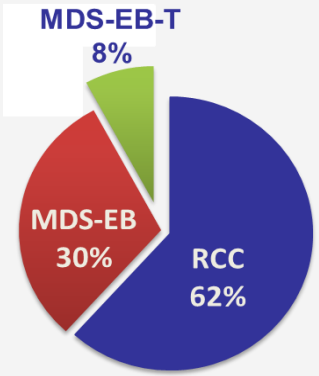
2001 WHO Classification

A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases Leukemia (2003) 17, 277–282

H Hasle[1], CM Niemeyer[2], JM Chessells[3], I Baumann[4], JM Bennett[5], G Kerndrup[6] and DR Head[7]

2016 WHO Classification:

Primary MDS	PB (%)	BM (%)
Refractory cytopenia of childhood (RCC)	< 2	< 5
MDS with excess blasts (MDS-EB)	2 – 19	5 – 19



Distribution of subtypes in the EWOG-MDS 98 study (n=381)

…….. (2016 WHO classification, p. 117)

"Children with MDS with excess blasts generally have relatively stable PB counts for weeks or months. Some cases diagnosed in children as AML with 20 – 29% blasts in PB and/or BM that have myelodysplastia-related changes including cases with myelodysplasia-related cytogenetic abnormalities may also be slowly progressive disease. These cases, categorized by the FAB classification as refractory anemia with excess blasts in transformation may lack the clinical features of acute leukaemia and may behave more like MDS than AML."

MDS in pediatric patients is different from MDS in adults

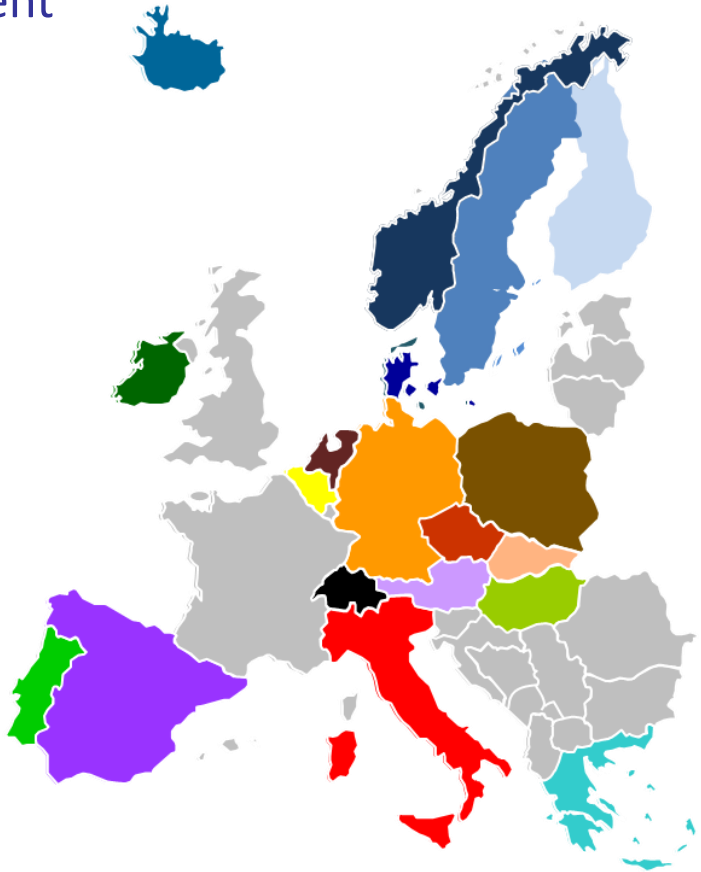
	Children (0-18 y)	Adults (older than age 40 y)
Incidence per million	1-4	>40
Refractory anemia with ringed sideroblasts (%)	<1	25
Associated IBMFSs and predisposition syndromes (%)	>30	<5
Familial aggregation	Present in a proportion of patients	Uncommon
Chromosomal aberrations (%) −7/7q− −5/5q−	 25-30 1	 10 20
Molecular aberrations	Presence of germ line mutations (eg, GATA2); less frequent somatic mutations; absent or exceptional spliceosomal mutations	Germ line mutations are less common; frequent somatic mutations; spliceosomal mutations are common
General aim of treatment	Curative	Often palliative

Locatelli, Strahm Blood 2018

EWOG-MDS Acknowledgement

National coordinators in 20 countries

Michael Dworzak, Austria
Barbara De Moerloose, Belgium
Jan Starý, Czech Republic
Henrik Hasle, Denmark
Kirsi Jahnukainen, Finland
Charlotte Niemeyer, Germany
Sophia Polychronopoulos, Greece
Krisztián Kállay, Hungary
Owen Smith, Ireland
Shlomit Barzilai, Israel
Shlomit Barzilai, Israel
Riccardo Masetti, Italy
Franco Locatelli, Italy
Jochen Büchner, Norway
Marek Ussowicz, Poland
Paula Kjollerstrom, Portugal
Oksana Fabri, Slovakia
Marko Kavcic, Slovenia
Albert Catala, Spain
Dominik Turkiewicz, Sweden
Markus Schmugge, Switzerland
Valérie De Haas, The Netherlands



Reference diagnostic laboratories in 20 European countries

Transplant teams of 20 European countries

I kindly acknowledge

Coordinating Study Center, Freiburg

Miriam Erlacher

Ayami Yoshimi

Brigitte Strahm

Christian Flotho,
Peter Nöllke,
Dirk Lebrecht,
Senthil Ramarmoorthy,
Cynthia Onditi,
and others

Wlodarski Lab

Marcin Wlodarski

Freiburg

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder

Sushree Sahoo

Victor Pastor

Emilia Kozyra

International Collaborators

Akiko Shimamura

David Williams

Mitch Weiss

Jean Soulier

UNIVERSITÄTS KLINIKUM FREIBURG
ZKJ ZENTRUM FÜR KINDER- UND JUGENDMEDIZIN

Thank you !

Freiburg Cathedral