Genetics of MDS

גנטיקה של תסמונות מיאלודיספלסטיות

Rafael Bejar MD, PhD

2nd Regional Symposium on MDS

Tel Aviv, Israel

March 5, 2020

UC San Diego
Moores Cancer Center

mds foundation
the myelodysplastic syndromes foundation, inc.
5-6 MARCH 2020, TEL AVIV, ISRAEL

Overview

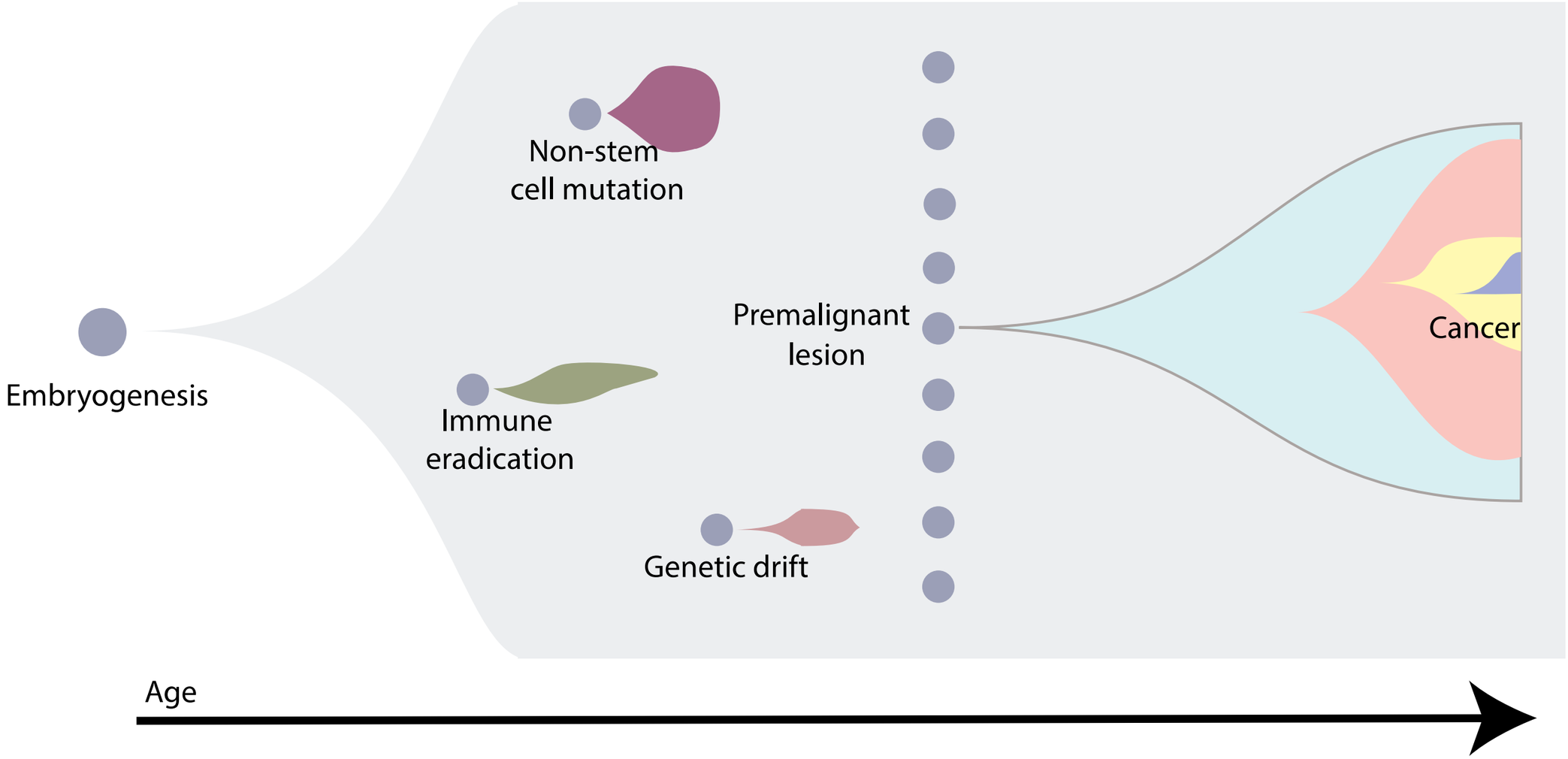
- MDS as a Clonal Disorder
- Landscape of Somatic Mutations
- Relationship to Other Myeloid Conditions
- Pathogenic Mechanisms of Mutations
- Clinical Implications
- Update on Plans from the IWG-PM

Welcome

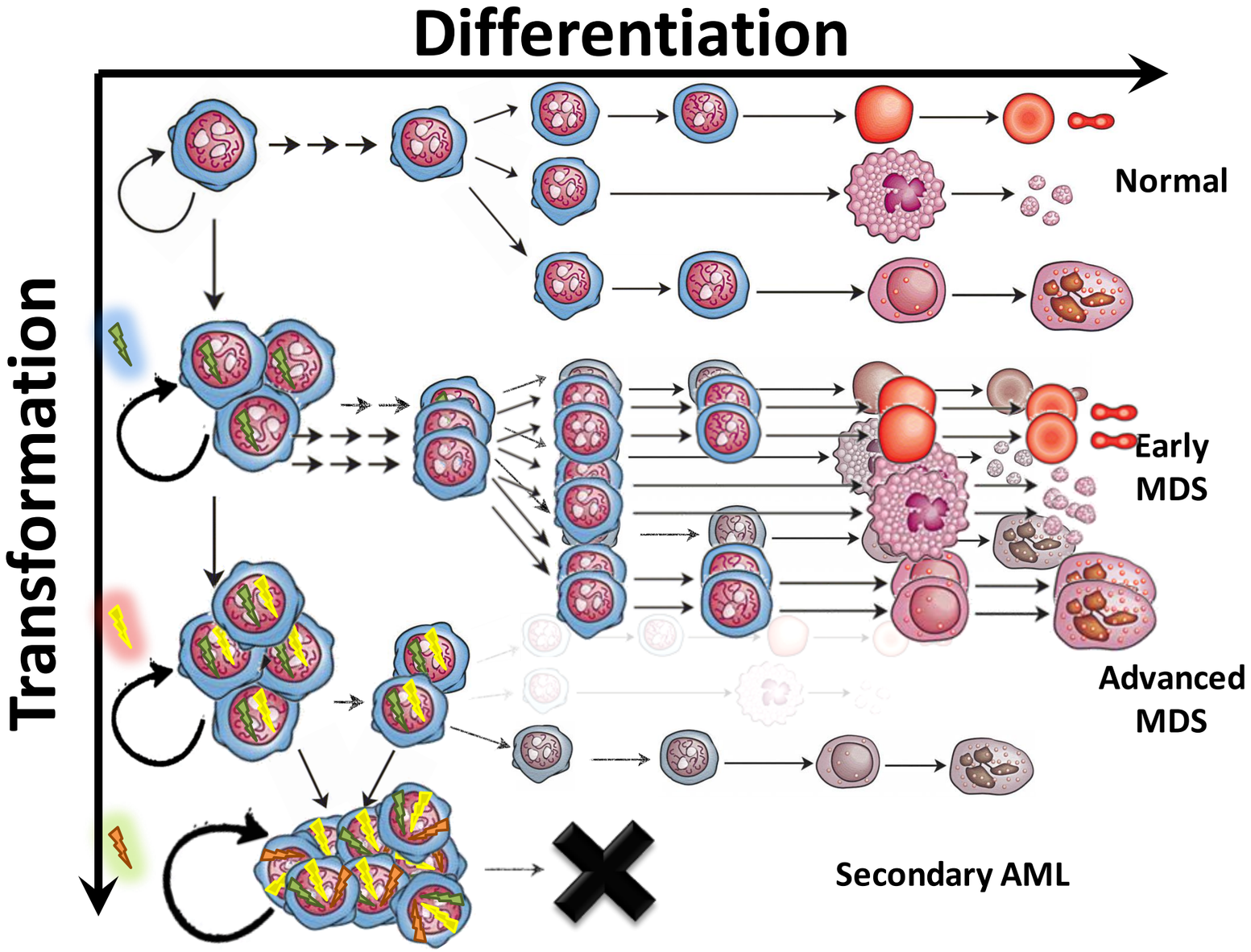

HOW TO PROPERLY
GREET SOMEONE DURING
THE CORONAVIRUS OUTBREAK
imgflip.com

MDS as a Clonal Disease

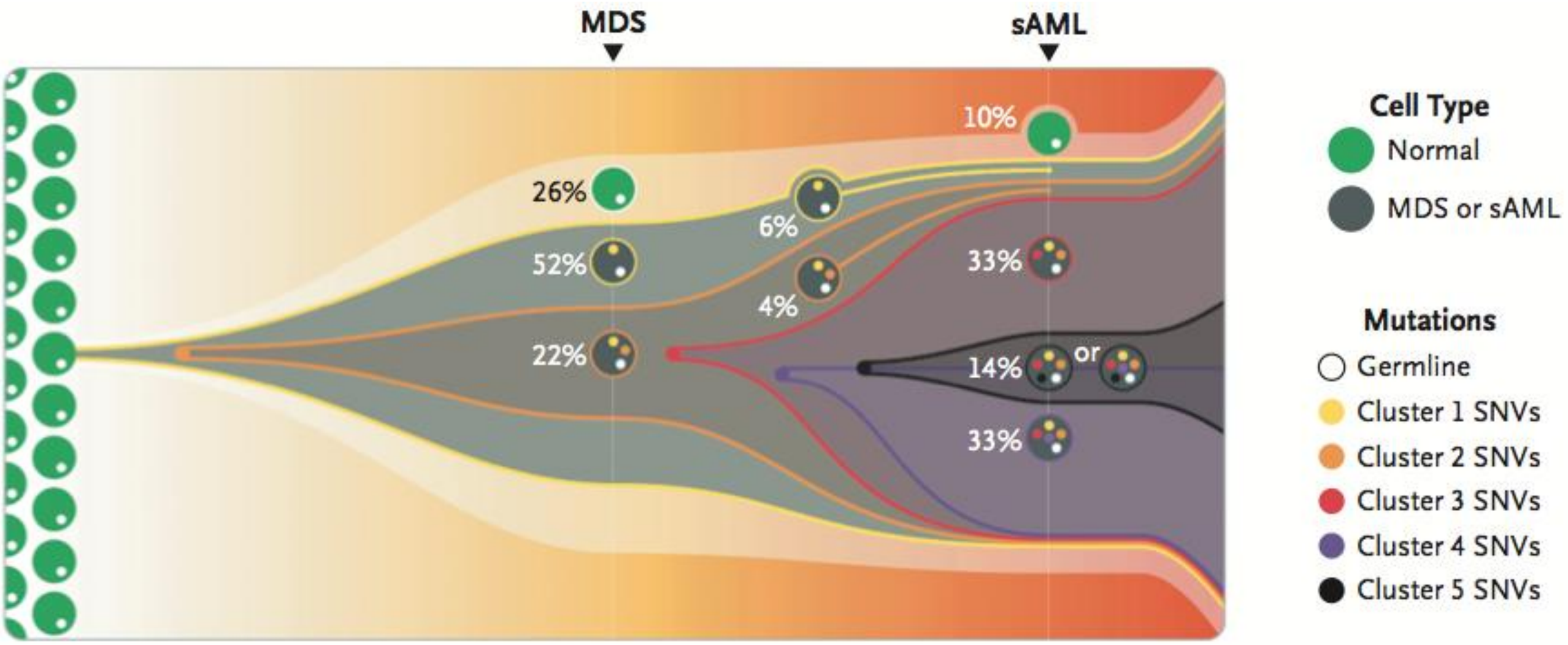
Clonality Alone is Not a Disease



Corrupted Hematopoiesis



Clonal Selection



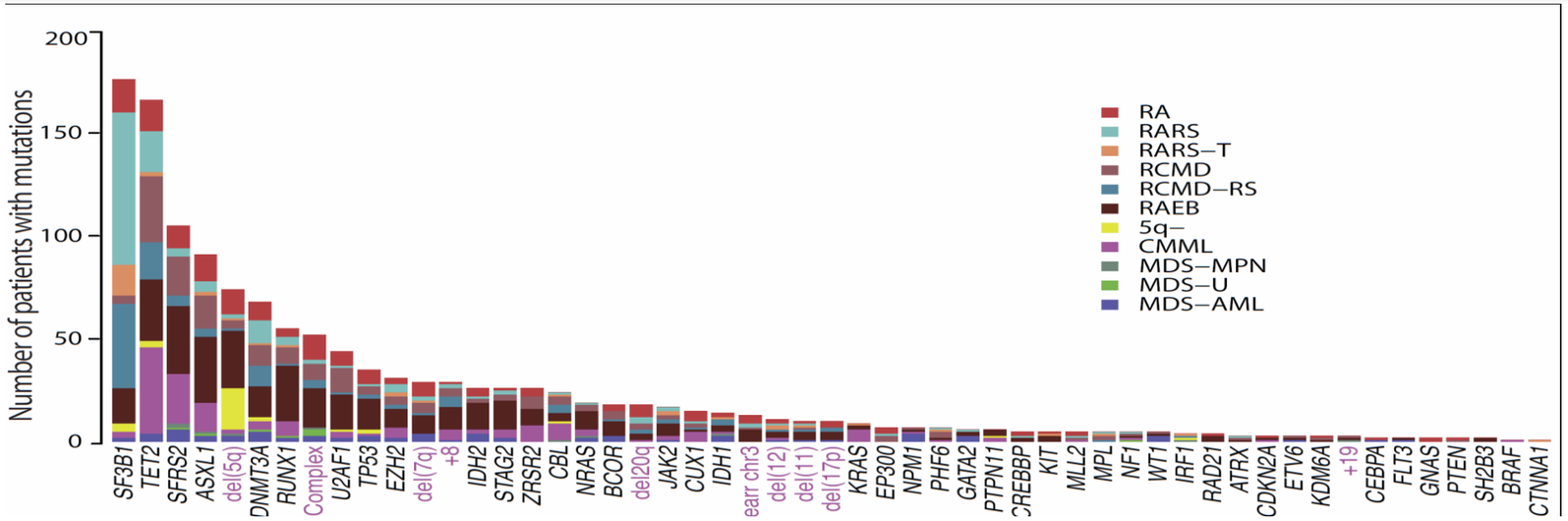
Walter et al, *NEJM* (2012)

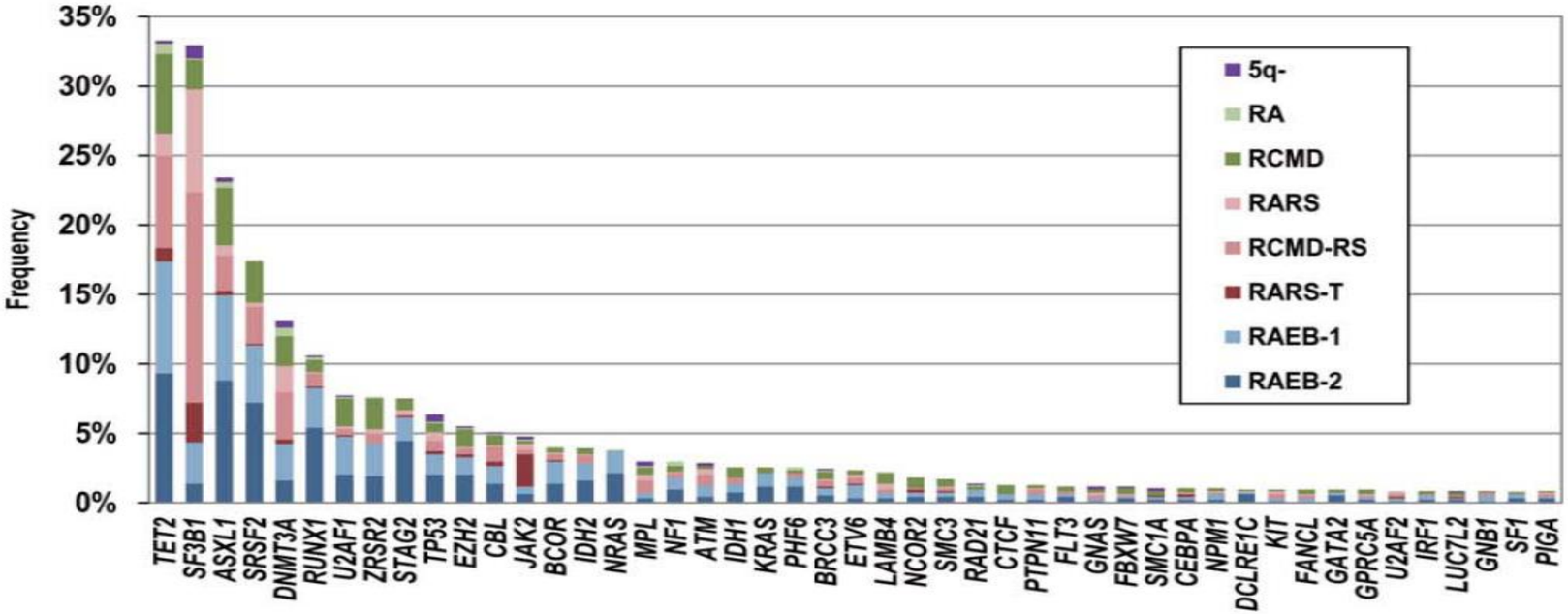
Genetic Abnormalities in MDS

Translocations/ Rearrangements
Rare in MDS
t(6;9)
i(17q)
t(1;7)
t(3;?)
t(11;?)
inv(3)
idic(X)(q13)

Somatic Mutations in MDS

Most Frequently Mutated Genes





2020

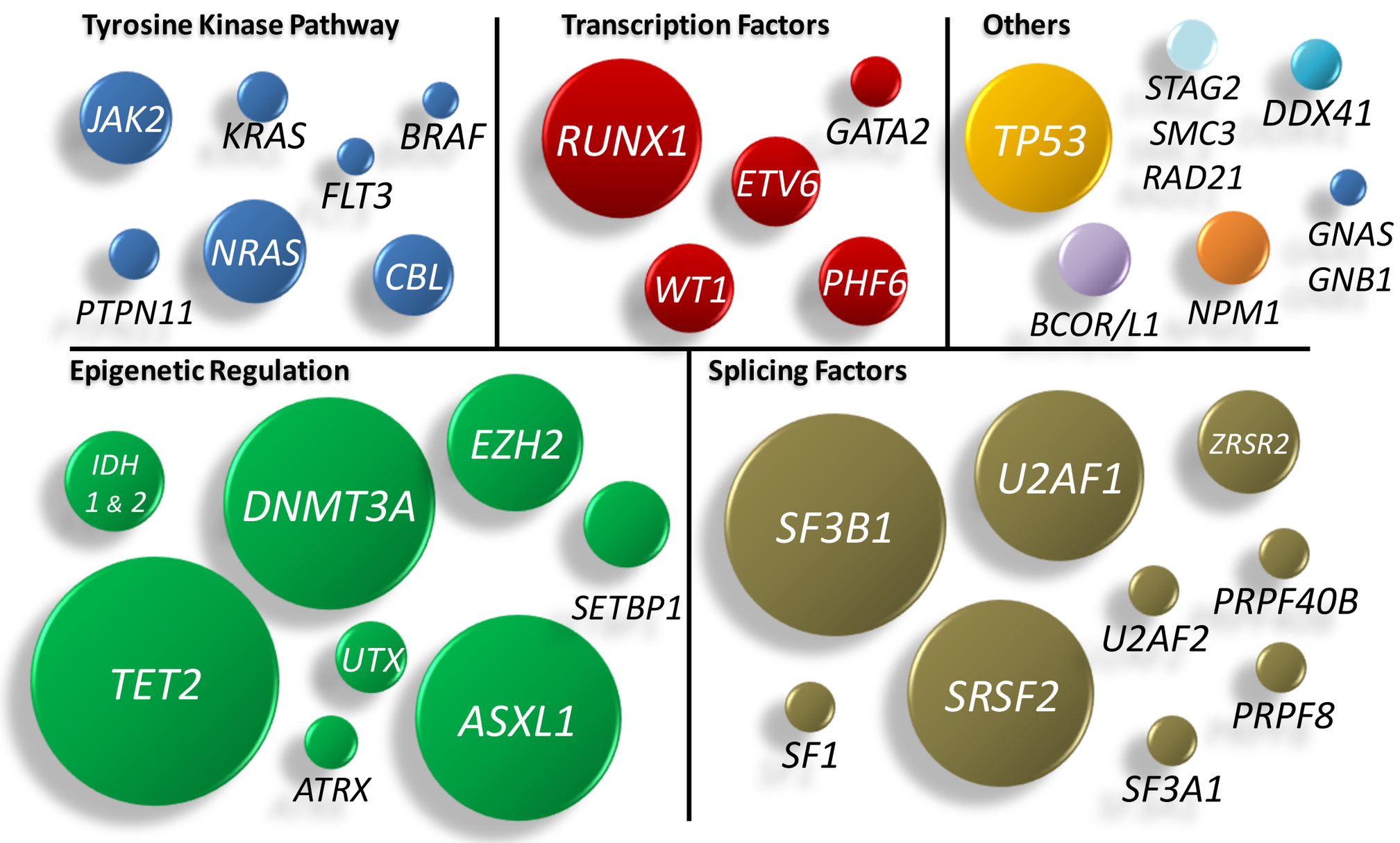
+

DDX41
CSNK1A1
ETNK1
NFE2
…

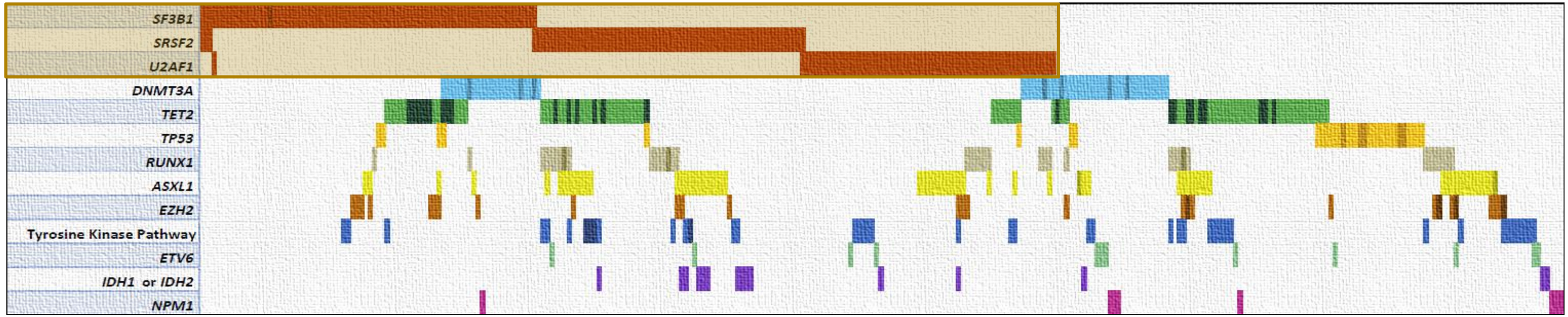
Papaemmanuil et al. *Blood*. 2013.

Haferlach et al. *Leukemia*. 2014.

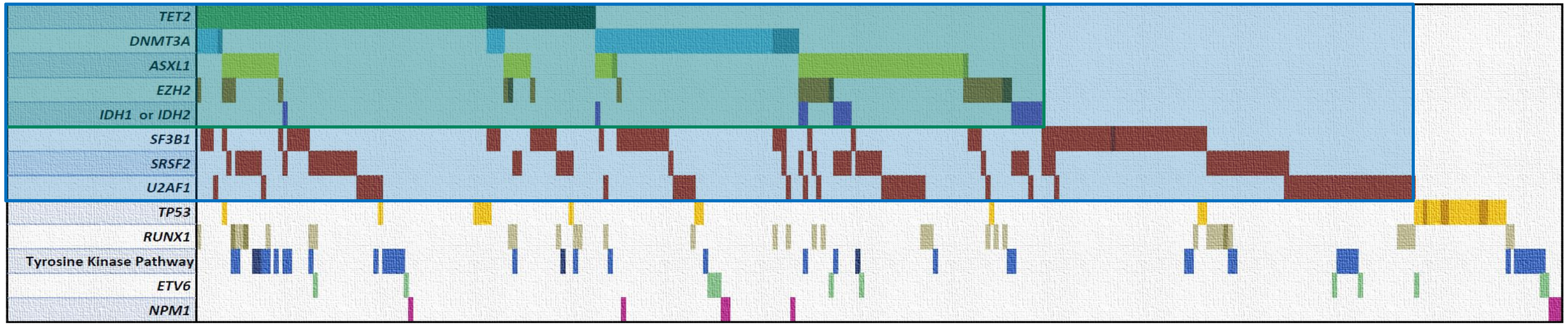
Most Frequently Mutated Genes



MDS Mutation Profiles



Myelodysplastic syndromes are diseases of the spliceosome and epigenetic regulation



Bejar et al. *NEJM*. 2011;**364**:2496-506.

Bejar et al. *JCO*. 2012;**30**:3376-82.

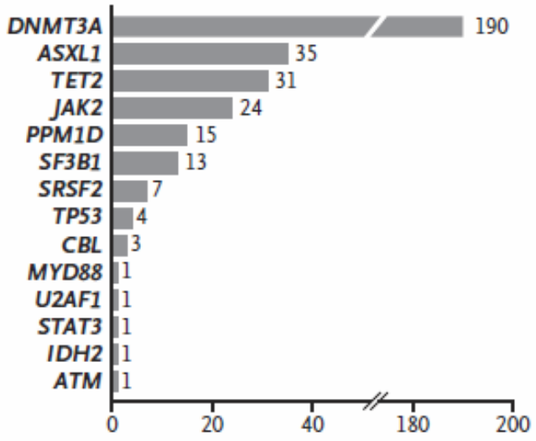
Patterns of Mutation

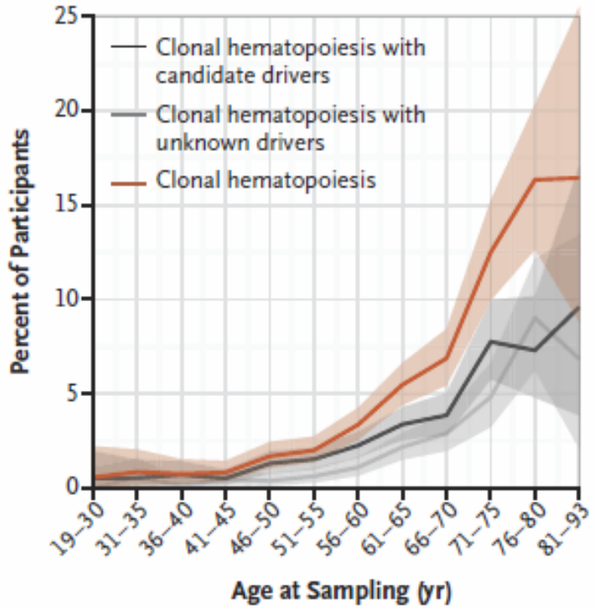
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S.,



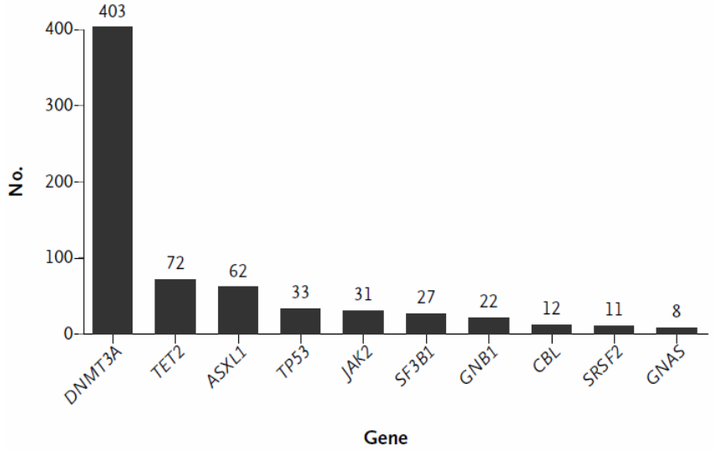


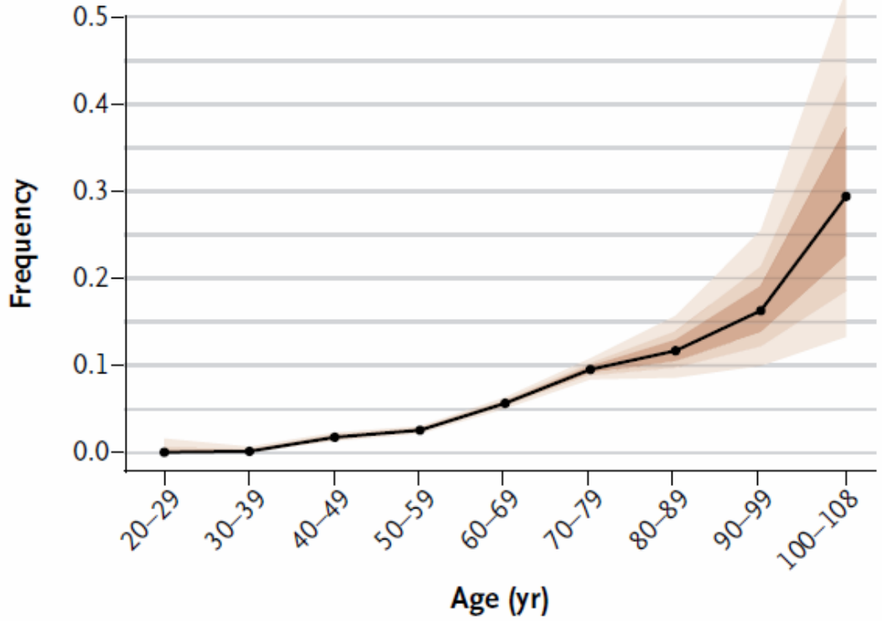
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

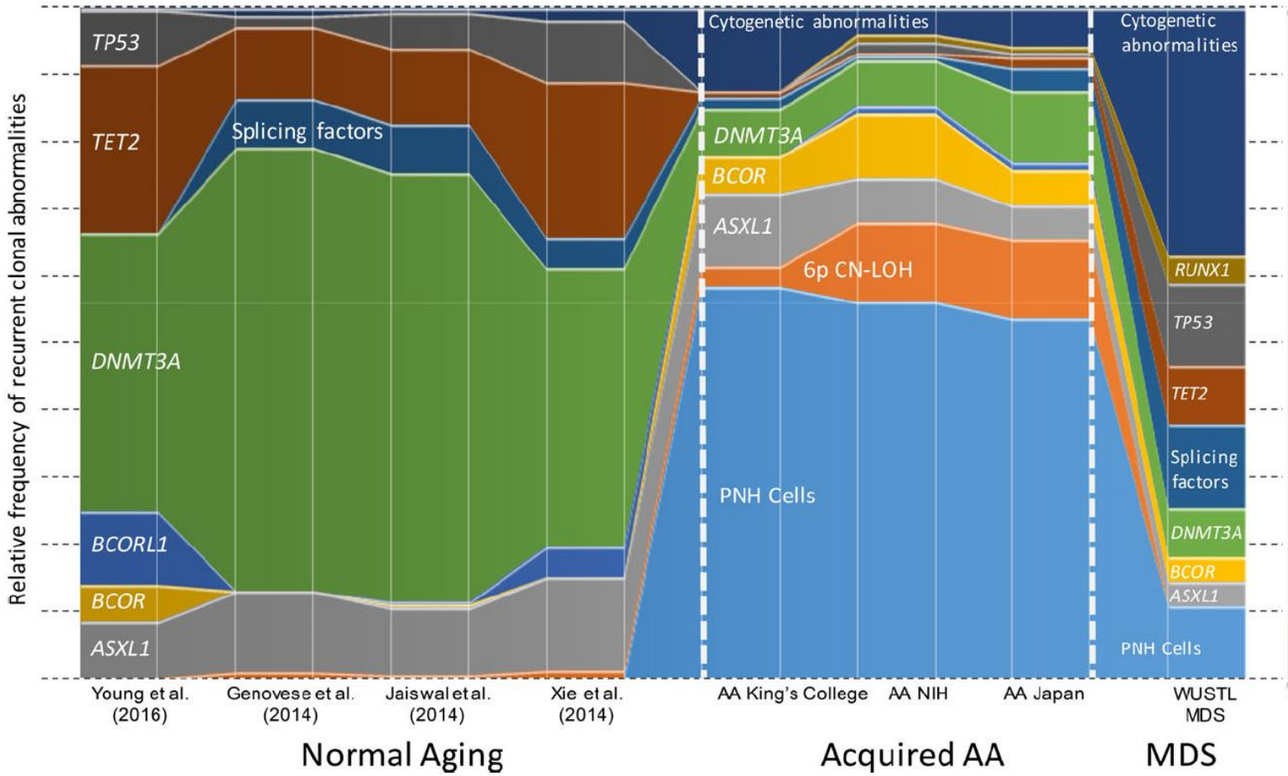
Siddhartha Jaiswal, M.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D.,





Mutation Pattern Comparisons

CHIP **AA** **MDS**



MPN **MDS**

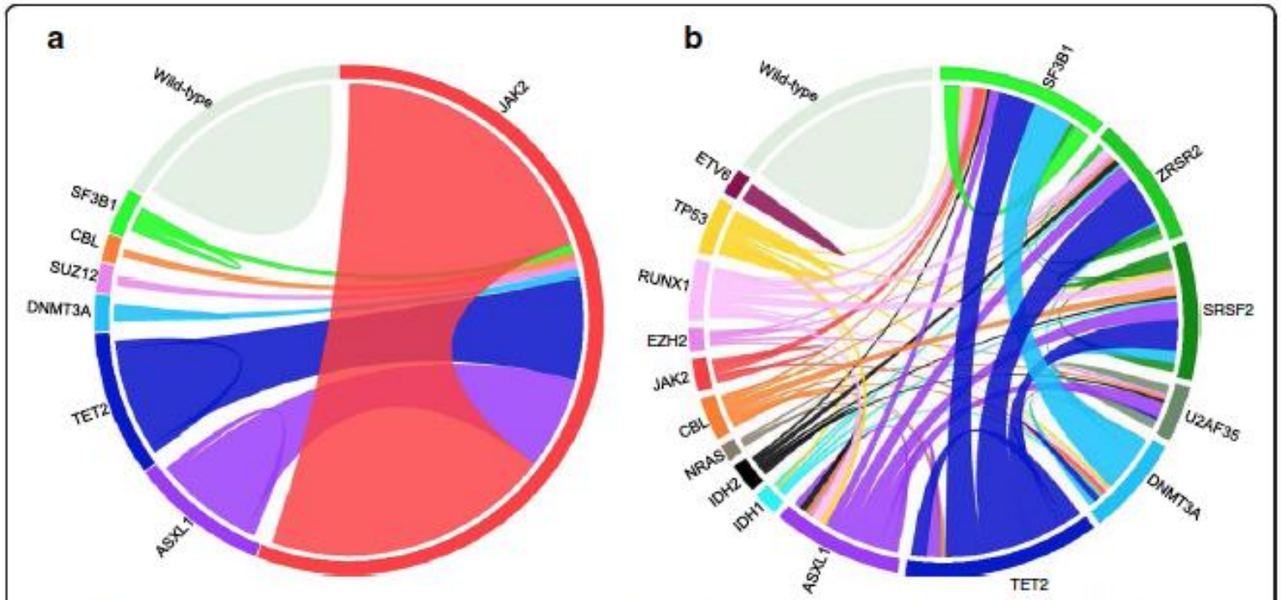


Figure 1 Circos diagrams depict the relative frequency and associations of the major mutations in MPNs (a) and MDSs (b), respectively based on data from our work [37] on 127 classic MPNs and from Damm's study [38] on 221 MDSs. Wild-type means that no disease allele has been detected in the genes listed.

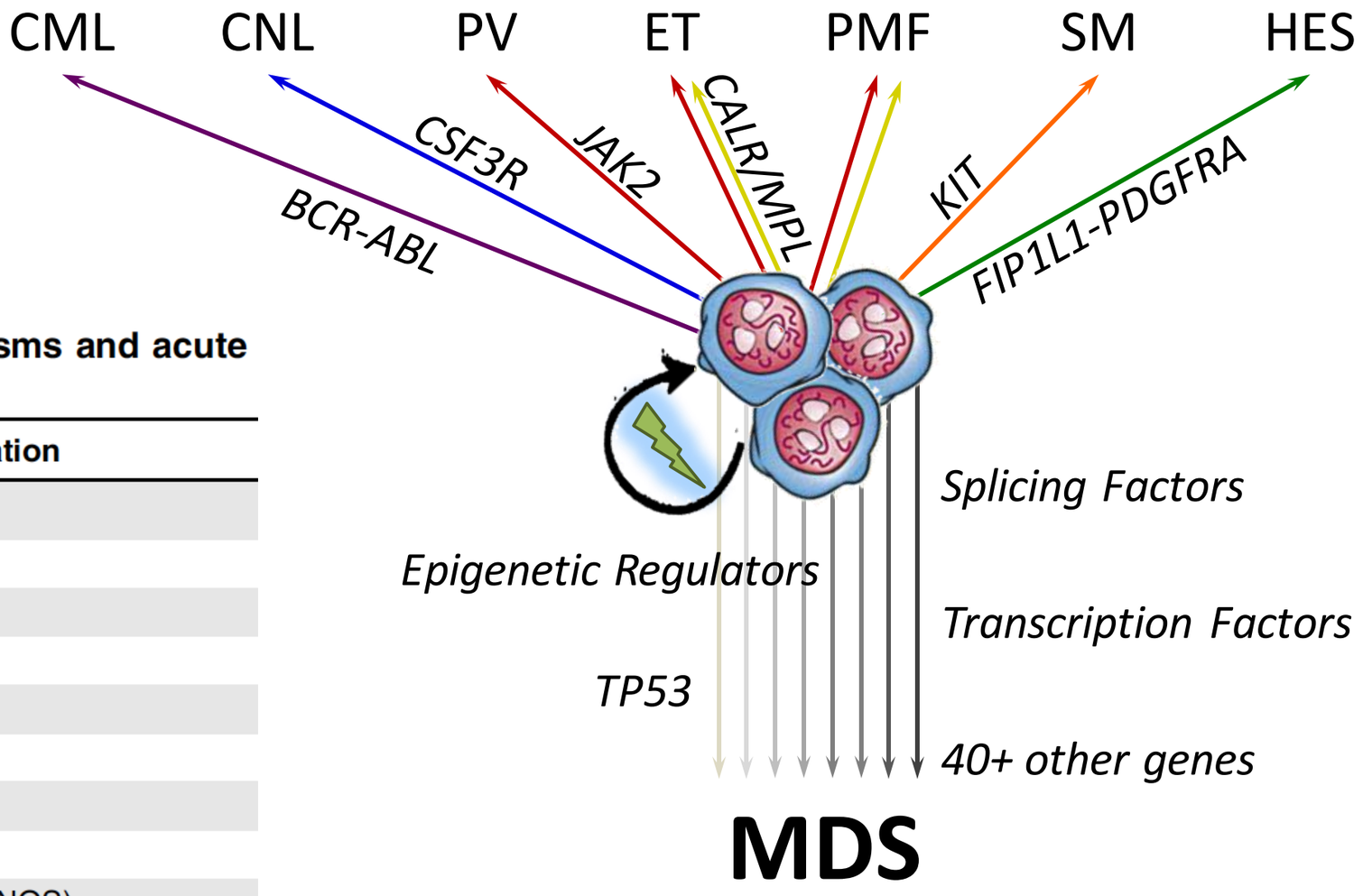
Stanley et al. *British Journal of Haematology* 2017, 177:509–525.

Murati et al. *BMC Cancer* 2012, 12:304.

Myeloproliferative Neoplasms

Table 1. WHO classification of myeloid neoplasms and acute leukemia

WHO myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis

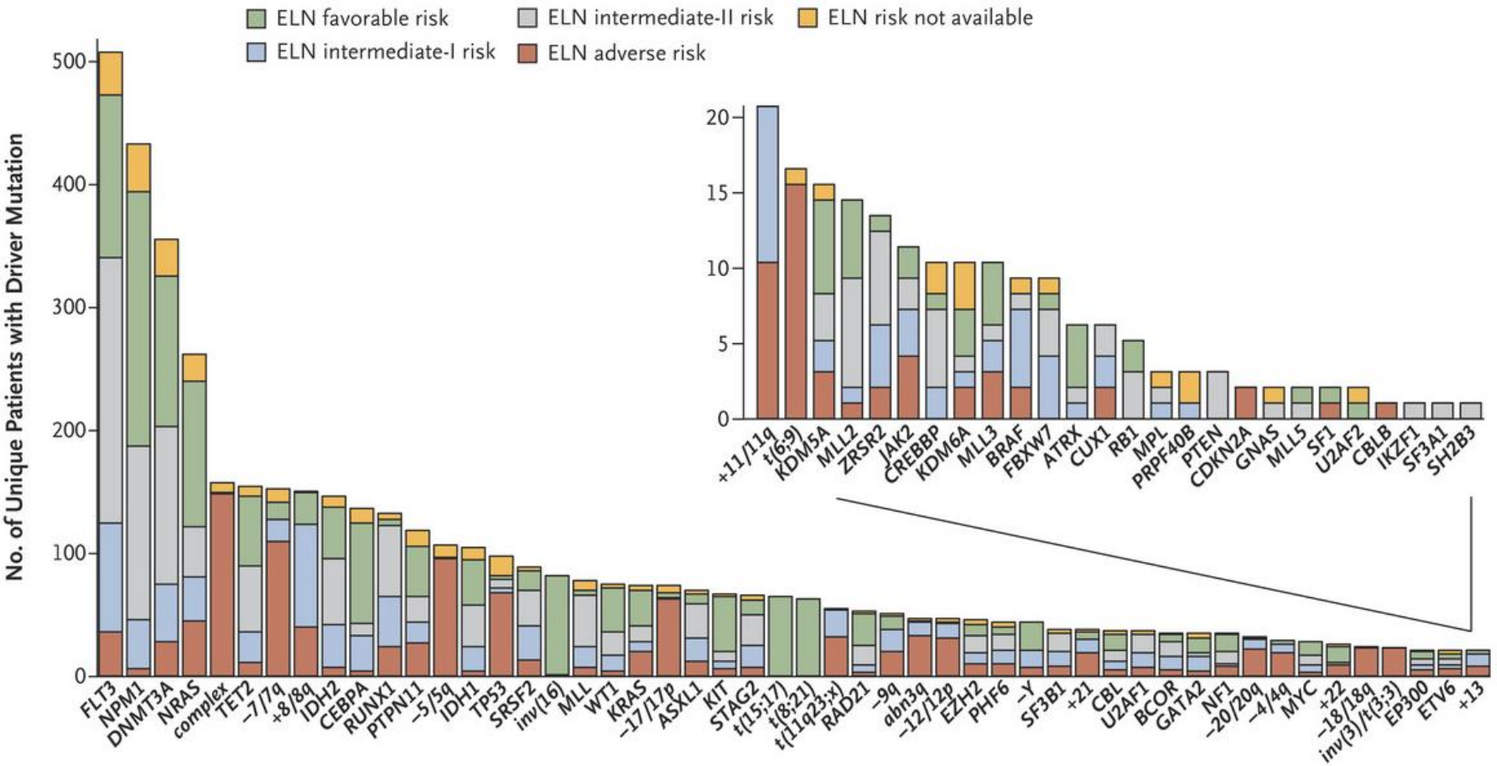


Arber et al. *Blood*. 2016;127(20):2391-2405.

Mutation Patterns in MDS vs. AML

Papaemmanuil et al. *Blood*. 2013.

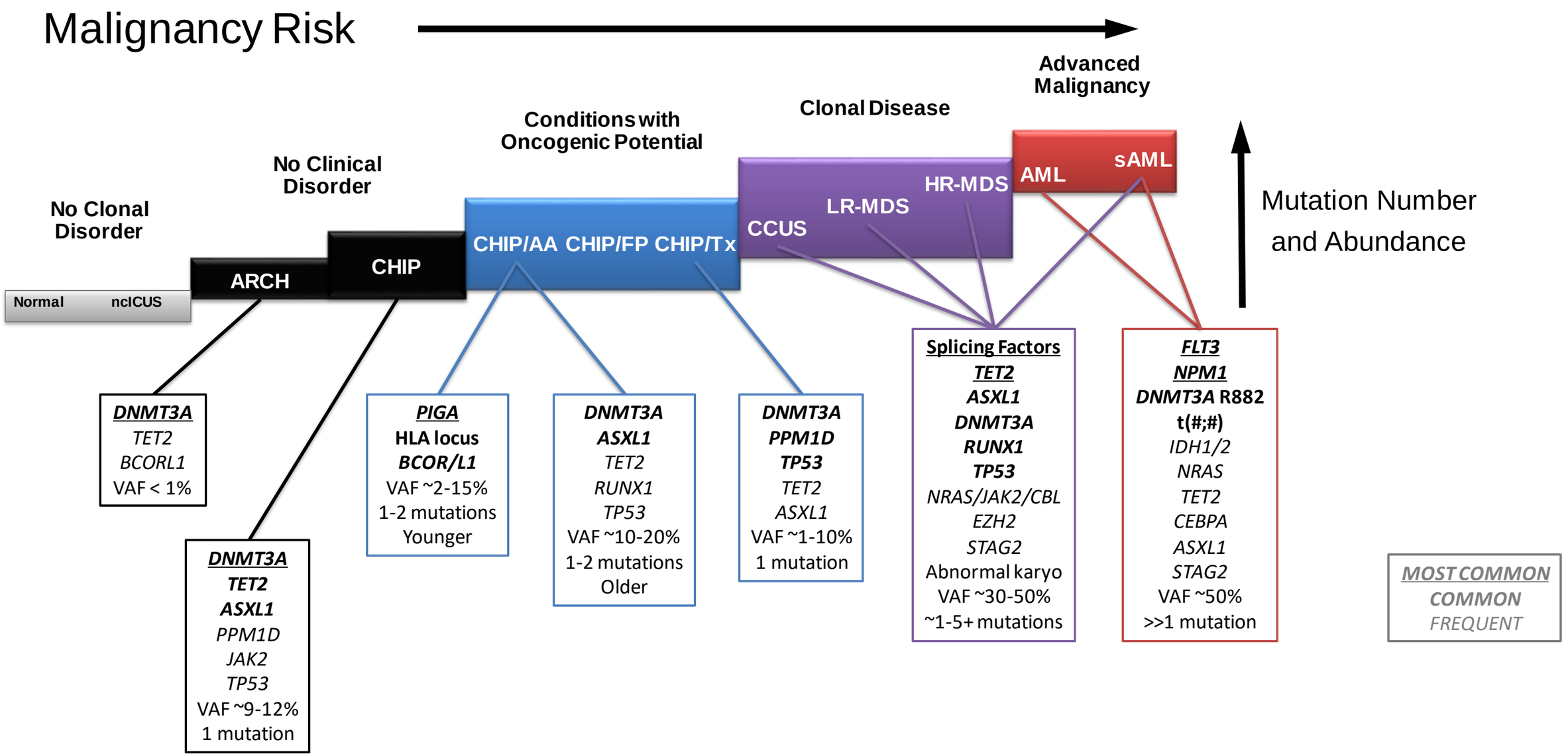
Papaemmanuil et al. *NEJM*. 2016.



MDS	AML
TET2	***FLT3***
SF3B1	***NPM1***
ASXL1	***DNMT3A***
SRSF2	***NRAS***
DNMT3A	*TET2*
RUNX1	*IDH2*
U2AF1	*CEBPA*
ZRSR2	*RUNX1*
TP53	*IDH1*
EZH2	*TP53*

Haferlach et al. *Leukemia*. 2013

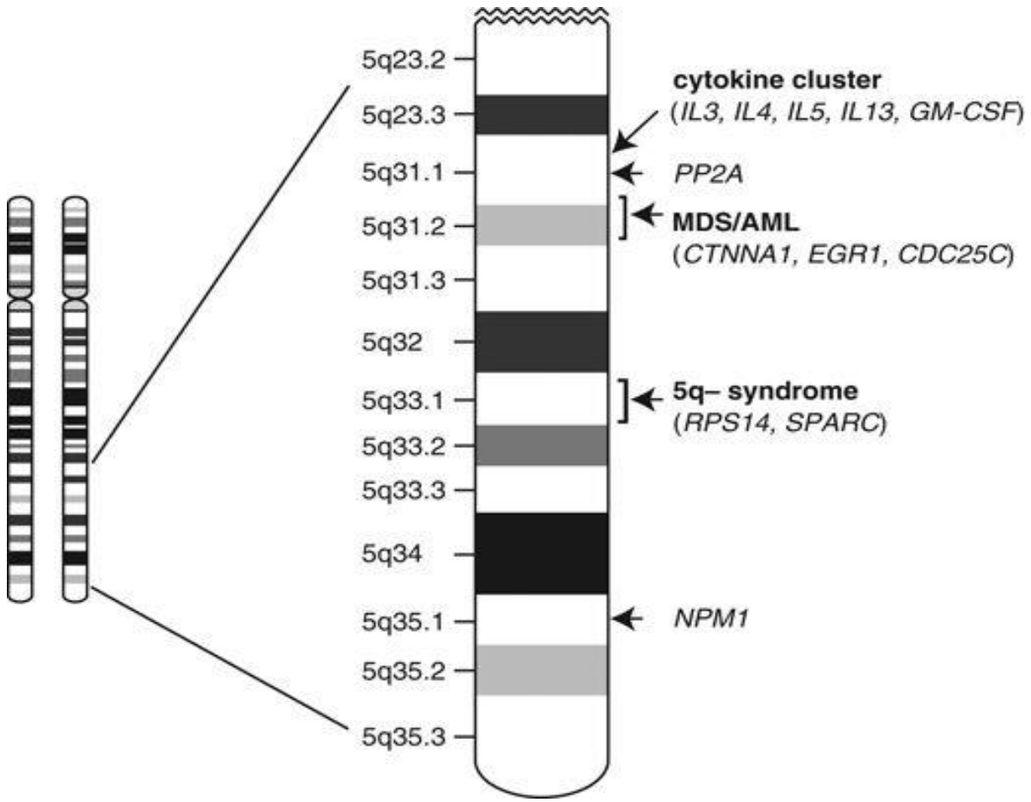
Mutation Comparisons

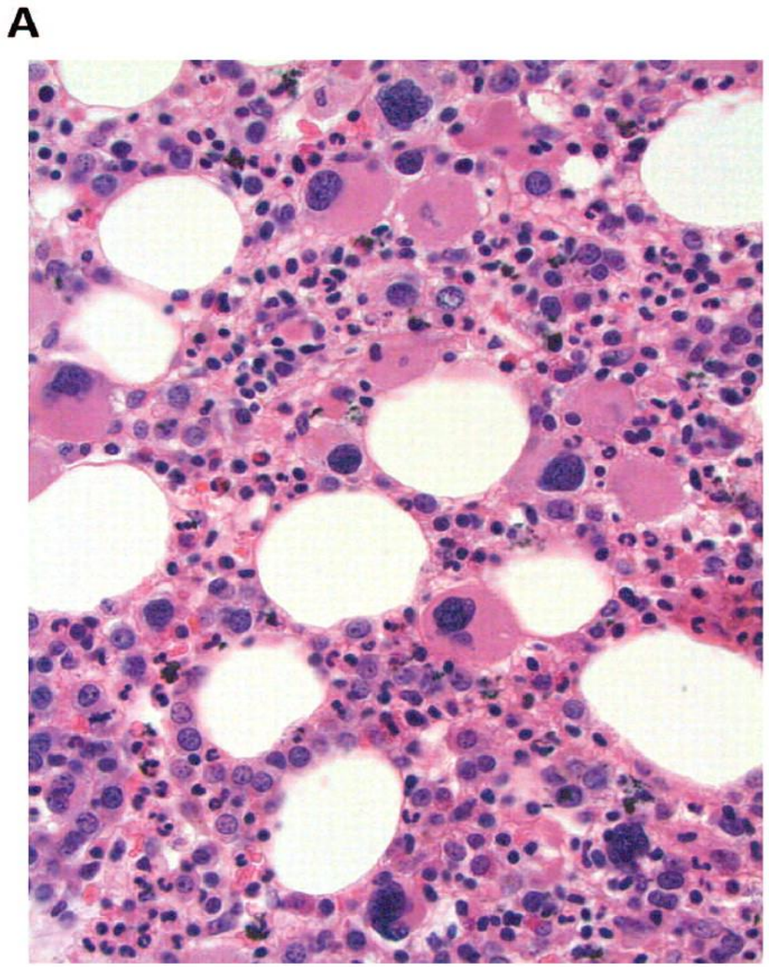


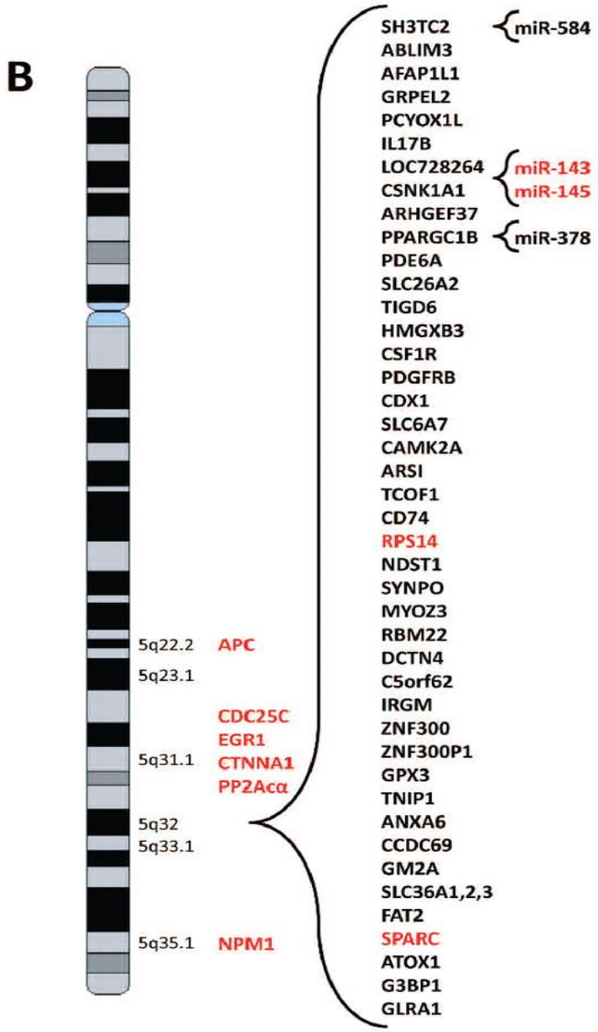
Bejar R. *Leukemia*. 2017 Sep;31(9):1869-1871.

Pathogenic Mechanisms

Haploinsufficiency in 5q- Syndrome

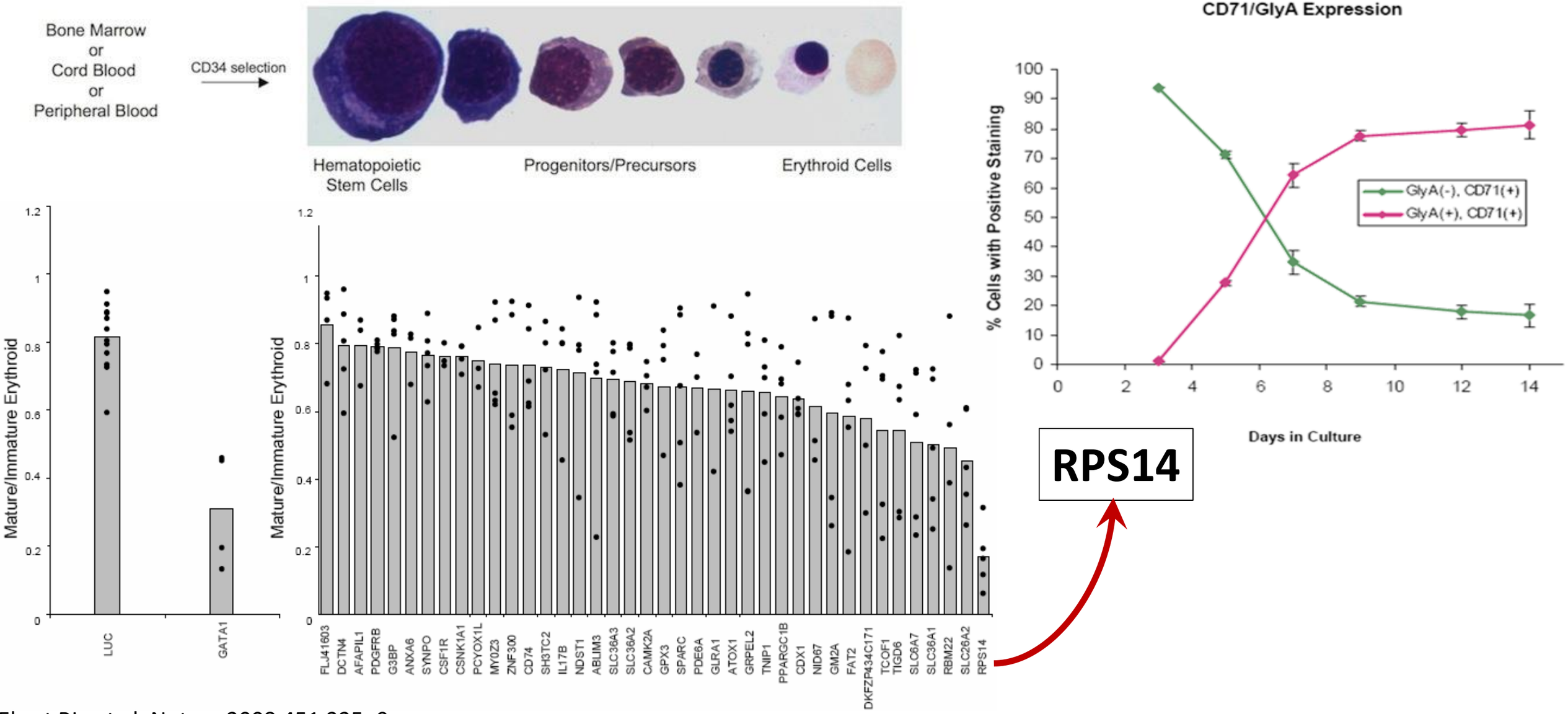






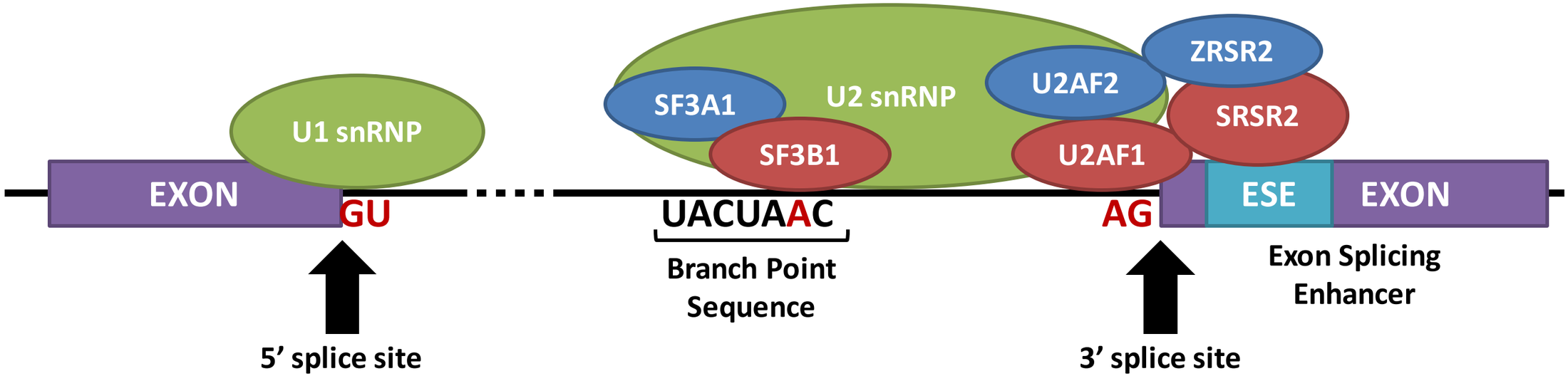
Ebert BL. *Leukemia* 2009;23:1252–6.

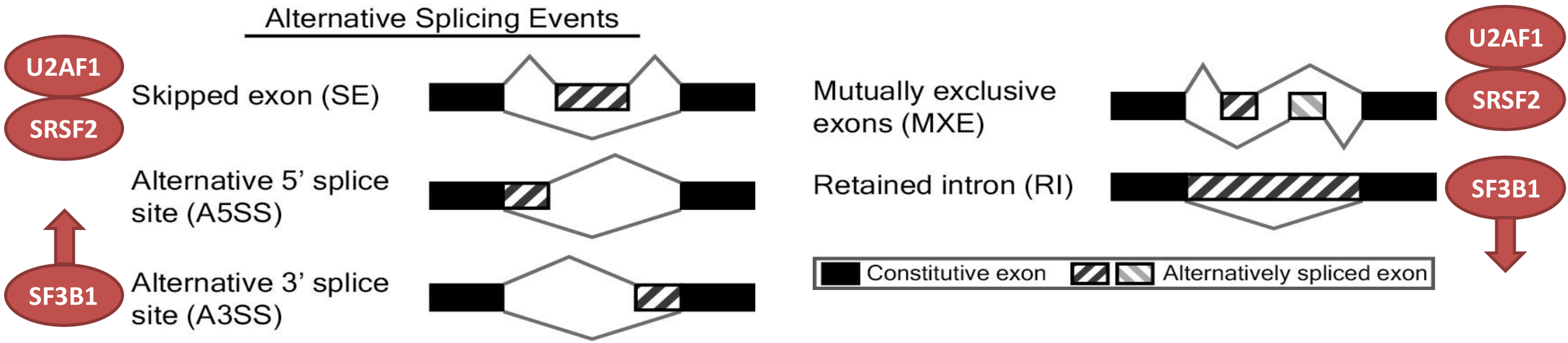
5q-minus Syndrome: *RPS14*



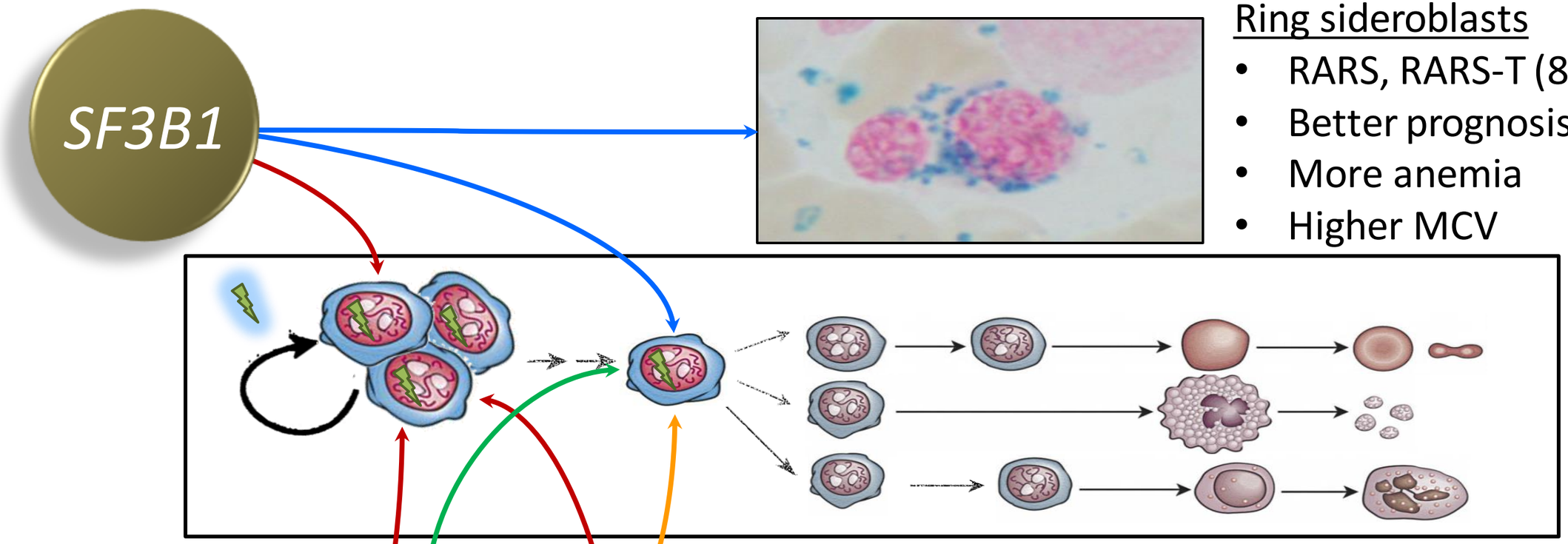
Ebert BL, et al. Nature 2008;451:335–9.

Splicing Factor Complexes

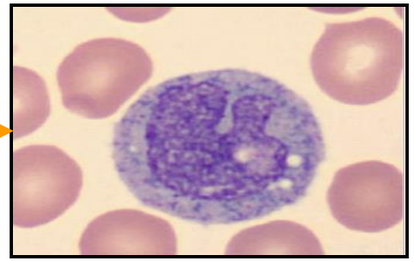




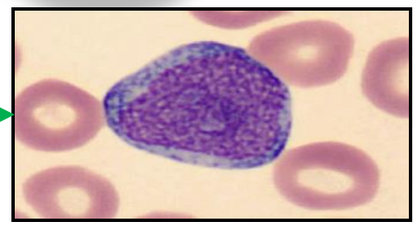
Stem vs. Progenitor Effects



Ring sideroblasts
- RARS, RARS-T (80+%)
- Better prognosis
- More anemia
- Higher MCV

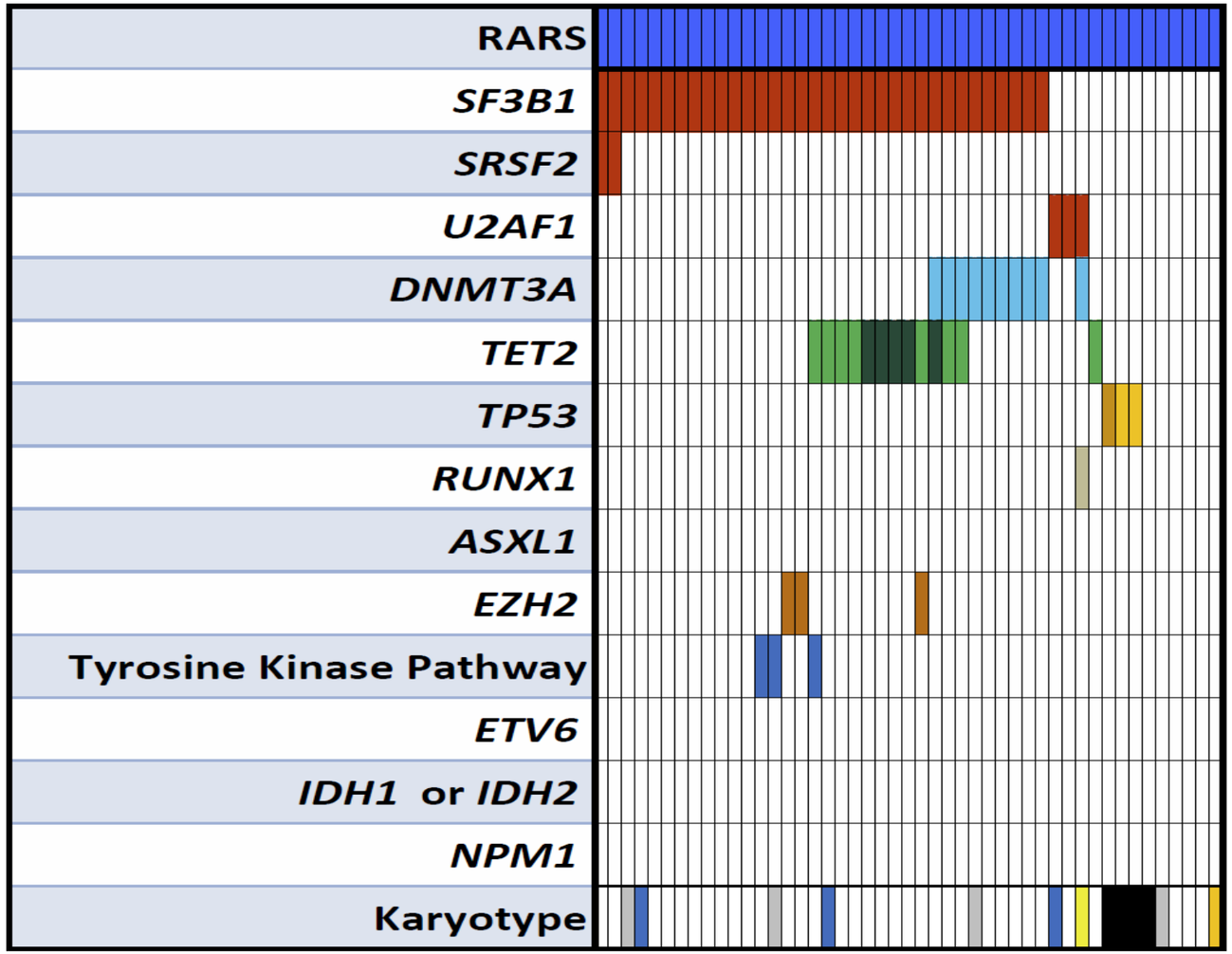


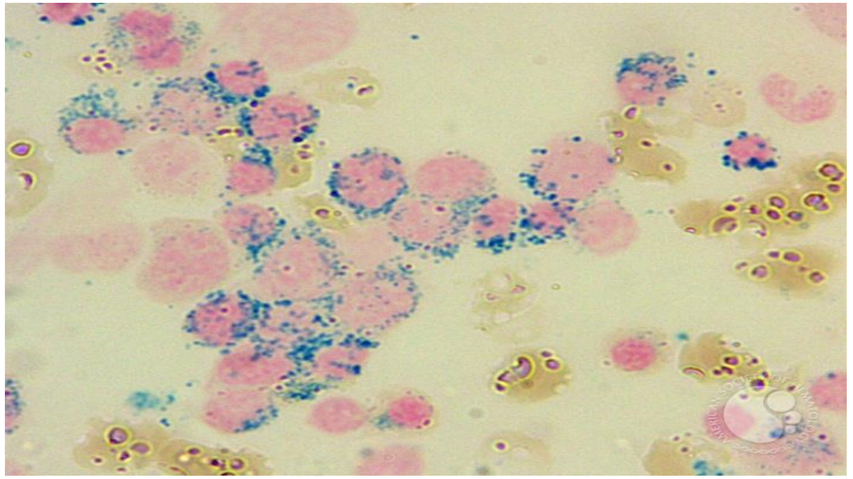
Monocytosis
- CMML (40+%)
- Worse prognosis

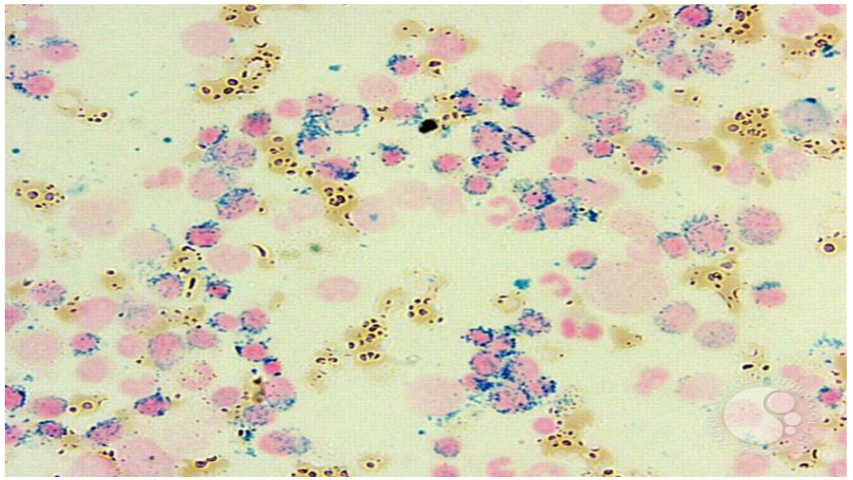


Linked to del(20q)?
- Risk of AML transformation
- Maybe worse prognosis

Ring Sideroblasts and *SF3B1* Mutation





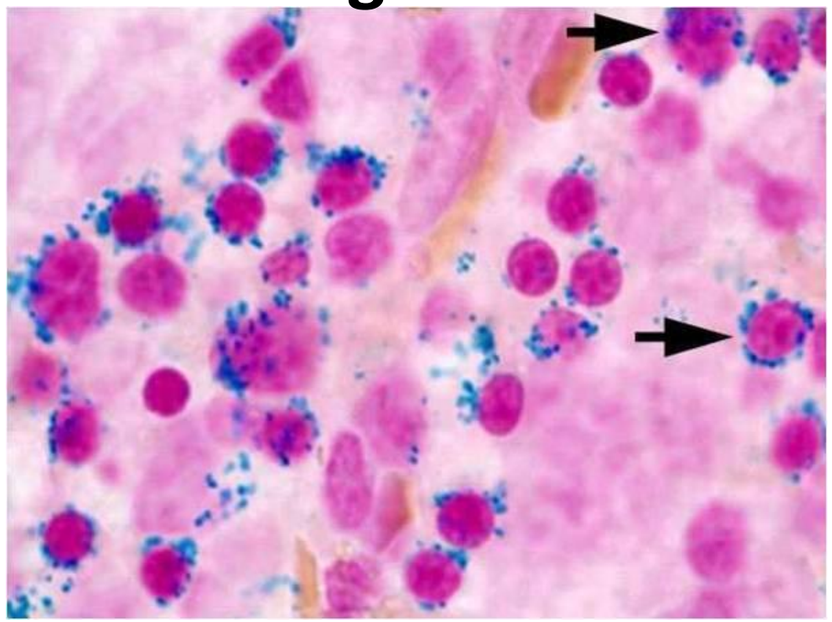


Bejar et al. *NEJM*. 2011;**364**:2496-506.

Bejar et al. *JCO*. 2012;**30**:3376-82.

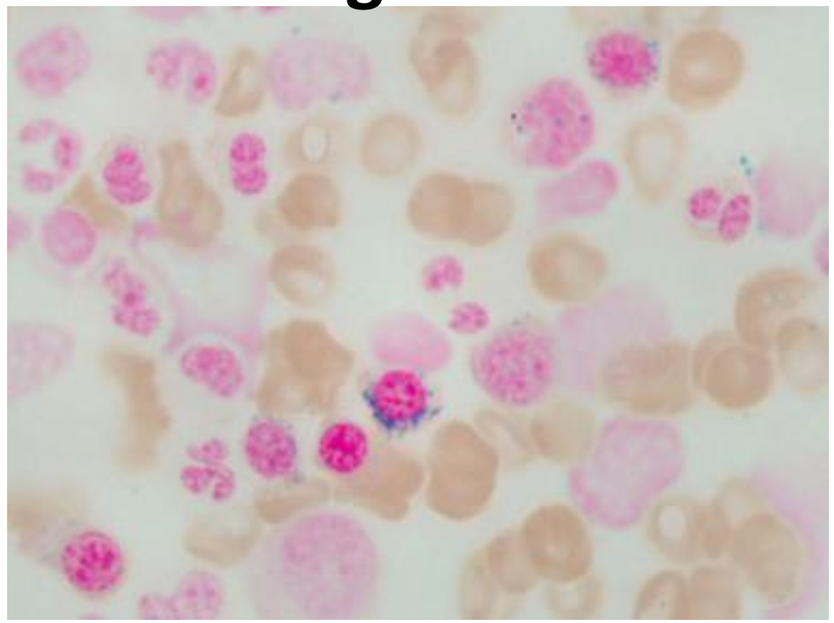
2016 WHO Guidelines

≥ 15% ring sideroblasts



MDS-RS

5-14% ring sideroblasts

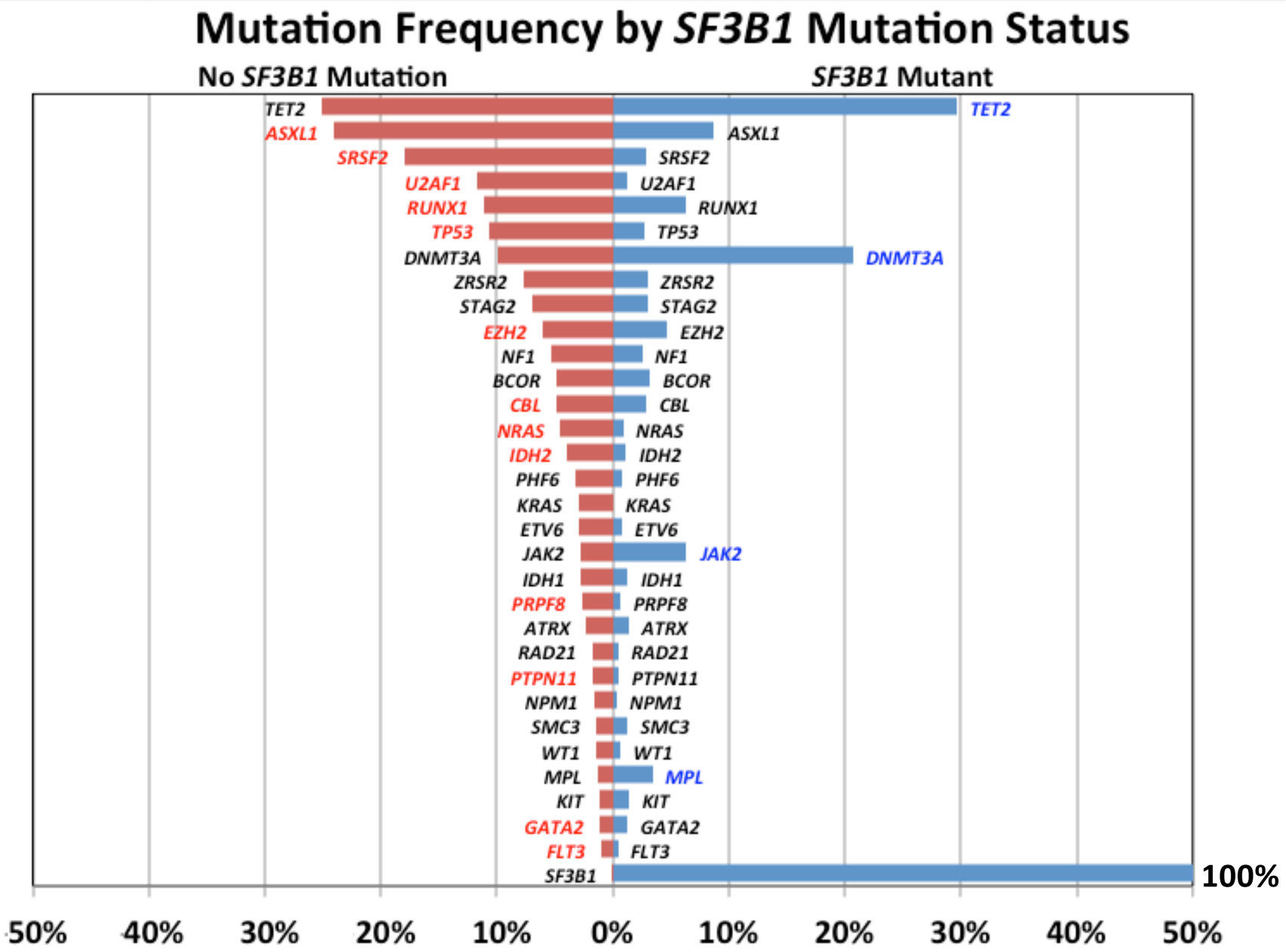


ICUS

+ *SF3B1* mutation

Arber et al. *Blood*. 2016; 127(20):2391-405.

Prognostic Interactions Between Mutated Genes



SF3B1 mutant MDS patients have fewer mutations in genes associated with greater disease risk.

(highlighted in red)

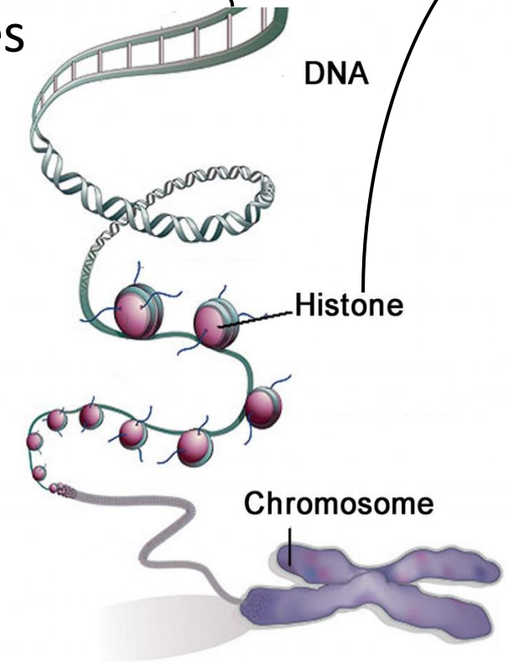
Epigenetic Regulators in MDS

DNA Methylation ⟷ **Histone Modifications**

Methylation of CpG dinucleotides

Heritable non-coding change

Associated with gene silencing



Many types of modifications:

methylation - acetylation - phosphorylation – SUMOlation - citrullination - ribosylation

Linked to different chromatic states

Can be associated with gene silencing, priming or expression

TET2

DNMT3A

IDH 1 & 2

JAK2

SETBP1

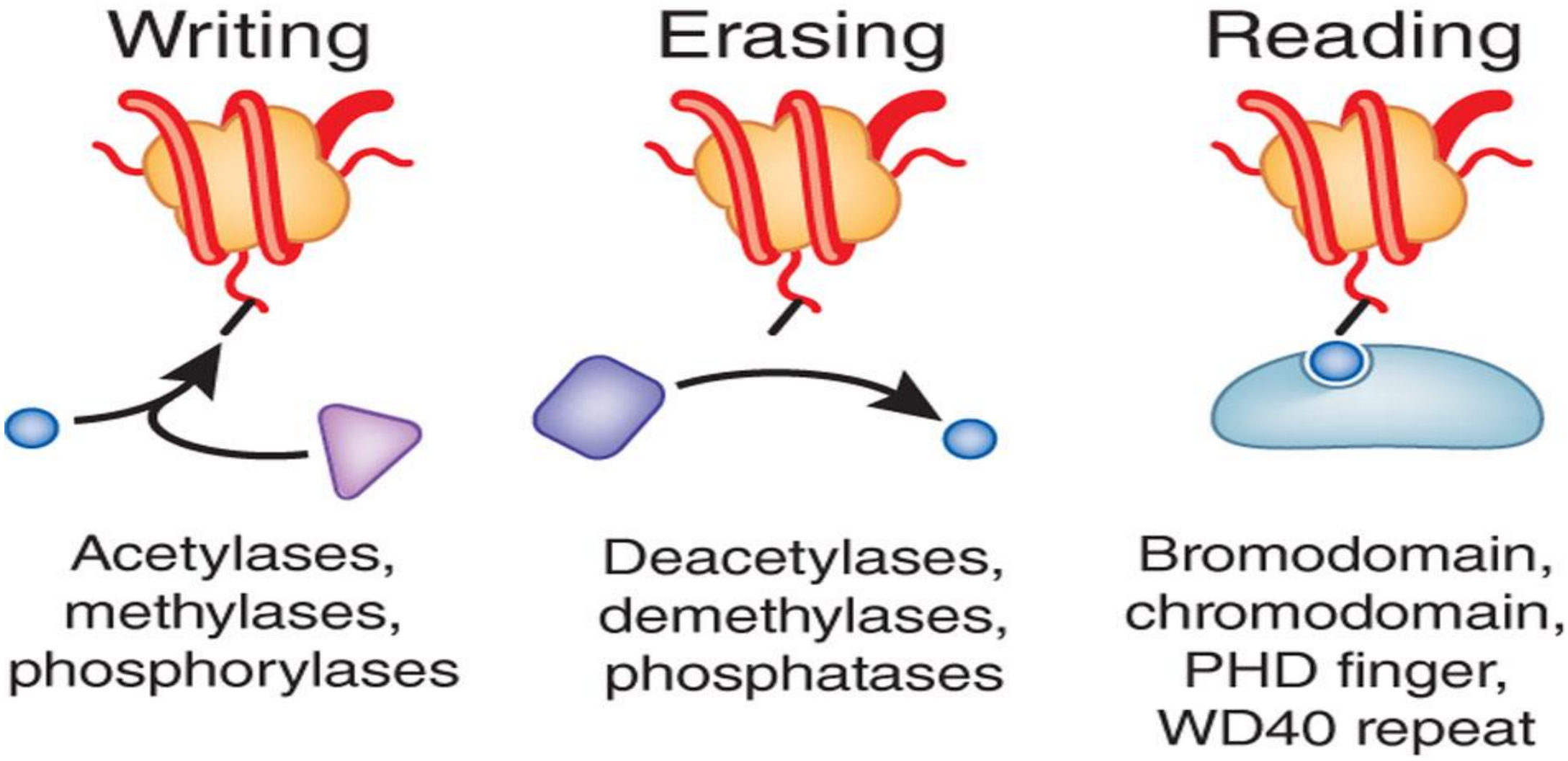
UTX

ASXL1

EZH2

ATRX

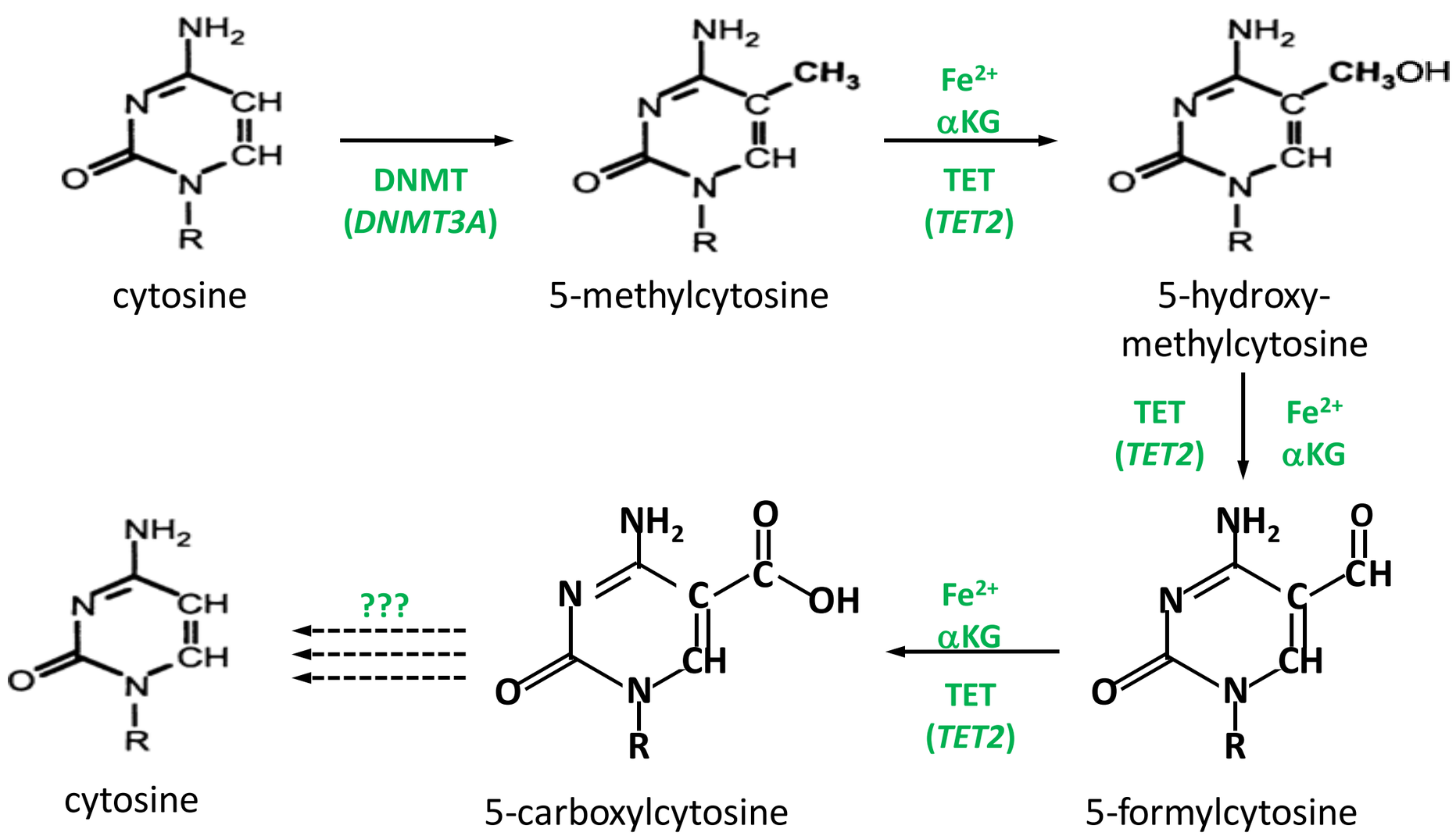
Epigenetic Regulators in MDS



DNMT3A and *TET2* Mutations in MDS

DNMT3A

TET2



Tahiliani et al. *Science.* **324**:930-935, 2009.

Ito et al. *Science.* **333**:1300-3, 2011.

IDH1 and *IDH2* Mutations in MDS

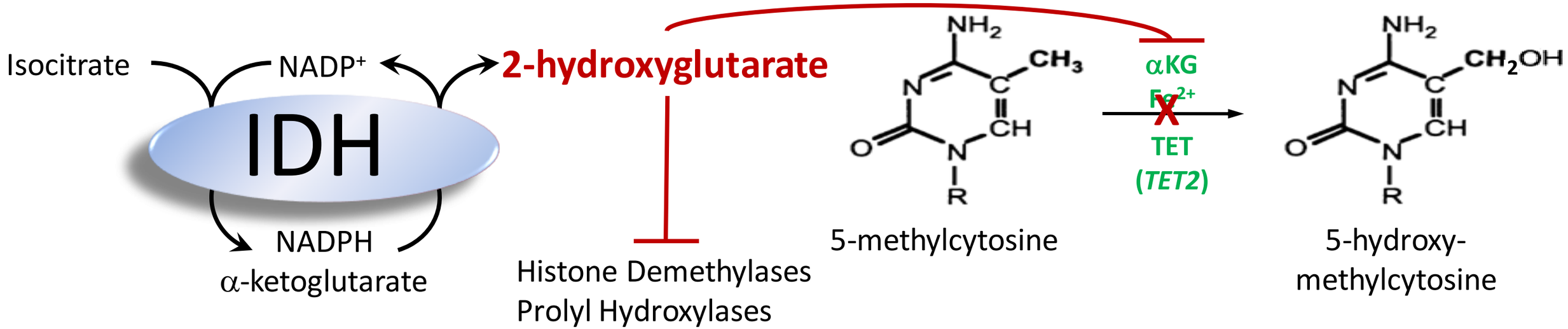
IDH1

Mutated rarely in MDS and more often in AML

Mutually exclusive with mutations of *TET2* and each other

IDH2

Mutations cause a *gain* of function - that drugs can target!



Xu et al. *Cancer Cell.* **19**:17-30, 2011.

Sasaki et al. *Nature.* **488**:656-9, 2012

Transcription Factors and Others

RUNX1

Master regulators of differentiation

ETV6

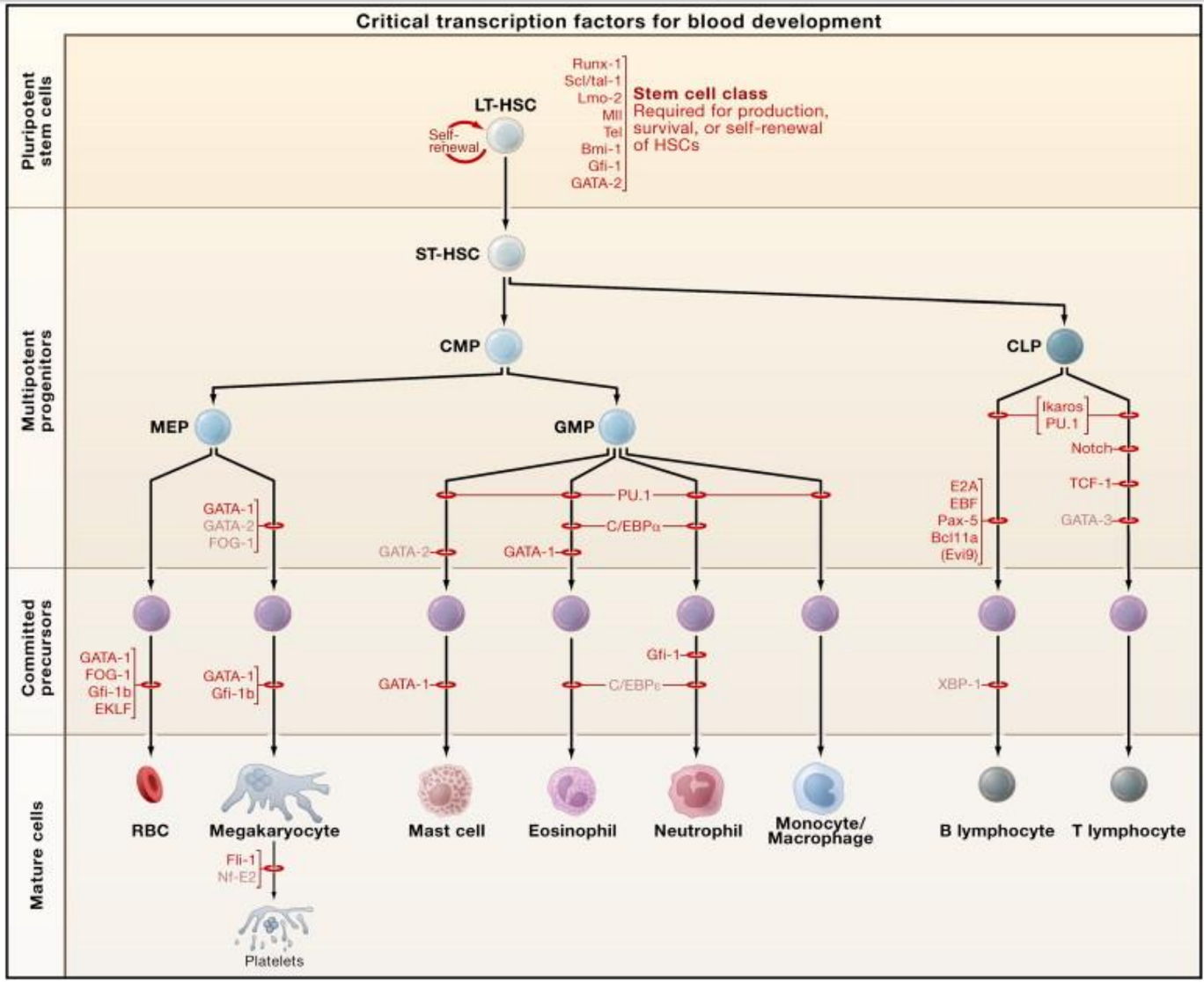
GATA2

TP53

Master regulator of stress/damage response

DDX41

Regulator of innate Immune signaling?



Clinical Implications

Analysis of Combined Datasets from the International Working Group for MDS-Molecular Prognosis Committee

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Donna Neuberg, ScD
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Mikkael A. Sekeres, MD, MS
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Claudia Haferlach, MD
Torsten Haferlach, MD
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Yasunobu Nagata, MD, PhD
Kenichi Yoshida, MD, PhD
Timothy A. Graubert, MD
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Elli Papaemmanuil, PhD
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Michael R. Savona, MD
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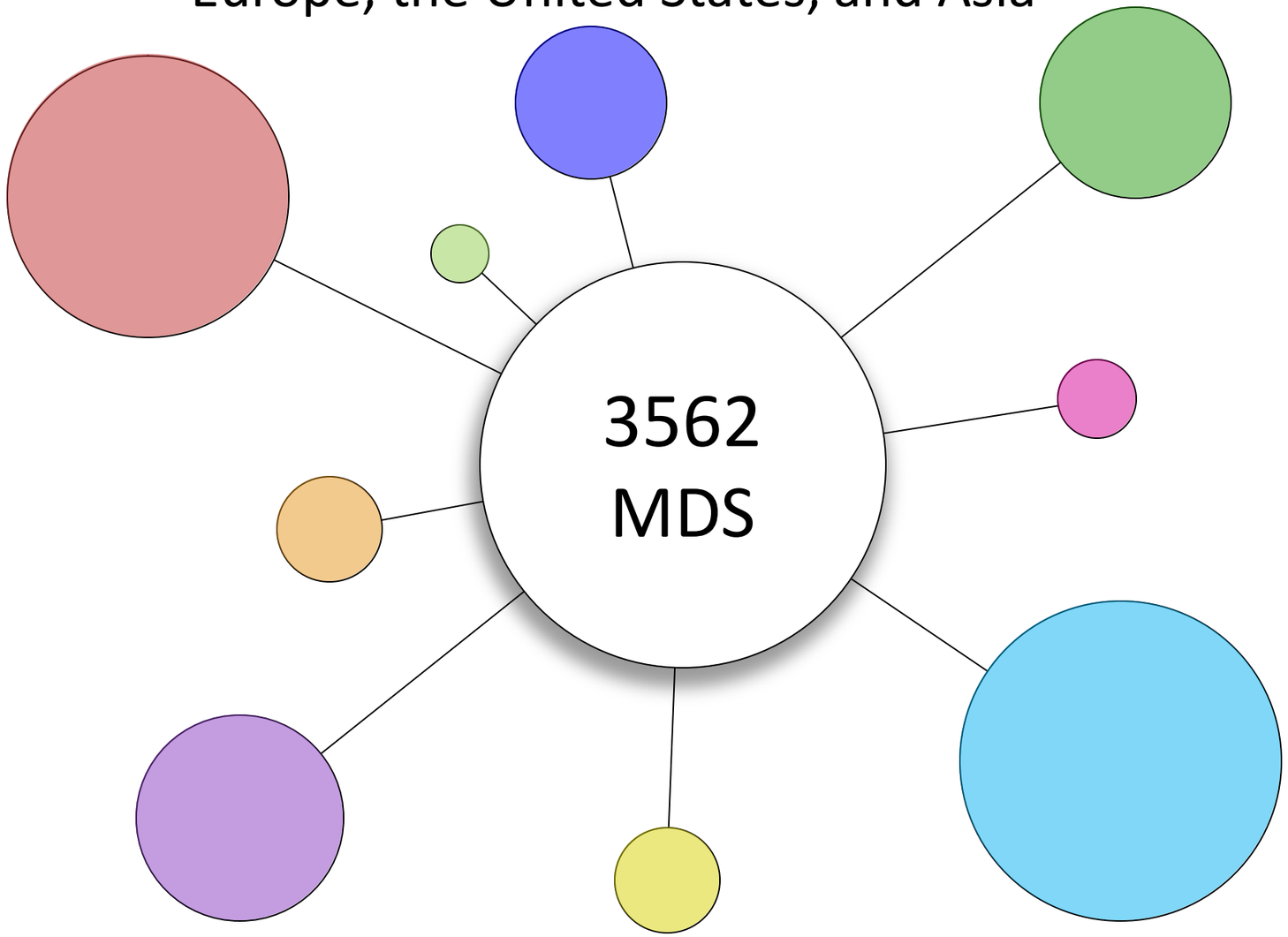
Luca Malcovati, MD
Aly Karsan, MD
Christina Ganster, PhD
Eva Hellström-Lindberg, MD, PhD
Jacqueline Boultwood, PhD
Andrea Pellagatti, PhD
Valeria Santini, MD
Lynn Quek
Paresh Vyas, MD
Heinz Tüchler
Peter L. Greenberg, MD
Rafael Bejar, MD, PhD

On behalf of the IWG for MDS investigators

mds foundation
the myelodysplastic syndromes foundation, inc.

IWG-PM Collaborative MDS Sample Compilation

MDS sample data collected from 19 centers in Europe, the United States, and Asia



Kristen Stevenson

Donna Neuberg

Heinz Tuechler

Data Summary

Clinical Features
- age and sex
- blast %
- karyotype
- hemoglobin
- platelet count
- neutrophil count

Overall Survival Data:
- available for 3359
- 3.6 years follow-up
- 1780 deaths
- median OS 2.65 years

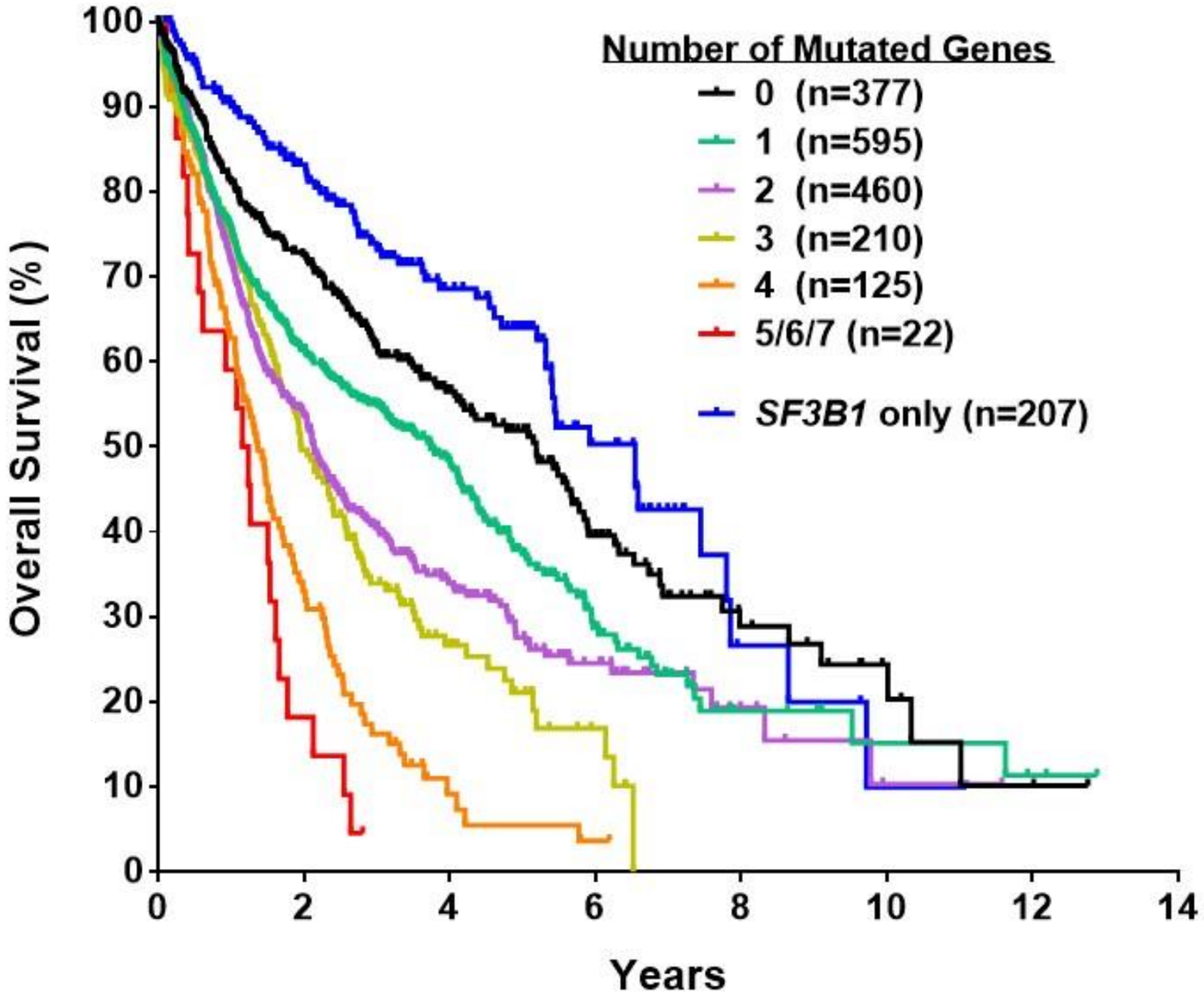
Treatment Status

Gene Mutations

Overall Survival by Mutation Number

17 genes sequenced in
1996 patients with OS data

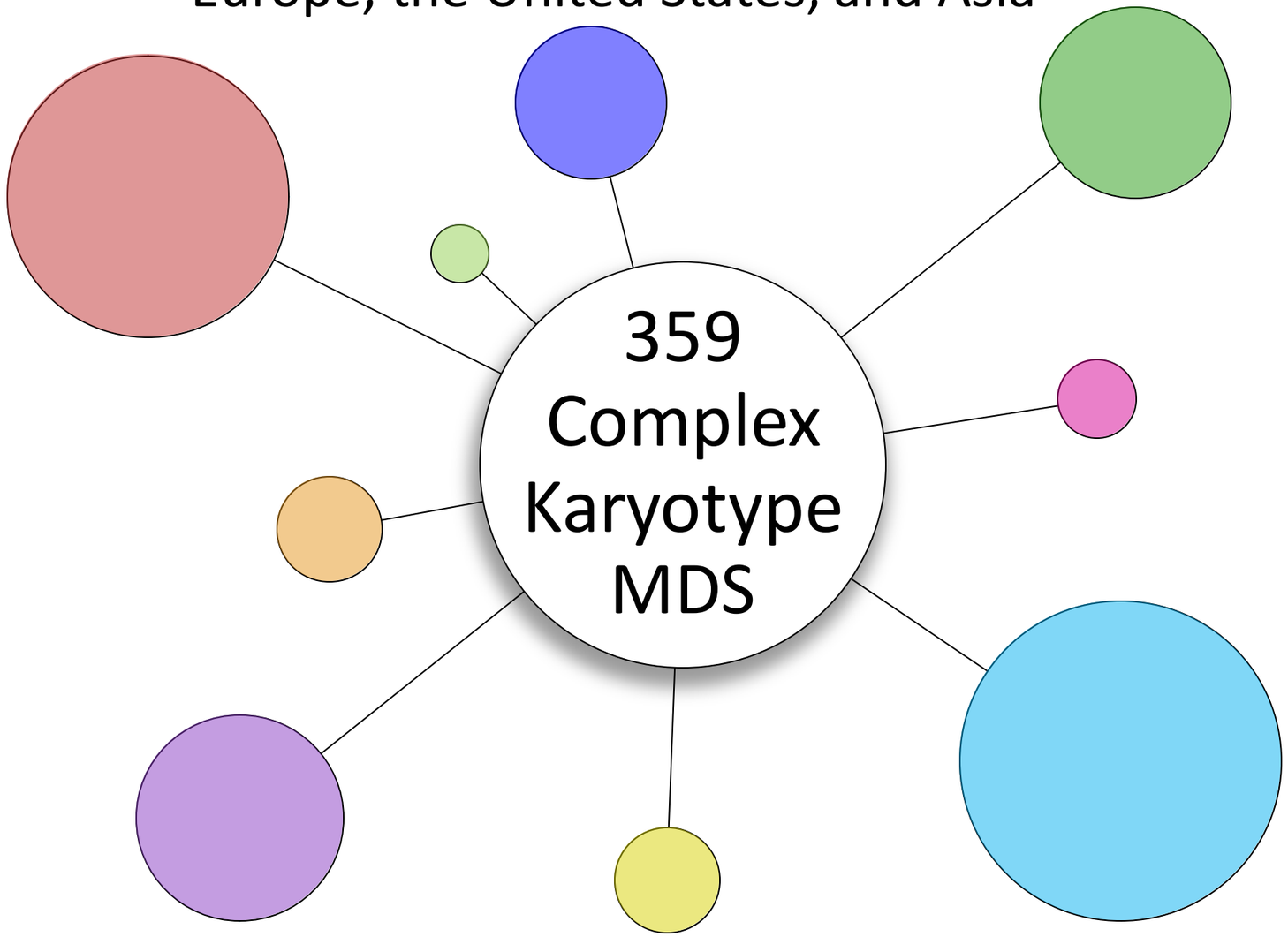
ASXL1	*NPM1*
CBL	*NRAS*
DNMT3A	*RUNX1*
ETV6	*SRSF2*
EZH2	*TET2*
IDH1	*TP53*
IDH2	*U2AF1*
JAK2	
KRAS	*SF3B1*



From the IWG-PM Collaborative Meta-analysis

IWG-PM Collaborative MDS Sample Compilation

MDS sample data collected from 19 centers in Europe, the United States, and Asia



Detlef Haase Kristen Stevenson Donna Neuberg Heinz Tuechler

Data Collected

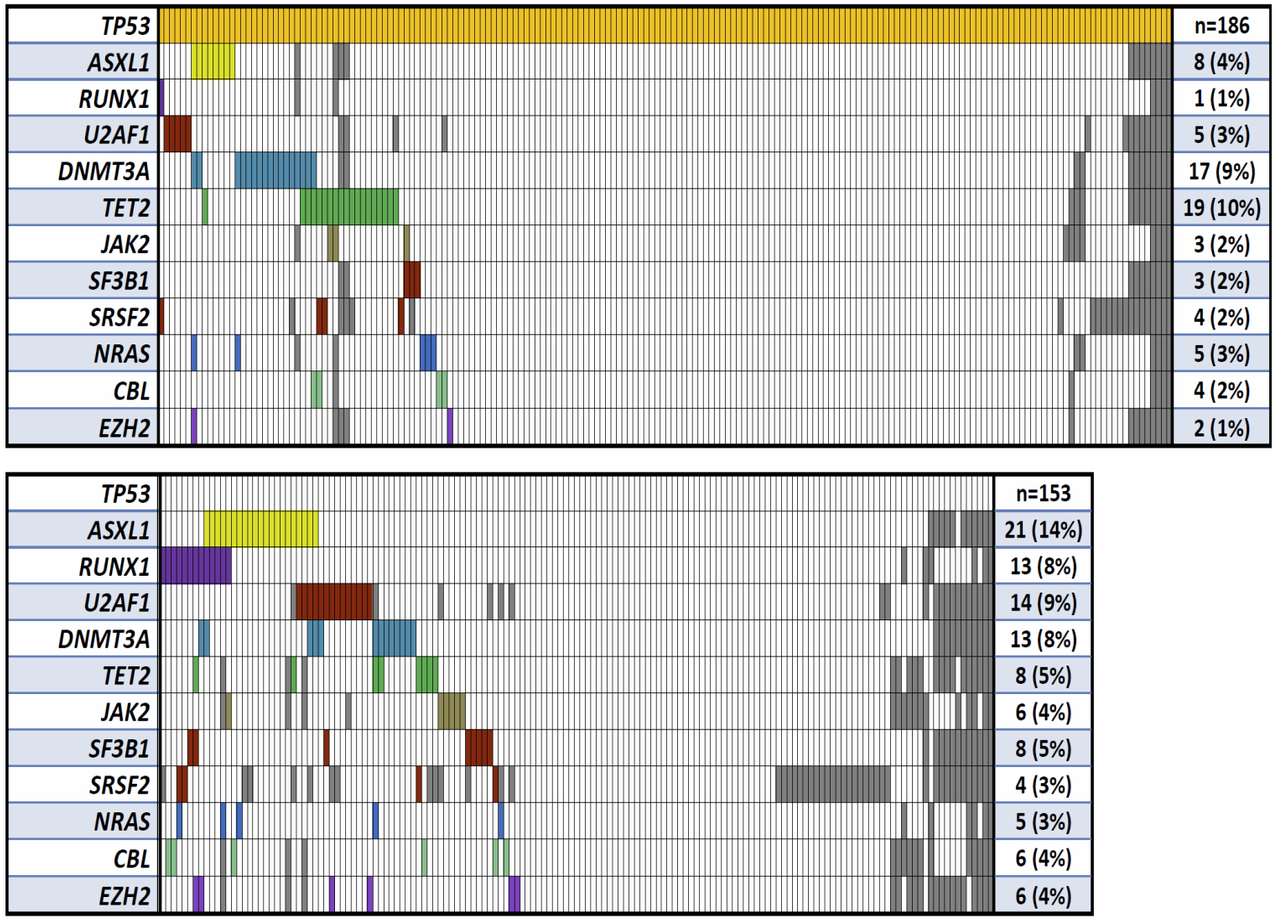
Karyotype parsed for:
- # of abnormalities
- del(5q)
- del(7q), -7
- abnormal chr 17, 3q, 9, …
- monosomal status

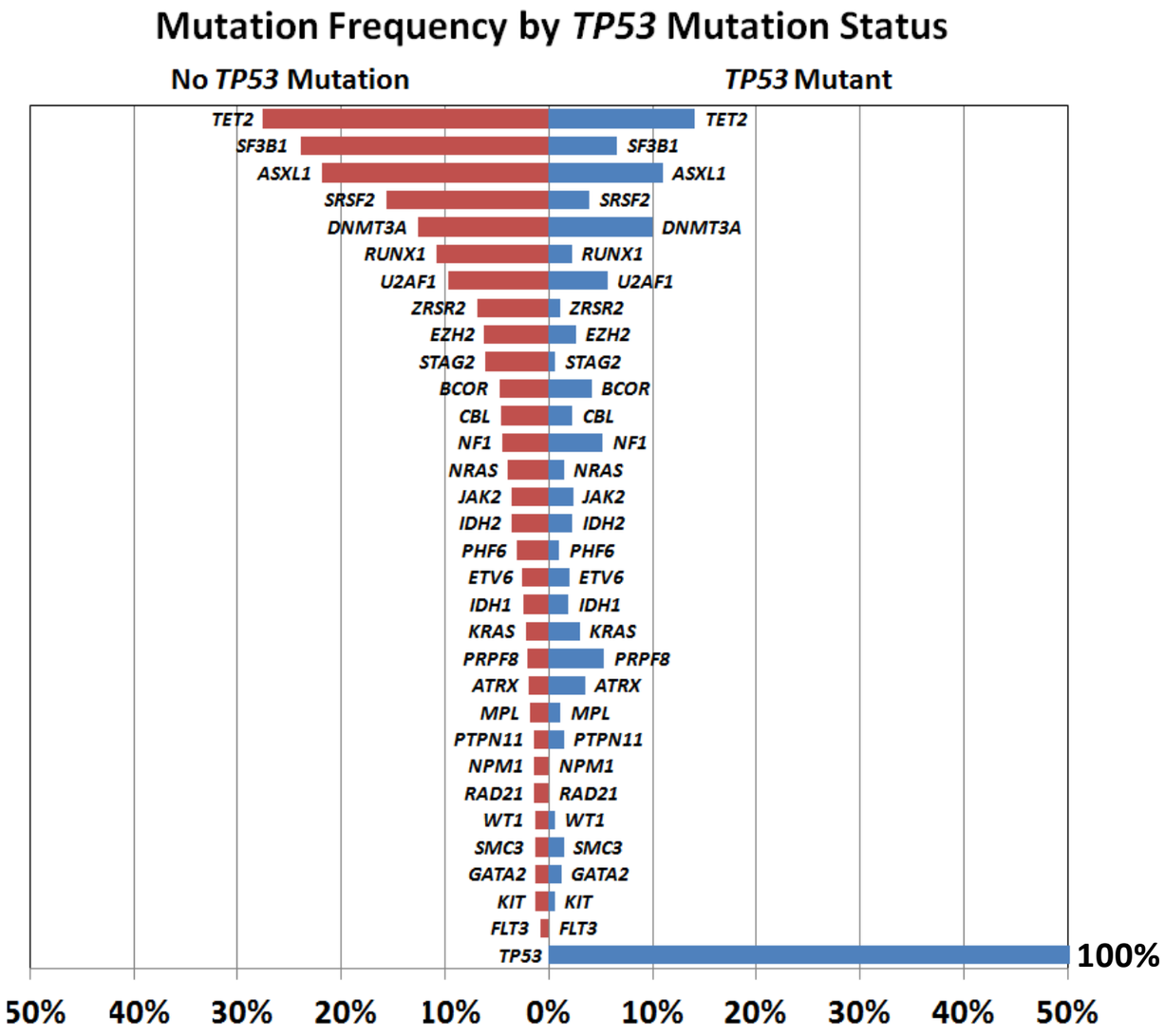
Clinical Features
- age and sex
- blast %
- hemoglobin
- platelet count
- neutrophil count

TP53 Mutation Status

Overall Survival

TP53 Co-mutation in MDS

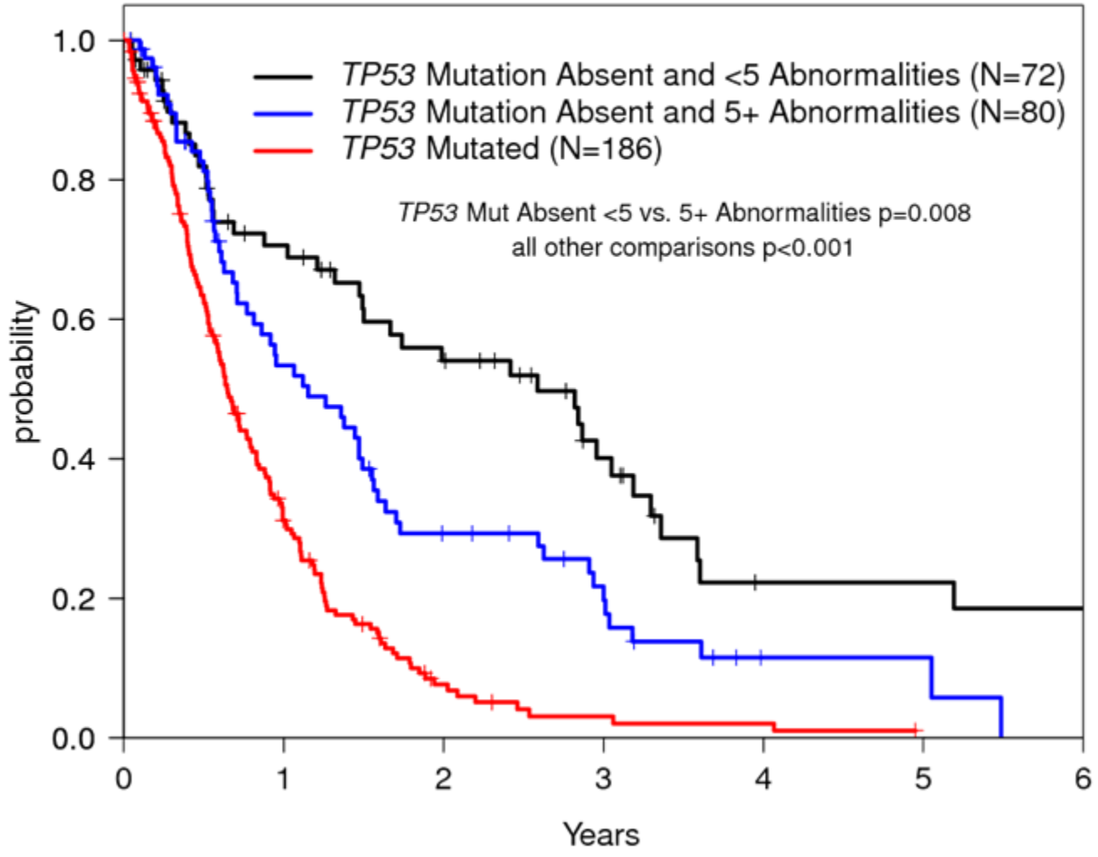




Haase et al. *Leukemia*. 2019 Jul;33(7):1747-58.

Multivariable Model – Karyotype Features and *TP53*

	Univariate		Multivariable	
Three element model	HR [95% CI]	p-value	HR [95% CI]	p-value
Monosomal Yes vs. No	1.95 [1.46-2.62]	<0.001	1.26 [0.91-1.75]	0.17
Number Abnormalities ≥5 vs. 4 or 3	2.26 [1.70-3.02]	<0.001	1.61 [1.16-2.24]	0.004
TP53 Mutation vs. No mutation	2.57 [1.97-3.34]	<0.001	2.12 [1.61-2.79]	<0.001



Median Overall Survival:

7.2 months

14.4 months

31.2 months

Haase et al. *Leukemia*. 2019 Jul;33(7):1747-58.

Update on IWG-PM Efforts on the Impact of Somatic Mutations in MDS

International Working Group for the prognosis of MDS

13 countries | 25 centers

Elsa Bernard

Elli Papaemmanuil

mds foundation
the myelodysplastic syndromes foundation, inc.

IWG-PM
INTERNATIONAL WORKING GROUP FOR THE PROGNOSIS OF MDS

International Working Group for the prognosis of MDS

Retrospective cohorts

N=1,682

Bejar et al 2011
Haferlach et al 2014
Papaemmanuil et al 2013

Prospective sequencing study

N=4,270

MSKCC IWG-PM Cohort
13 countries 25 centers

Validation

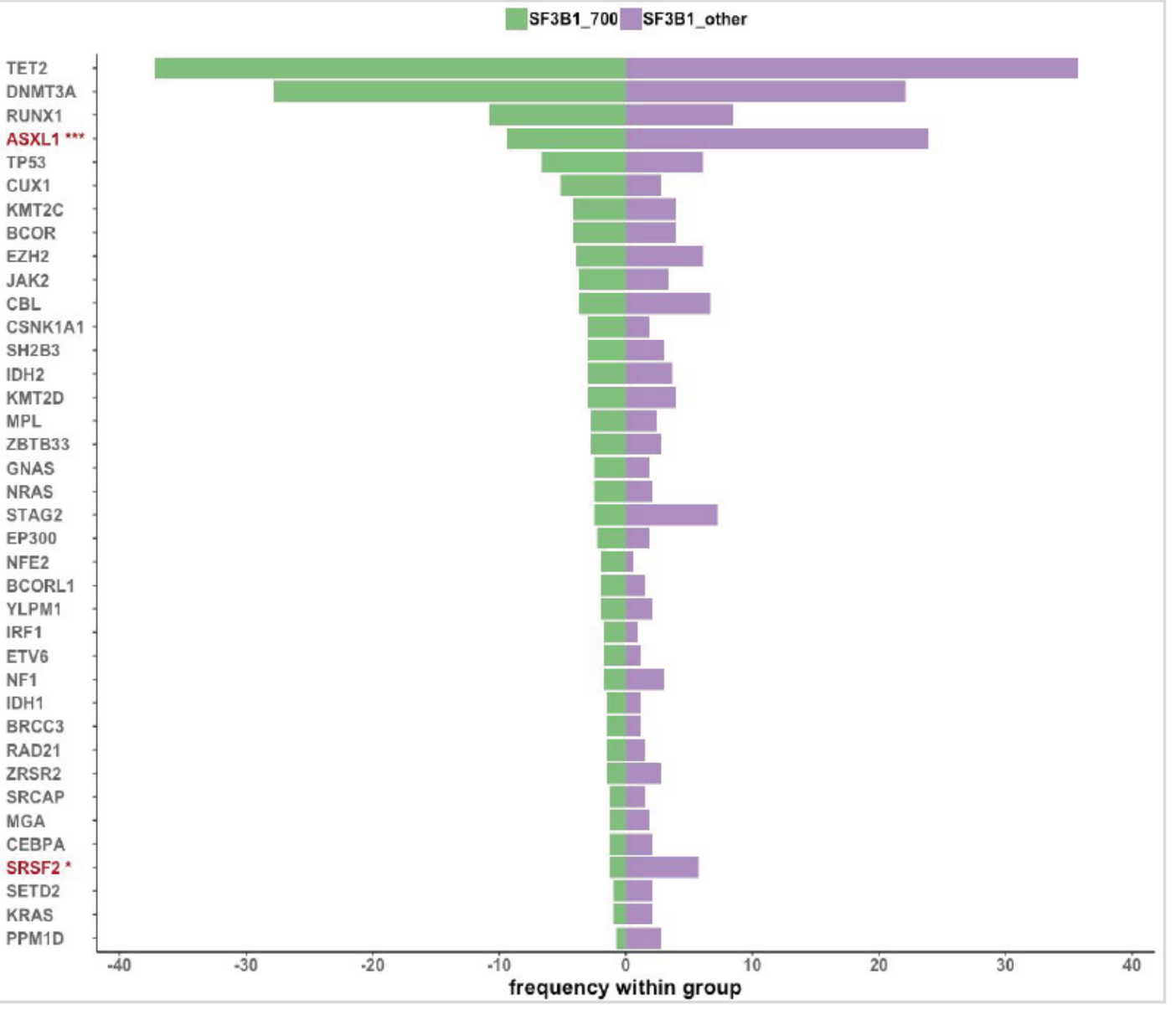
N to be determined

Cleveland
MD Anderson

Sequencing:

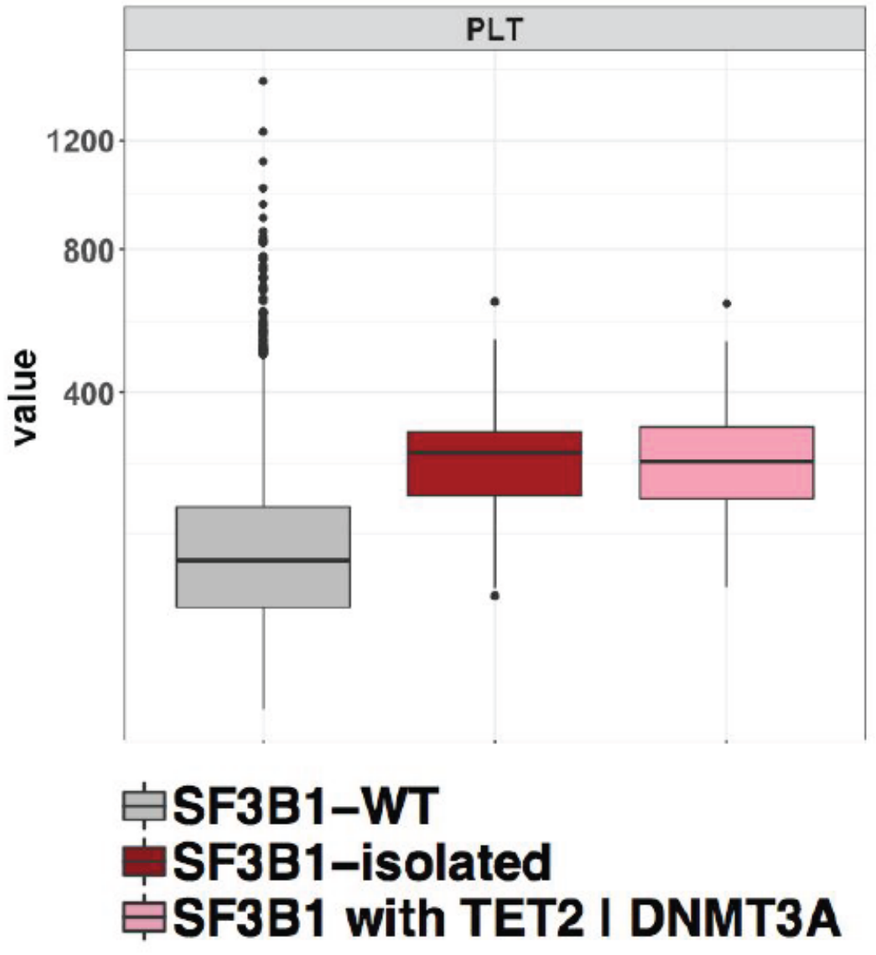
155 myeloid genes
Genome-wide copy number probes
Focal regions of LOH
Panel information available on request
Unmatched setting
Coverage 600-800x

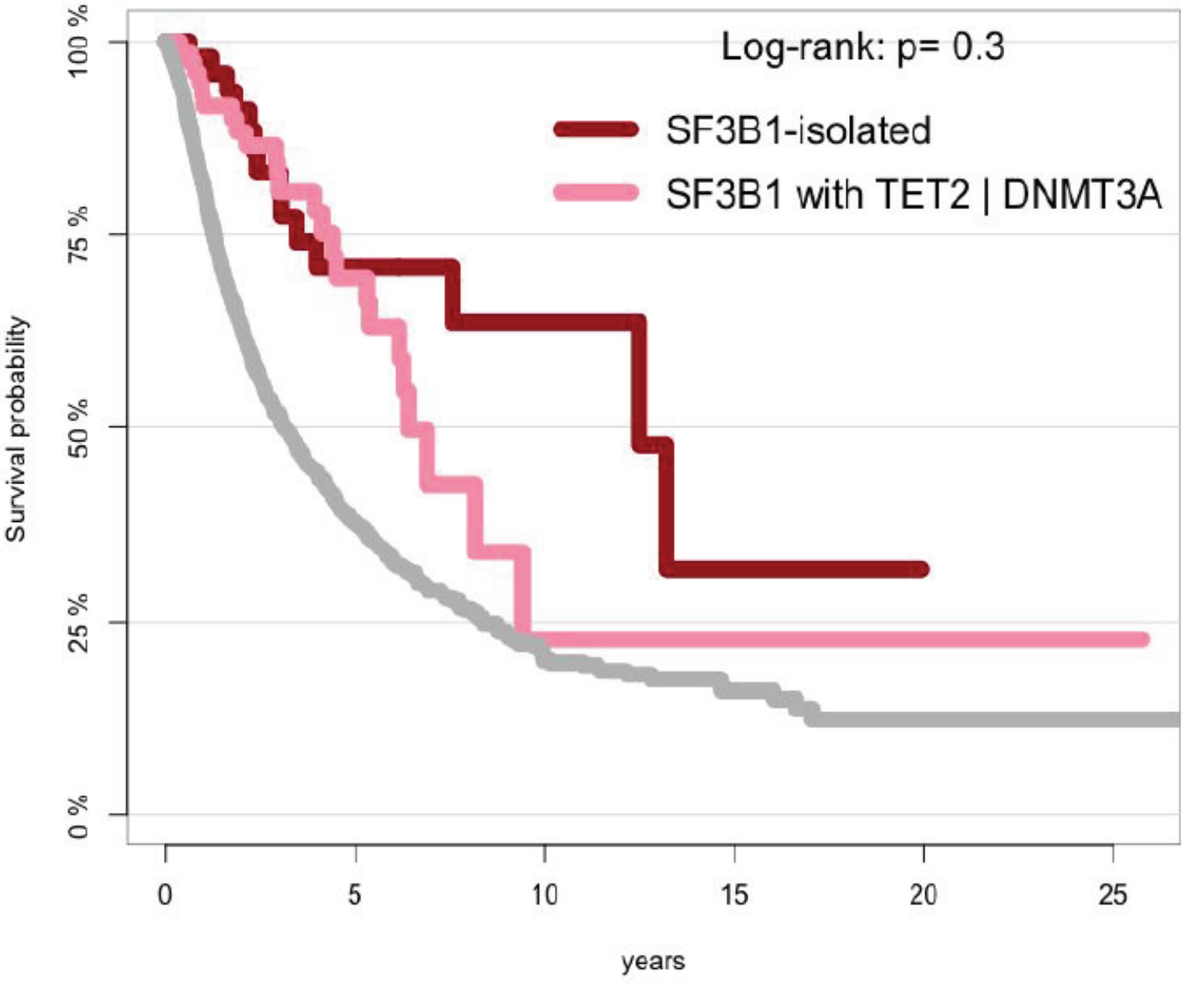
Detailed map of co-mutations: *SF3B1* K700 other



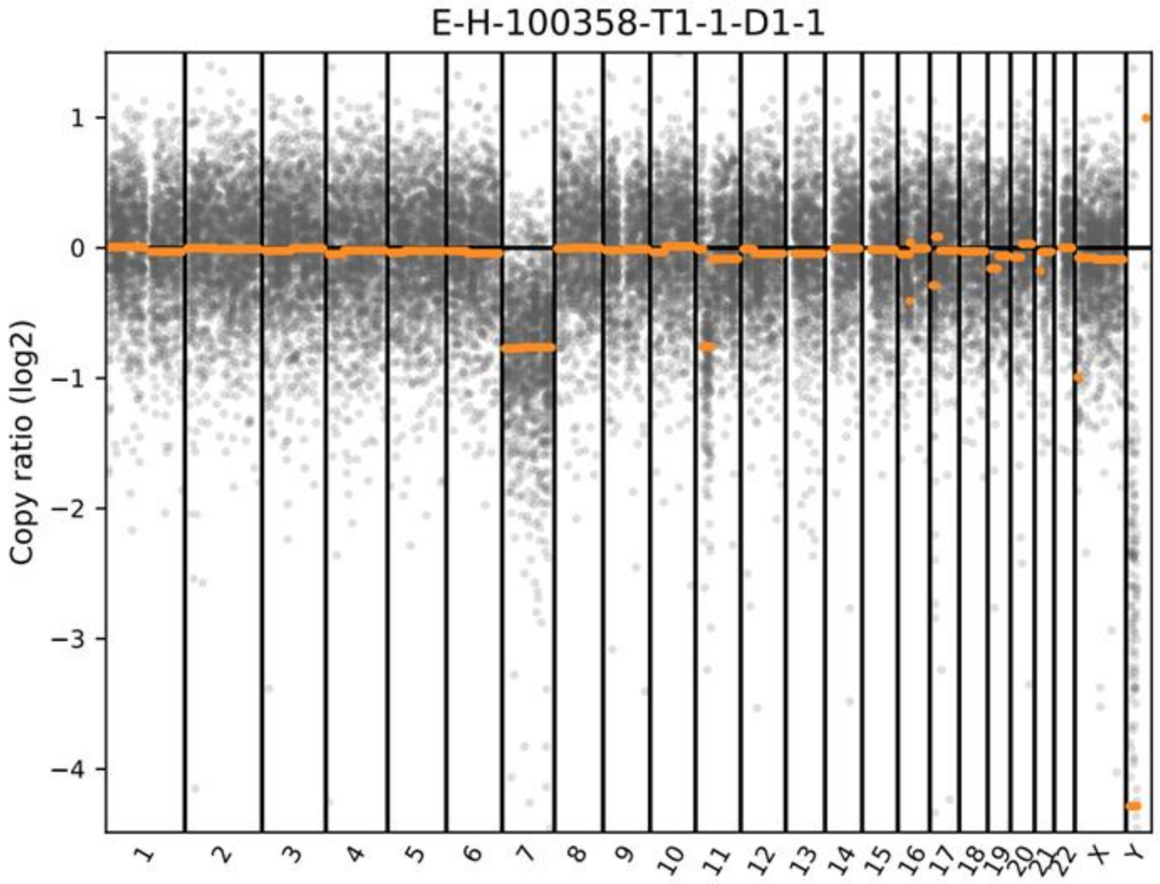
SF3B1 phenotype and outcome shift with co-mutators

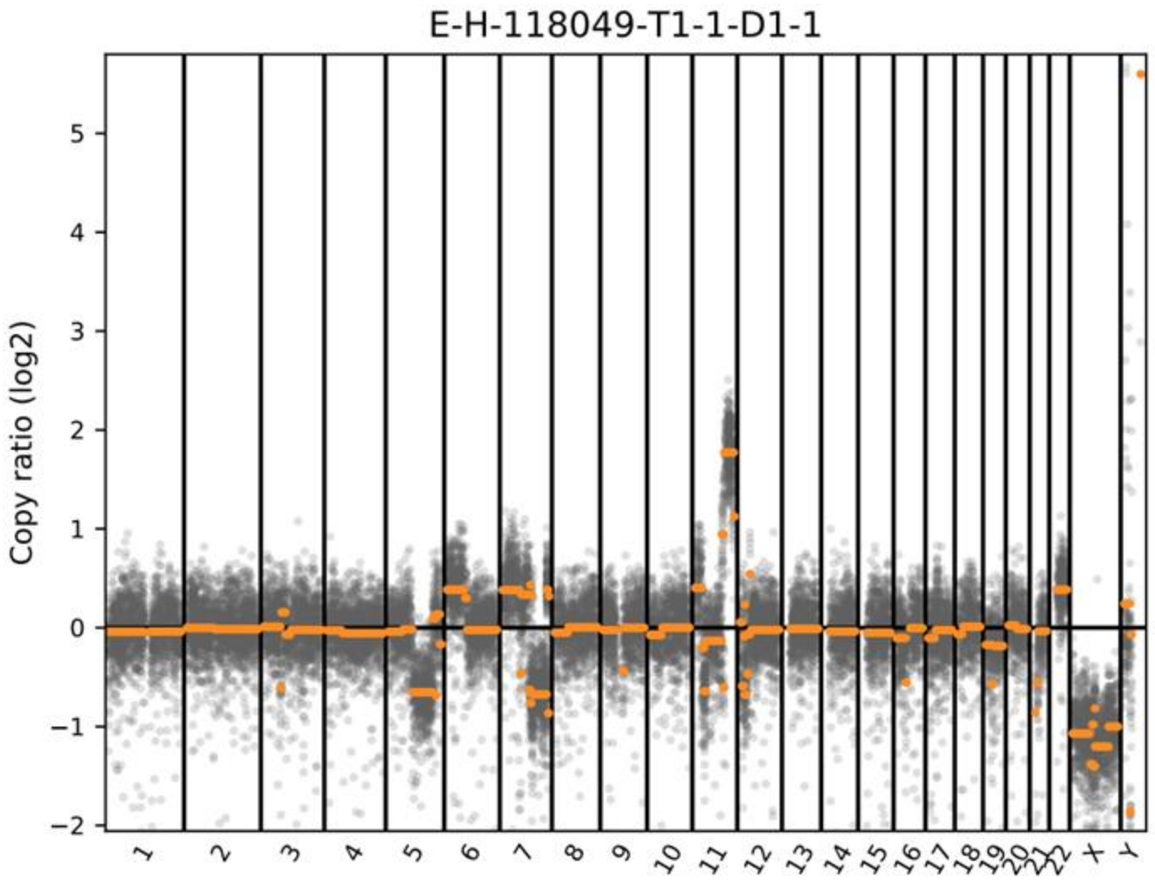
SF3B1 isolated or with *TET2* | *DNMT3A* — No shift



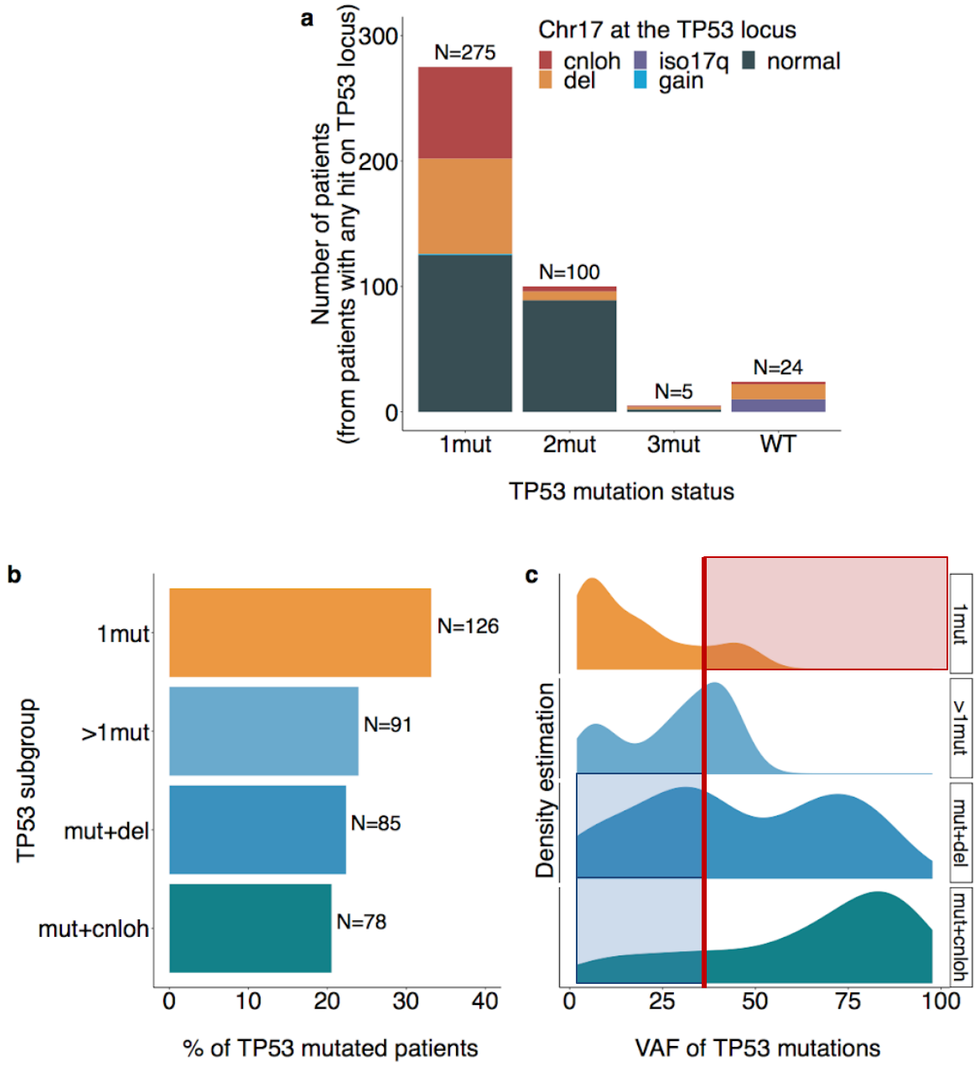


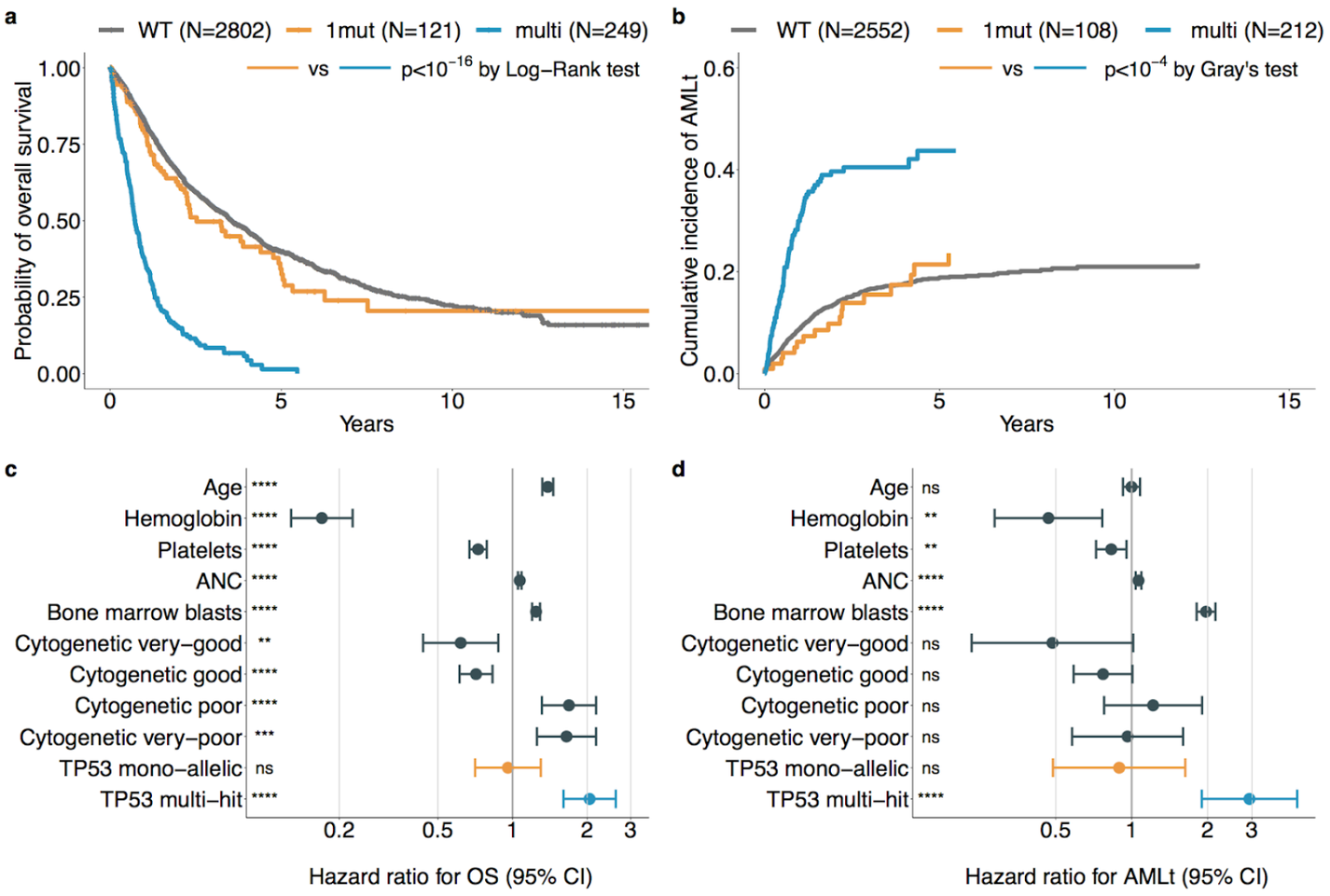
Copy Number and LOH Detection





TP53 Mutation Configuration





Elsa Bernard and Elli Papaemmanuil *et al.* on behalf of the IWG-PM

Summary

- MDS is a genetically heterogeneous clonal disorder caused by a wide variety of pathogenic mechanisms
- Mutations are not specific to MDS, but certain patterns of mutation are characteristic
- Somatic (and germline) mutations convey important clinical information
- These variants will soon be formally incorporated into the classification and risk assessment for MDS

MDS at UC San Diego

MDS Center of Excellence at UC San Diego

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AA·MDS INTERNATIONAL FOUNDATION

mds foundation the myelodysplastic syndromes foundation, inc.

MDS CENTERS OF EXCELLENCE

All of our PATIENTS and INFUSION CENTER nurses and staff!

UC San Diego
MOORES CANCER CENTER