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Predisposizione germinale alle neoplasie ematologiche: nuove prospettive di indagine molecolare

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Germline predisposition to myeloid neoplasms

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Daniel A. Arber,[1] Attilio Orazi,[2] Robert Hasserjian,[3] Jürgen Thiele,[4] Michael J. Borowitz,[5] Michelle M. Le Beau,[6] Clara D. Bloomfield,[7] Mario Cazzola,[8] and James W. Vardiman[9] (Blood. 2016 May 19;127(20):2391-405)

REVIEW ARTICLE OPEN

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms (Leukemia. 2022 Jul;36(7):1703-1719)

blood Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

(Blood. 2022 Sep;140(11):1200-1228)

Genetic germline variants are increasingly recognized as predisposing patients to myeloid neoplasms and aplastic anemia

Myeloid neoplasms associated with germline predisposition include AML, MDS, MPN, and MDS/MPN that arise in individuals with genetic conditions associated with increased risk of myeloid malignancies

→ 5-15% of adult MDS/AML cases are caused by germline predisposition (PMID: 36900380)

Table 10. Subtypes of myeloid neoplasms associated with germline predisposition.

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
• Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
• Germline *DDX41* P/LP variant[a]
• Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
• Germline *GATA2* P/LP variant (GATA2-deficiency)
• Bone marrow failure syndromes
◦ Severe congenital neutropenia (SCN)
◦ Shwachman-Diamond syndrome (SDS)
◦ Fanconi anaemia (FA)
• Telomere biology disorders
• RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
• Down syndrome[a,b]
• Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
• Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
• Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a]Lymphoid neoplasms can also occur.
[b]See respective sections.
[c]Ataxia is not always present.
P pathogenic, *LP* likely pathogenic.

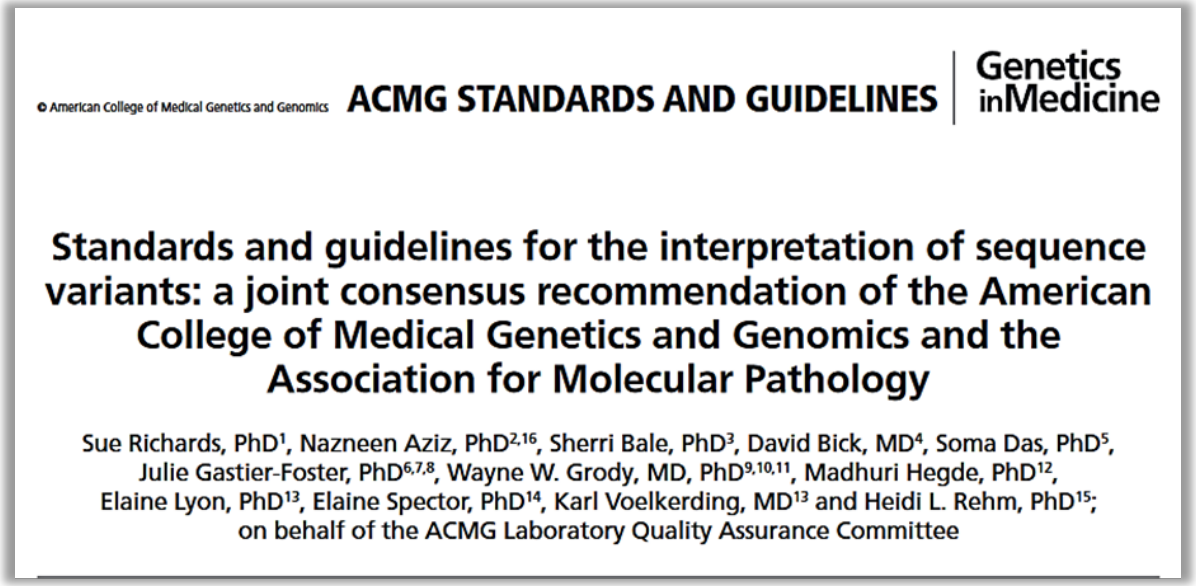
Germline mutation analysis

Core panel of sequenced genes				
ANKRD26	*TP53*	*CSF3R*	*RPS17*	*TERC*
CEBPA	*MPL*	*ELANE*	*RPS19*	*TERT*
DDX41	*FANCA*	*G6PC3*	*RPS24*	*TINF2*
DHX34	*FANCB*	*GFI1*	*RPS26*	*CBL*
ERCC6L2	*FANCC*	*HAX1*	*SBDS*	*KRAS*
ETV6	*FANCD1 (BRCA2)*	*JAGN1*	*DNAJC21*	*NF1*
GATA2	*FANCD2*	*WAS*	*CTC1*	*NRAS*
MECOM	*FANCE*	*GATA1*	*DKC1*	*PTPN11*
RUNX1	*FANCF*	*RPL5*	*NHP2*	*RAF1*
SAMD9	*FANCG*	*RPL11*	*NOP10*	*RIT1*
SAMD9L	*FANCI*	*RPL35A*	*PARN*	*SOS1*
SRP72	*FANCJ (BRIP1)*	*RPS10*	*RTEL1*	*RBM8A*

- DNA from peripheral blood granulocytes (DNA from T-lymphocytes or buccal cells used as a germline control tissue)
- 60 genes reported in peer-reviewed literature as consistently mutated in congenital syndrome or disorder predisposing to myeloid neoplasm
- Next generation DNA sequencing (NGS) (Illumina)

Variant interpretation and classification

Implementation of American College of Medical Genetics and Genomics and the Association for Molecular Pathology (**ACMG-AMP**) guidelines for interpretation of germline sequence variants



(Genet Med. 2015 May; 17(5): 405–424)

- ACMG-AMP guidelines recommend the application of several criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data)
- The criteria are organized by type and “strength”, supporting Pathogenic or Benign impact of a variant
- A set of rules was developed to combine criteria, in order to classify variants into five categories:
  - **Pathogenic (P)**
  - **Likely pathogenic (LP)**
  - **Benign (B)**
  - **Likely benign (LB)**
  - **Uncertain significance (VUS)**

Somatic mutation analysis

Gene	Target Region (exon)	Gene	Target Region (exon)	Gene	Target Region (exon)	Gene	Target Region (exon)
ABL1	4–6	*DNMT3A*	full	*KDM6A*	full	*RAD21*	full
ASXL1	12	*ETV6/TEL*	full	*KIT*	2, 8–11, 13 + 17	*RUNX1*	full
ATRX	8-10 and 17–31	*EZH2*	full	*KRAS*	2 + 3	*SETBP1*	4 (partial)
BCOR	full	*FBXW7*	9 + 10 + 11	*MLL*	5–8	*SF3B1*	13–16
BCORL1	full	*FLT3*	14 + 15 + 20	*MPL*	10	*SMC1A*	2, 11, 16 + 17
BRAF	15	*GATA1*	2	*MYD88*	3–5	*SMC3*	10, 13, 19, 23, 25 + 28
CALR	9	*GATA2*	2–6	*NOTCH1*	26-28 + 34	*SRSF2*	1
CBL	8 + 9	*GNAS*	8 + 9	*NPM1*	12	*STAG2*	full
CBLB	9, 10	*HRAS*	2 + 3	*NRAS*	2 + 3	*TET2*	3–11
CBLC	9, 10	*IDH1*	4	*PDGFRA*	12, 14, 18	*TP53*	2–11
CDKN2A	full	*IDH2*	4	*PHF6*	full	*U2AF1*	2 + 6
CEBPA	full	*IKZF1*	full	*PTEN*	5 + 7	*WT1*	7 + 9
CSF3R	14–17	*JAK2*	12 + 14	*PTPN11*	3 + 13	*ZRSR2*	full
CUX1	full	*JAK3*	13				

- DNA from peripheral blood granulocytes (DNA from T-lymphocytes used as a control tissue)
- Commercial sequencing research panel of 54 key genes known to be involved in myeloid malignancies
- Next generation DNA sequencing (NGS) (Illumina)
- Variants considered as candidate somatic mutations were finally tagged as oncogenic, based on the information derived from peer-reviewed literature, the Catalog of Somatic Mutations in Cancer, in silico variant effect predictors, inclusion of the mutated aminoacid in a conserved/functional protein domain.

Germline predisposition to myeloid neoplasms in adults with marrow hypocellularity

Adult patients

↓

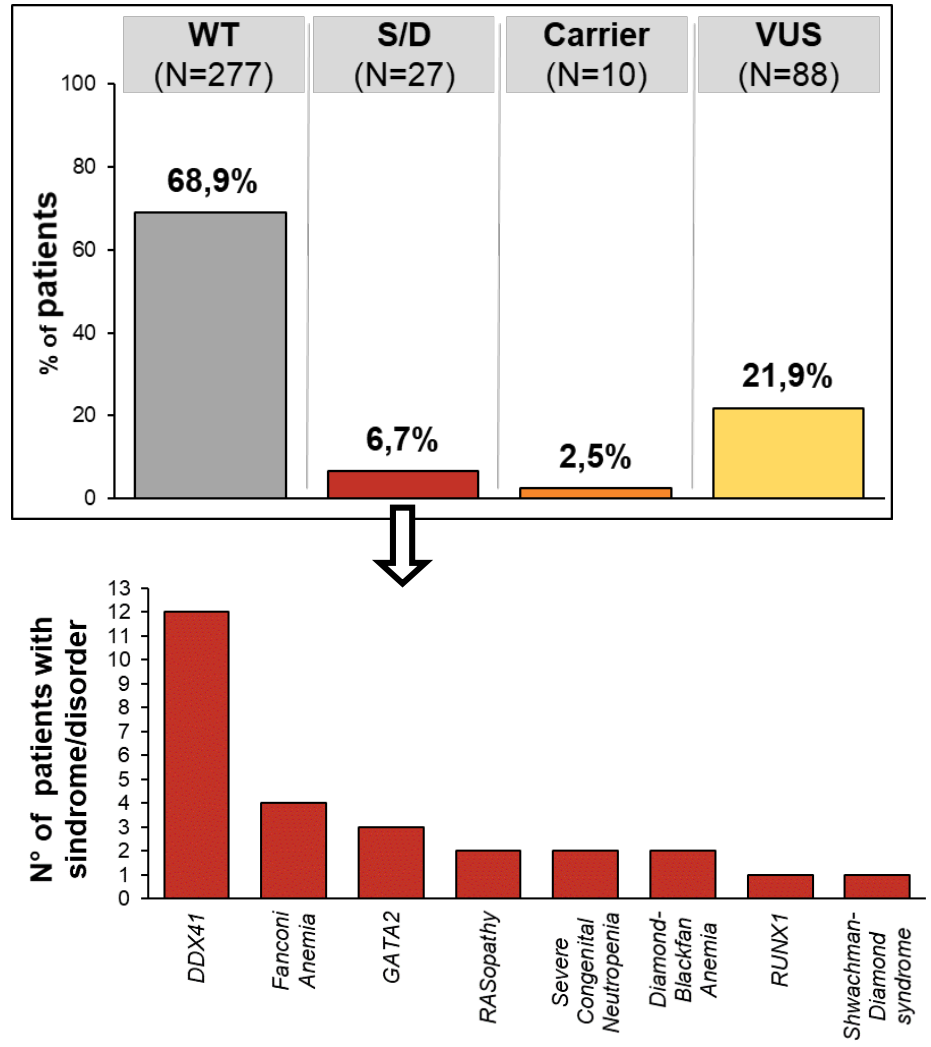
Unexplained cytopenia

Osteo-medular biopsy (BOM)

↓

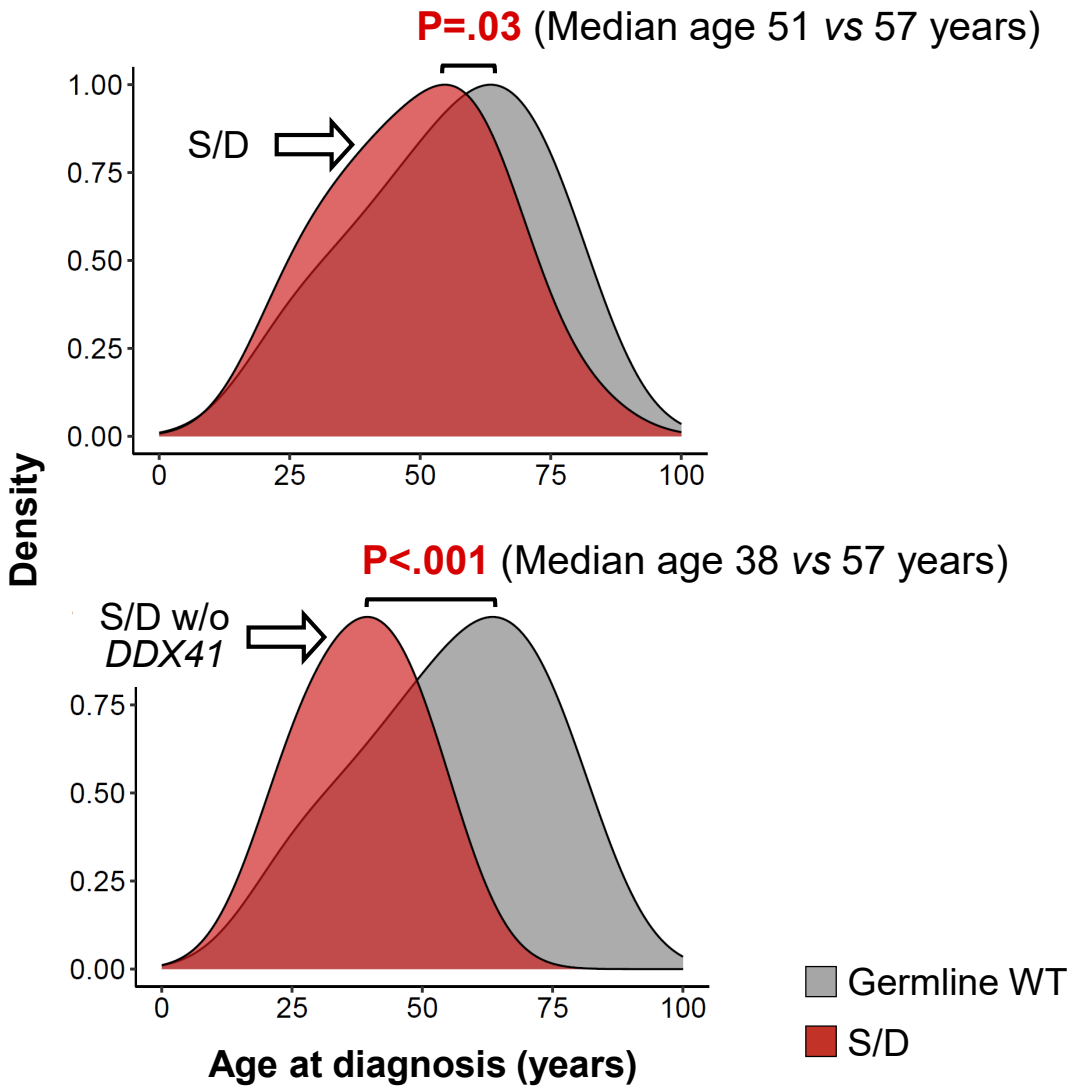
Bone marrow hypocellularity

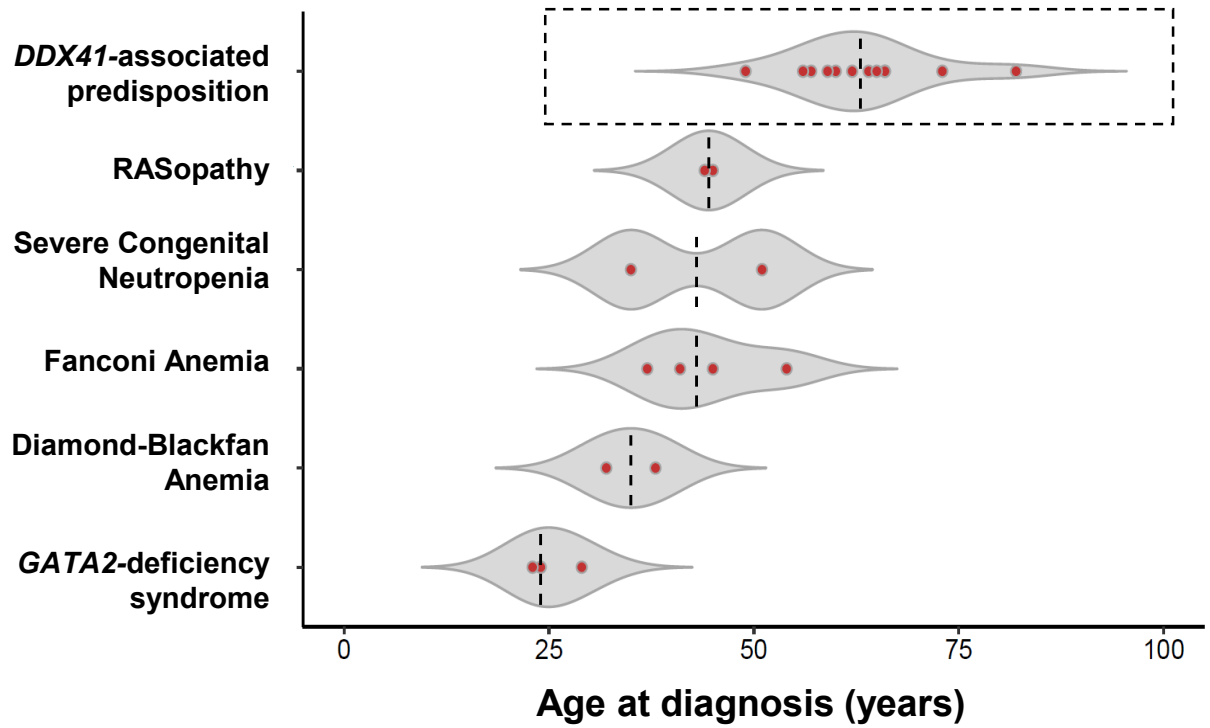
Variable	
N. of patients	402
Age (yrs) (median, range)	56 (18-86)
Sex (F/M)	203/199
Hemoglobin (g/dl) (median, range)	11.8 (3.9-17.4)
MCV (fL) (median, range)	95 (60-124)
WBC (x10^9/L) (median, range)	3.5 (0.5-28.51)
ANC (x10^9/L) (median, range)	1.63 (0.09-9.77)
PLT (x10^9/L) (median, range)	129 (1-666)
Diagnosis according to standard work-up:	
- Idiopathic cytopenia of undetermined significance	162 (40%)
- Clonal cytopenia of undetermined significance	26 (6%)
- Myeloid neoplasm:	173 (43%)
- Acute myeloid leukemia	11 (6%)
- Myelodysplastic syndrome	148 (86%)
- MDS single lineage dysplasia	19 (13%)
- MDS multilineage dysplasia	60 (41%)
- MDS with ring sideroblasts	8 (5%)
- MDS excess blasts	51 (34%)
- MDS del(5q)	8 (6%)
- MDS, unclassified	2 (1%)
- Myelodysplastic/Myeloproliferative neoplasm	14 (8%)
- Aplastic anemia	41 (10%)
- Non-severe	27 (66%)
- Severe	14 (34%)
Bone marrow cellularity (%) (median, range)	25 (5-50)
- ≤25%	206 (51%)
- Reduced for age	196 (49%)



Molteni E, Bono E, *et al*. Blood 2023

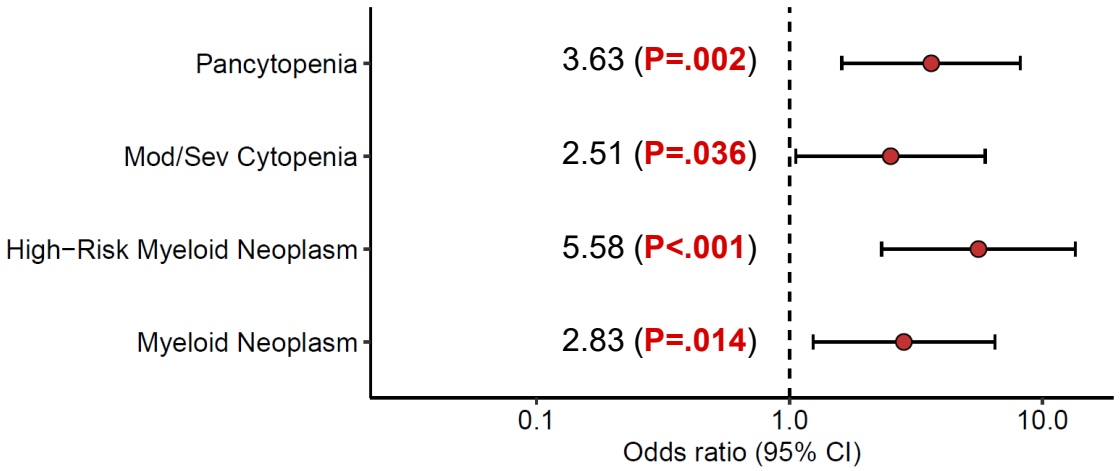
Age distribution at the time of standard hematologic diagnosis in patients with or without predisposition syndromes/disorders

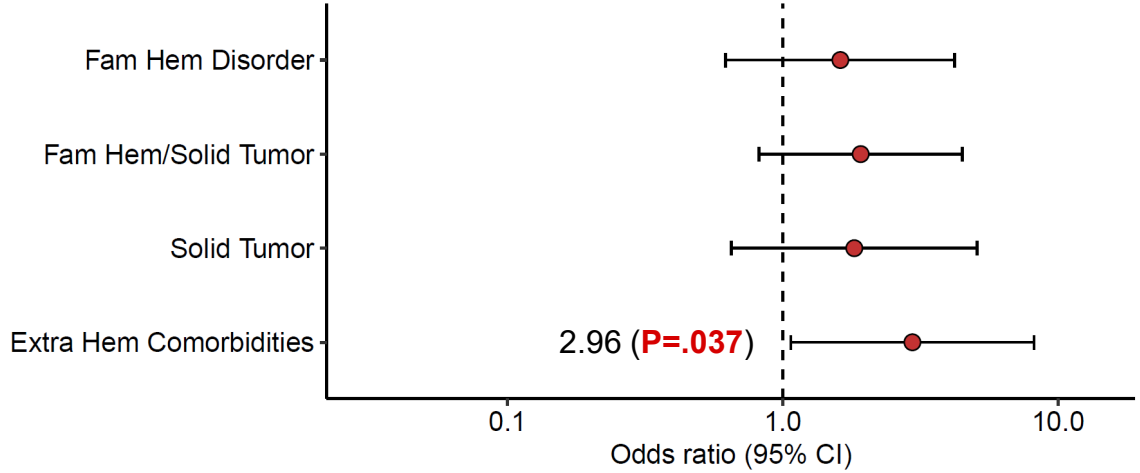




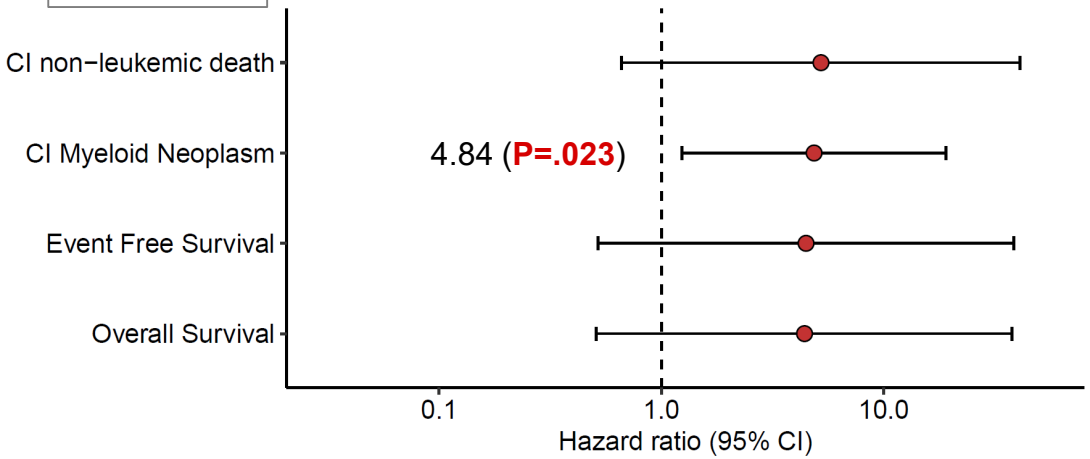
Molteni E, Bono E, *et al*. Blood 2023

Clinical correlates of predisposition syndromes/disorders in adults with marrow hypocellularity





ICUS/AA



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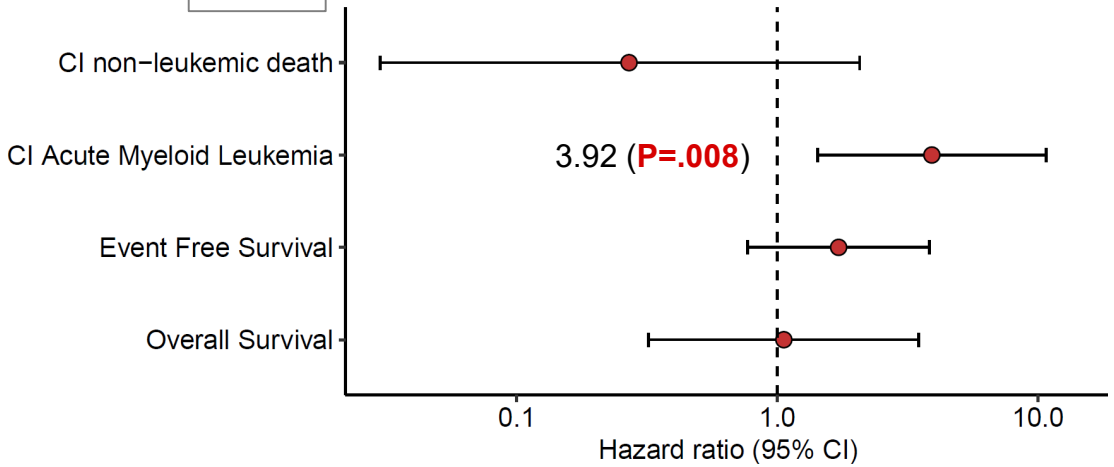
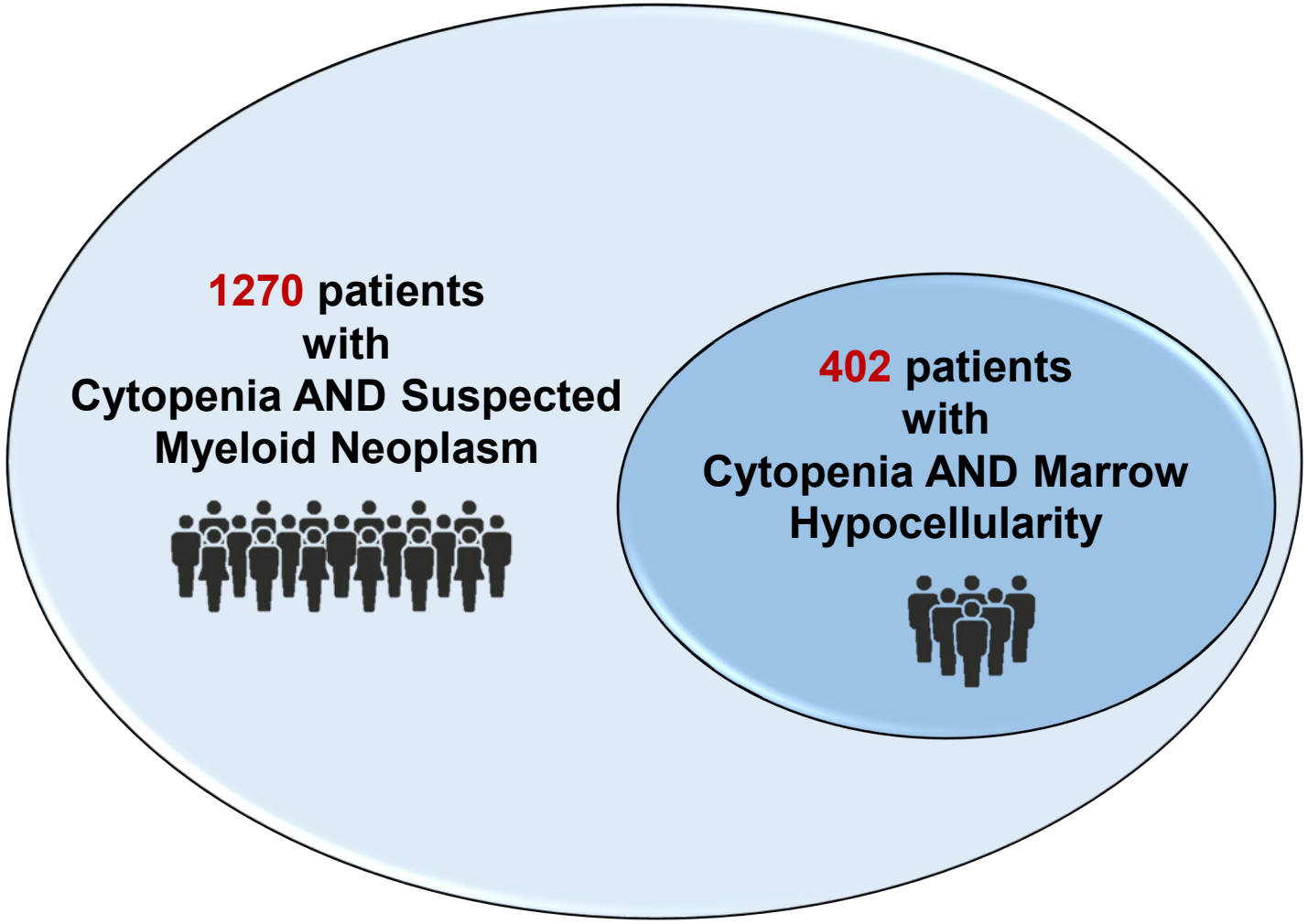


Molteni E, Bono E, *et al*. Blood 2023

Germline predisposition in adults with cytopenia and suspected myeloid neoplasm

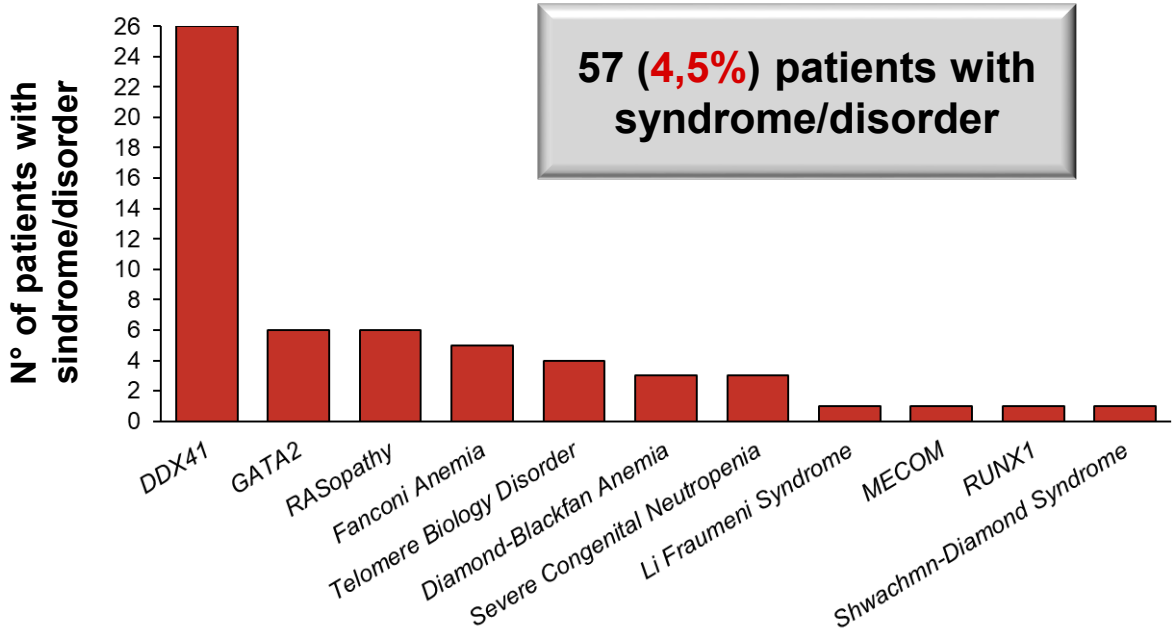


Germline predisposition in adults with cytopenia and suspected myeloid neoplasm

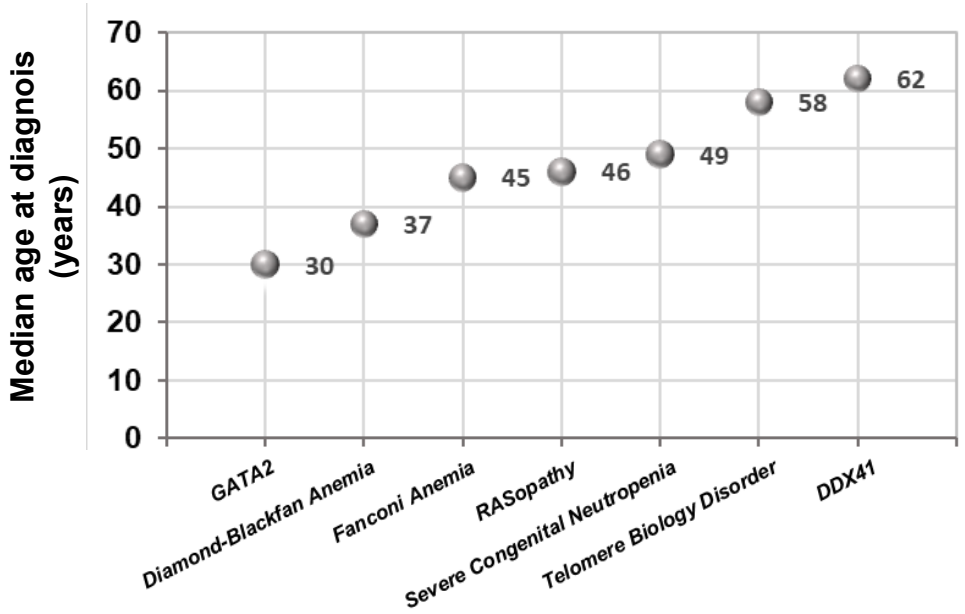
Variable	
N. of patients	**1270**
Age (yrs) (median, range)	62 (18-90)
Sex (F/M)	573/697
Diagnosis according to standard work-up:	
- Idiopathic cytopenia of undetermined significance / Clonal cytopenia of undetermined significance (ICUS/CCUS)	315 (25%)
- Myeloid neoplasm (MN):	855 (67%)
- Acute myeloid leukemia (AML)	82 (9%)
- Myelodysplastic syndrome (MDS)	631 (74%)
- Myelodysplastic/Myeloproliferative neoplasm (MDS/MPN)	126 (15%)
- Myeloproliferative neoplasm (MPN)	16 (2%)
- Aplastic anemia / Bone marrow failure (AA/BMF)	51 (4%)
- Other	49 (4%)

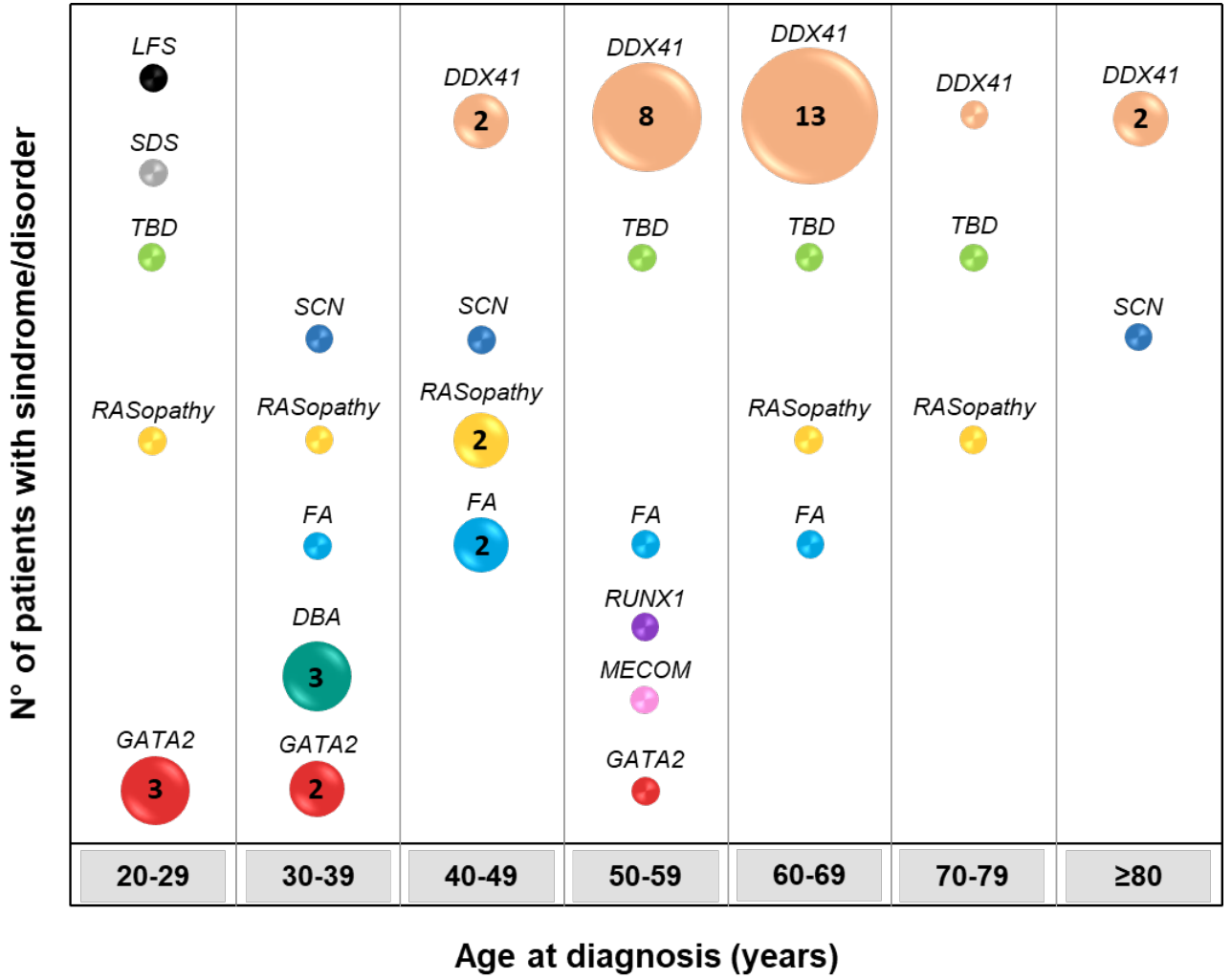
27 (6,7%) patients with syndrome/disorder
(adults with marrow hypocellularity)

57 (4,5%) patients with syndrome/disorder

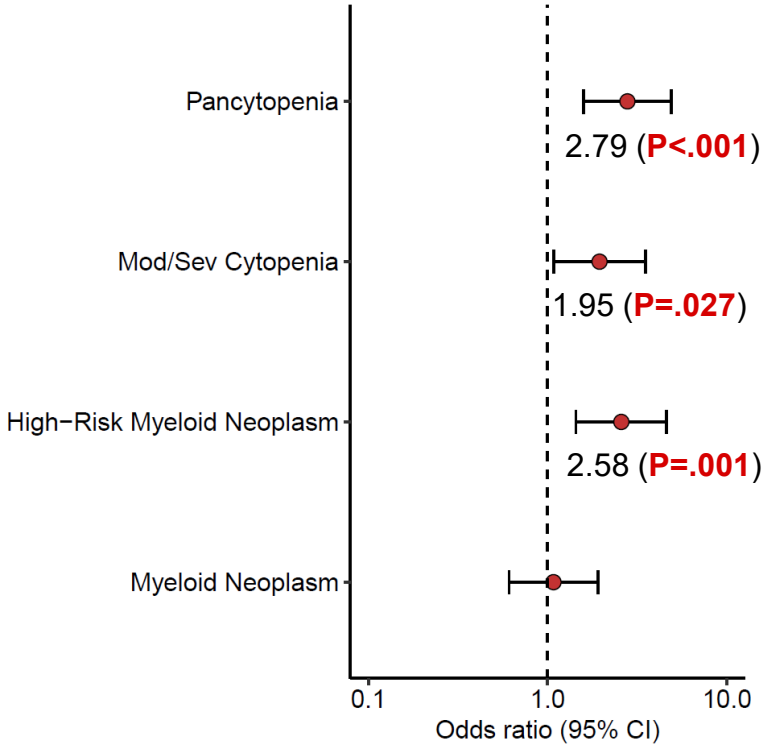


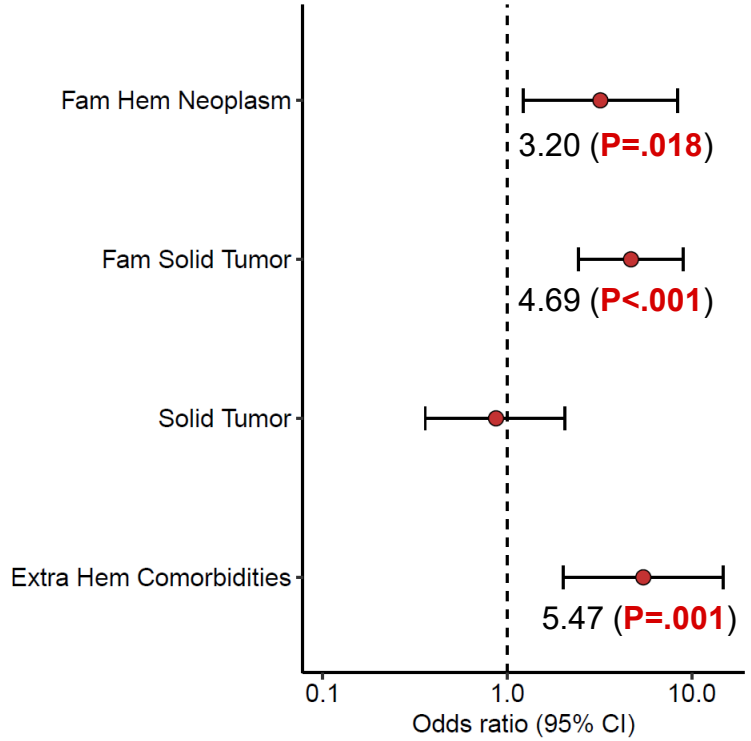
Correlation of age of hematologic diagnosis and predisposition syndromes/disorders

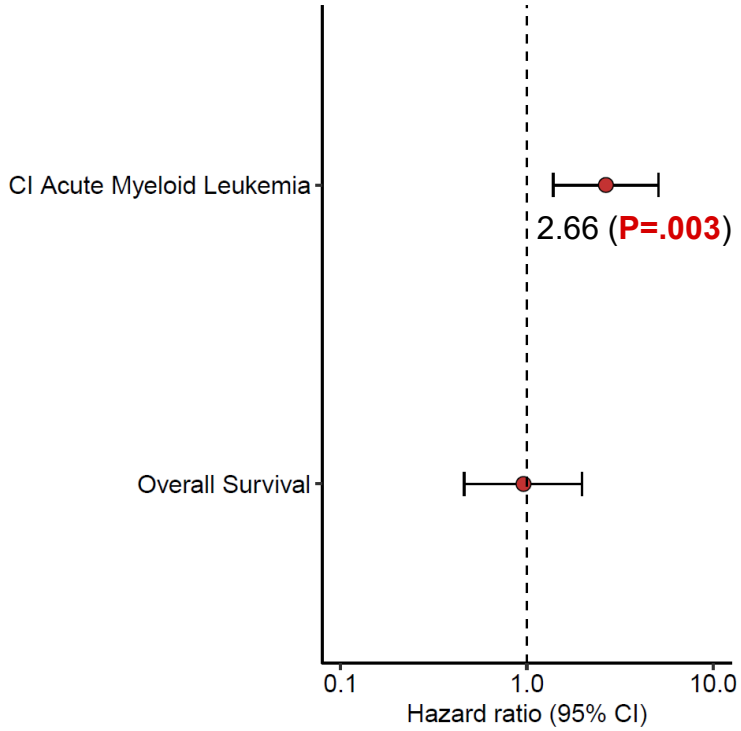




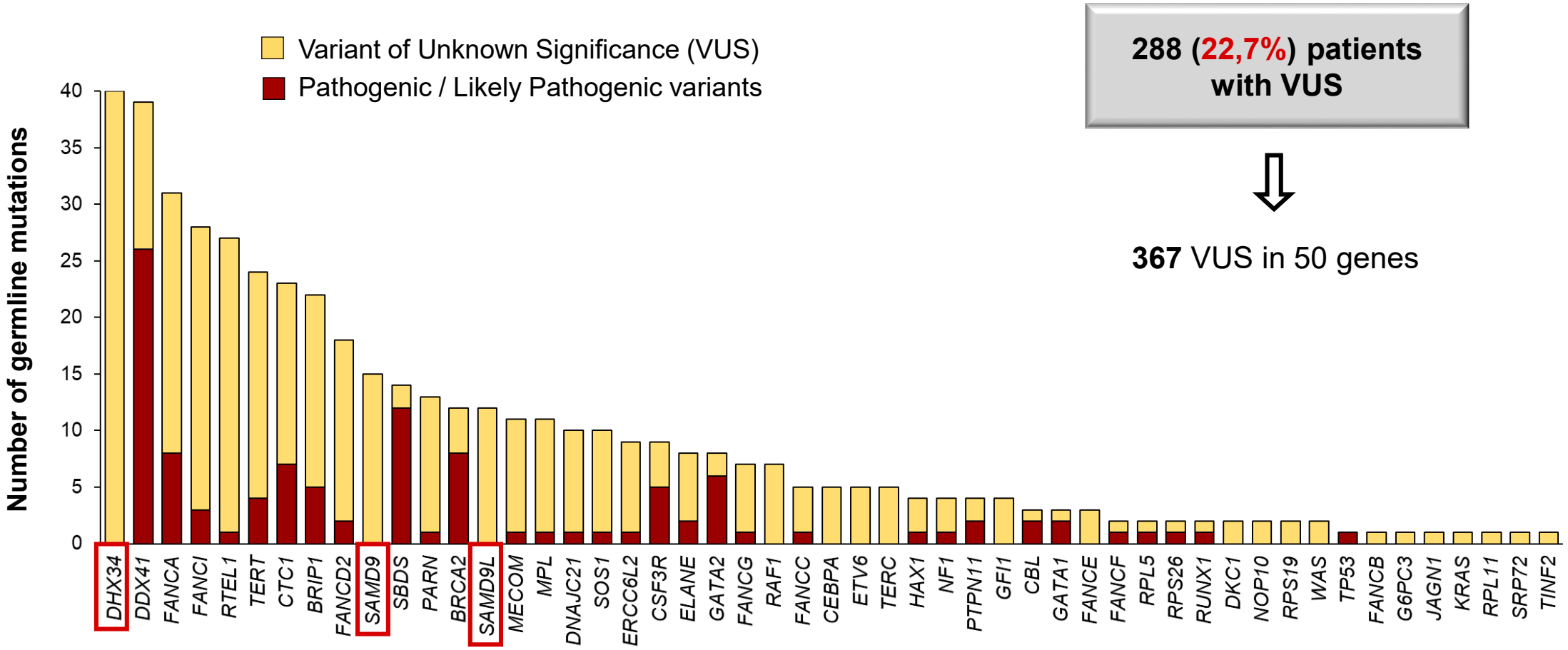
Clinical correlates of predisposition syndromes/disorders







Germline variants of unknown significance in genes associated with predisposition to myeloid neoplasms



288 (22,7%) patients with VUS

⇩

367 VUS in 50 genes

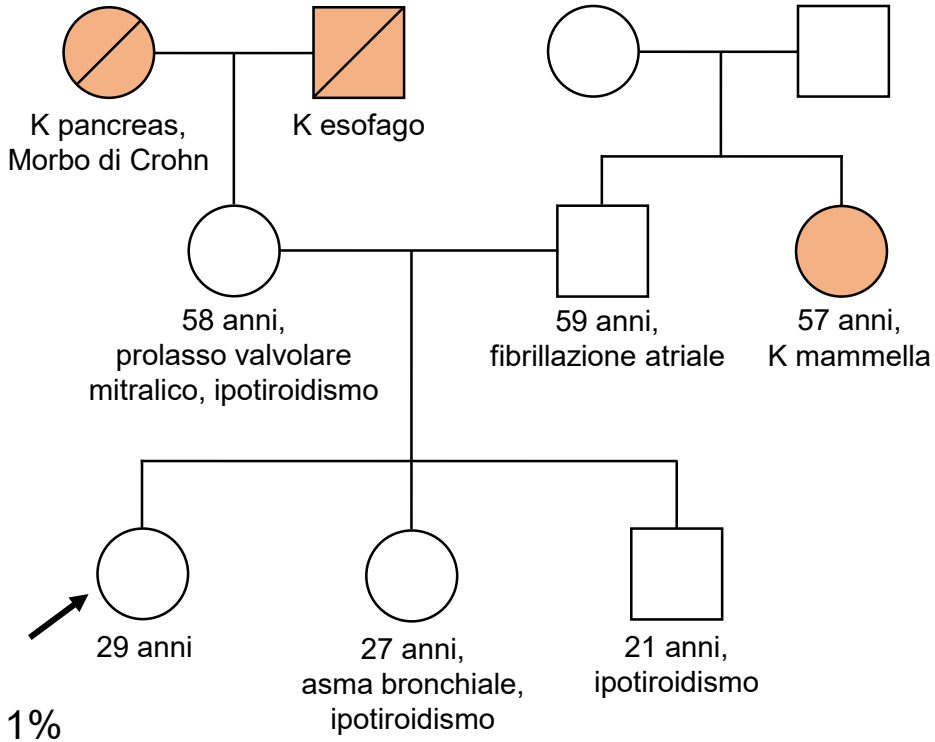
Predisposizione germinale alle neoplasie mieloidi: caso clinico (1)

Donna di 29 anni

- Cistiti ricorrenti fino a 3 anni
- Menarca precoce (9 anni)
- Prolasso valvolare mitralico
- Dal 2015: gastrite cronica
- Dal 2016: extrasistolia in terapia con betabloccante
- 2019: tiroidite di Hashimoto; tiroidectomia totale per carcinoma papillare

- **2007**: primo riscontro di pancitopenia di grado lieve-moderato
- **2016**: prima valutazione ematologica presso altro centro
  → mieloaspirato nella norma; citogenetica 46,XX
- **2017**: peggioramento pancitopenia
  Biopsia osteo-midollare (BOM): cellularità 20-25% (ridotta per l'età), blasti 1%
- **2020**: prima visita Ematologia Policlinico San Matteo Pavia
  BOM: cellularità 40% (ridotta per l'età), blasti 1%. Citogenetica: 46,XX
  Citopenia di incerto significato (ICUS)

Familiarità per neoplasia solida



Predisposizione germinale alle neoplasie mieloidi: caso clinico (1)

- **2020: NGS GERMINALE**

  ***GATA2* c.988C>T; p.R330X in eterozigosi**

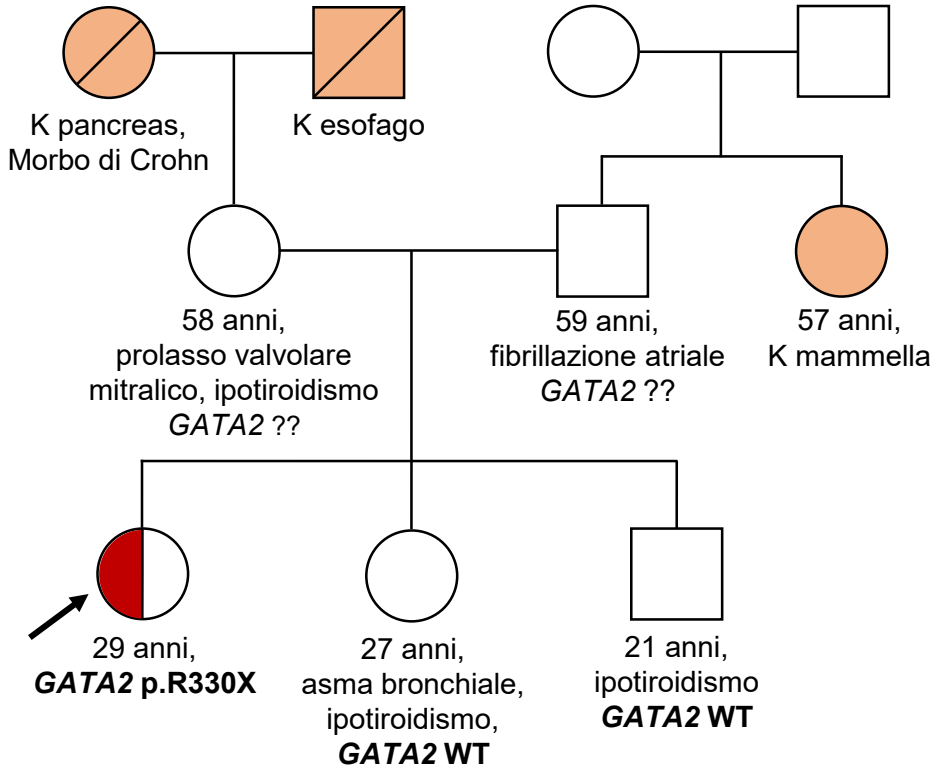
  PATOGENETICA

  Sindrome da deficit di GATA2

  NGS GERMINALE della fratria: *GATA2* wild type (WT)

- **2020**: NGS SOMATICO: wild type (WT)

Familiarità per neoplasia solida



Predisposizione germinale alle neoplasie mieloidi: caso clinico (1)

- **2021**: Consulenza genetica Azienda Ospedale - Università Padova

  ***GATA2* c.988C>T; p.R330X PATOGENETICA**

  Indicazioni sulla probabilità di trasmissione del difetto genetico alla prole. Suggerite diagnosi prenatale precoce o diagnosi preimpianto.

  - **Maggio**: aborto spontaneo primo trimestre (gravidanza naturale)
- **2022**: Gravidanza naturale a termine ♀
- **2023**: Consulenza presso Genetica Medica Policlinico San Matteo Pavia

  Analisi mutazionale di *GATA2* sulla figlia (WT)
- **2023**: rivalutazione con monitoraggio molecolare in stabilità clinica (pancitopenia di grado lieve-moderato)

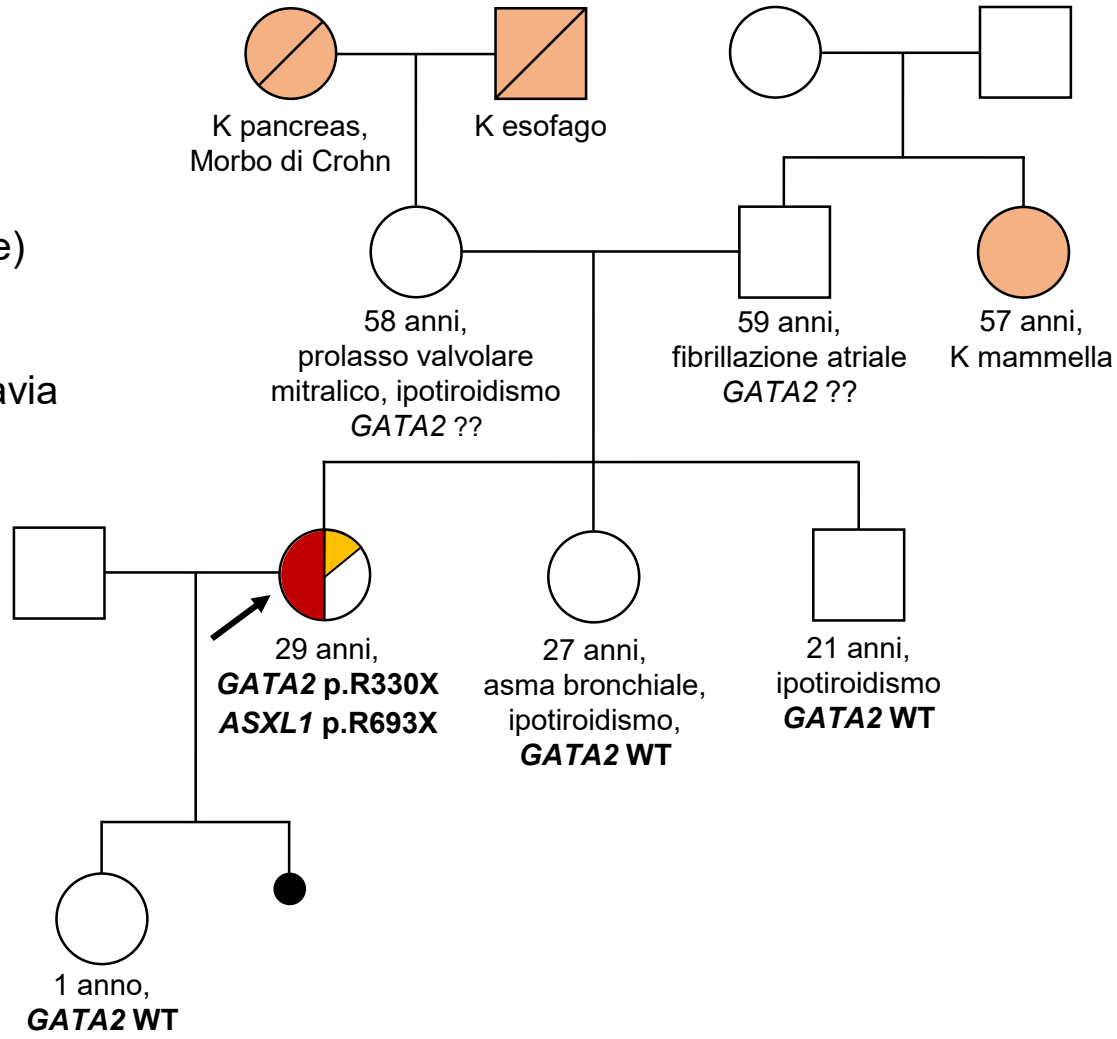
  NGS SOMATICO

  ***ASXL1* c.2077C>T; p.R693X (VAF 4,4%)**

  PATOGENETICA

  Citopenia clonale di incerto significato (CCUS)

Familiarità per neoplasia solida



Predisposizione germinale alle neoplasie mieloidi: caso clinico (2)

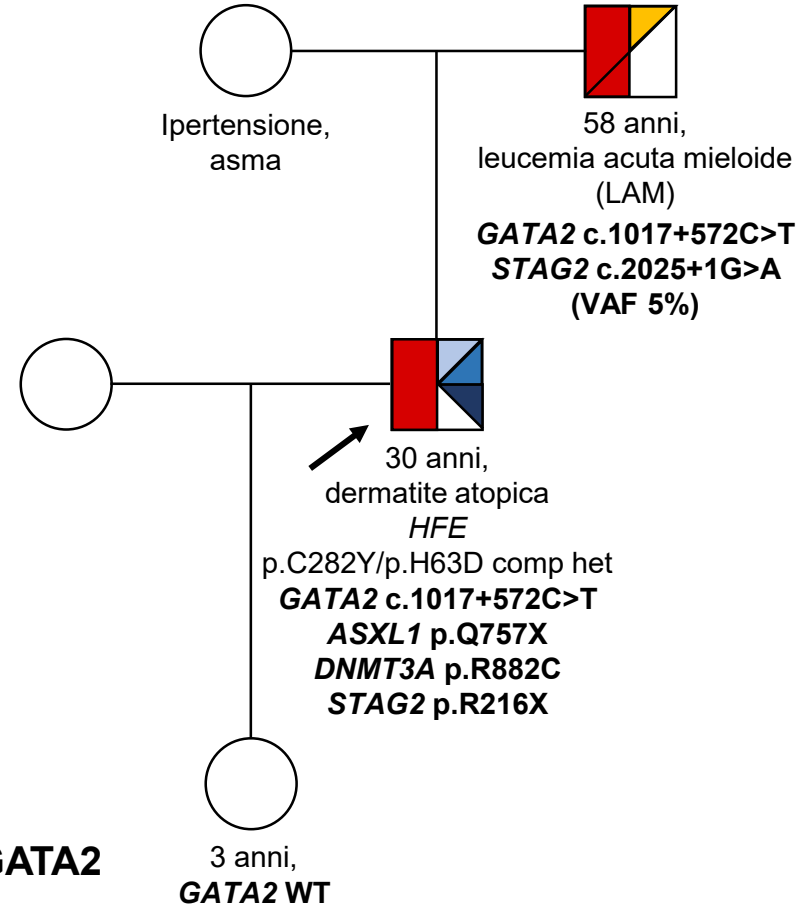
Uomo di 30 anni

- **1997-2013**: leucopenia stabile di grado lieve-moderato non ulteriormente indagata
- **2014**: prima visita Ematologia Policlinico San Matteo Pavia. Leucopenia stabile.
  Familiarità per neoplasia ematologica (padre con recente diagnosi di LAM)
  Mutazioni germinali del gene *HFE* p.C282Y/p.H63D in eterozigosi composta
  → Diagnosi di emocromatosi tipo 1
- **2022**: BOM: cellularità 30-40% (ridotta per l'età), blasti 1%. Citogenetica 46,XY

NGS GERMINALE: *GATA2* c.1017+572C>T in eterozigosi
PATOGENETICA

NGS SOMATICO: *ASXL1* c.2269C>T; p.Q757X (VAF 8%)
***DNMT3A* c.2644C>T; p.R882C (VAF 12%)**
***STAG2* c.646C>T; p.R216X (VAF 19%)**
PATOGENETICHE

Sindrome mielodisplastica (MDS, NOS with MLD) in sindrome da deficit di GATA2



- **2023**: Consulenza presso Genetica Medica Policlinico San Matteo Pavia
  Analisi mutazionale di *GATA2* sulla figlia (WT)

Sindrome da deficit di GATA2

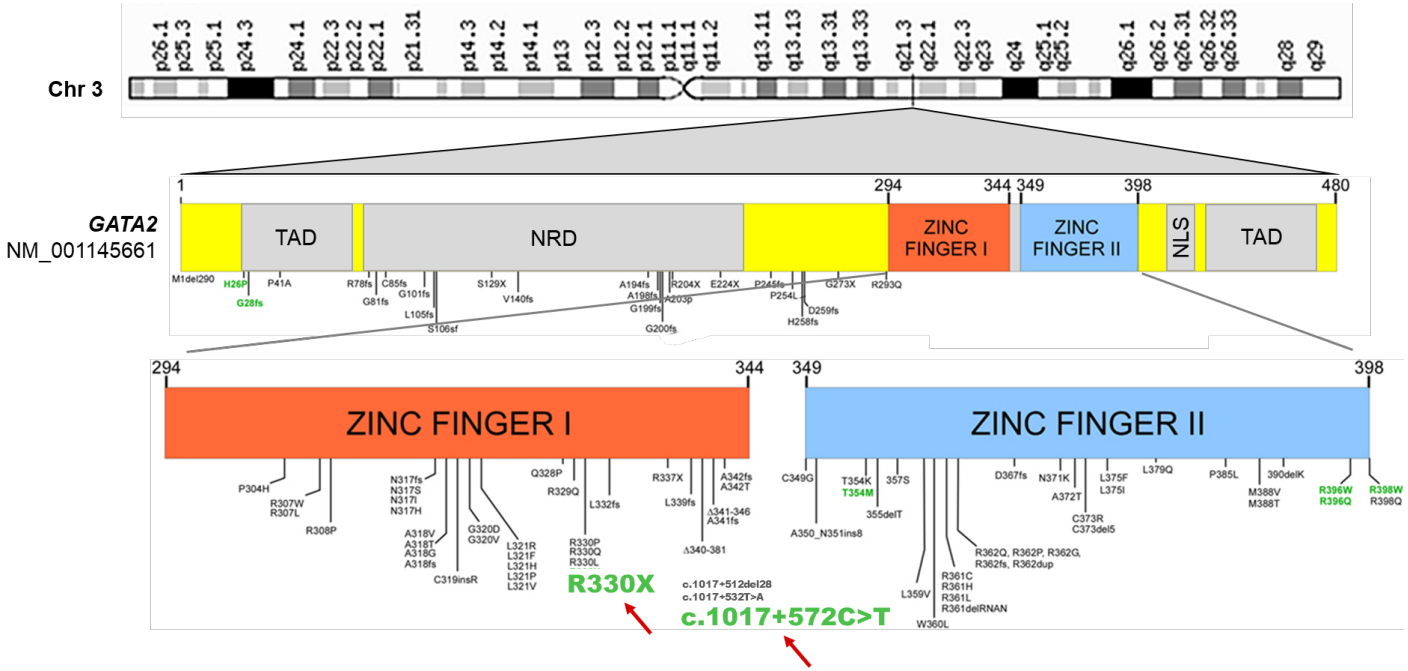
Ereditarietà autosomica dominante (AD) nel 50% dei pazienti riportati in letteratura, de novo nel 5% dei casi, o con insorgenza incerta (AD/de novo) nei restati casi (Homan CC. *et al*. Hum Mutat. 2021;42(11):1399-1421).

<u>Deficit di GATA2</u>:

- Insufficienza midollare associata in vario grado a sintomi sistemici a livello polmonare, endocrinologico, dermatologico, autoimmune, neurosensoriale…
- Sindrome MonoMac (monocitopenia associata ad infezioni virali e batteriche ricorrenti), sindrome di Emberger (sordità congenita e linfedema)
- Predisposizione a sindrome mielodisplastica (MDS) e leucemia acuta mieloide (LAM)

GATA2: fattore trascrizionale che lega il DNA a livello delle sequenze consenso (A/T)GATA(A/G) tramite i due domini Zinc finger

Mutazioni germinali di *GATA2* non sono sufficienti per lo sviluppo una neoplasia mieloide che insorge a seguito dell'acquisizione di alterazioni somatiche molecolari (*ASXL1*, *STAG2, KRAS, SETBP1*) e/o citogenetiche (-7, del7, +8) (PMID: 26492932, 28637621, 29296959, 37406166)



REGULAR ARTICLE

blood advances

ASXL1 and *STAG2* are common mutations in GATA2 deficiency patients with bone marrow disease and myelodysplastic syndrome

Robert R. West,[1] Katherine R. Calvo,[2] Lisa J. Embree,[1] Weixin Wang,[2] Laura M. Tuschong,[1] Thomas R. Bauer Jr,[1] Desiree Tillo,[3] Justin Lack,[4] Stephenie Droll,[2] Amy P. Hsu,[5] Steven M. Holland,[5] and Dennis D. Hickstein[1]

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(Blood Adv. 2022 Feb 8;6(3):793-807)

REGULAR ARTICLE

blood advances

Somatic mutational landscape of hereditary hematopoietic malignancies caused by germline variants in *RUNX1*, *GATA2*, and *DDX41*

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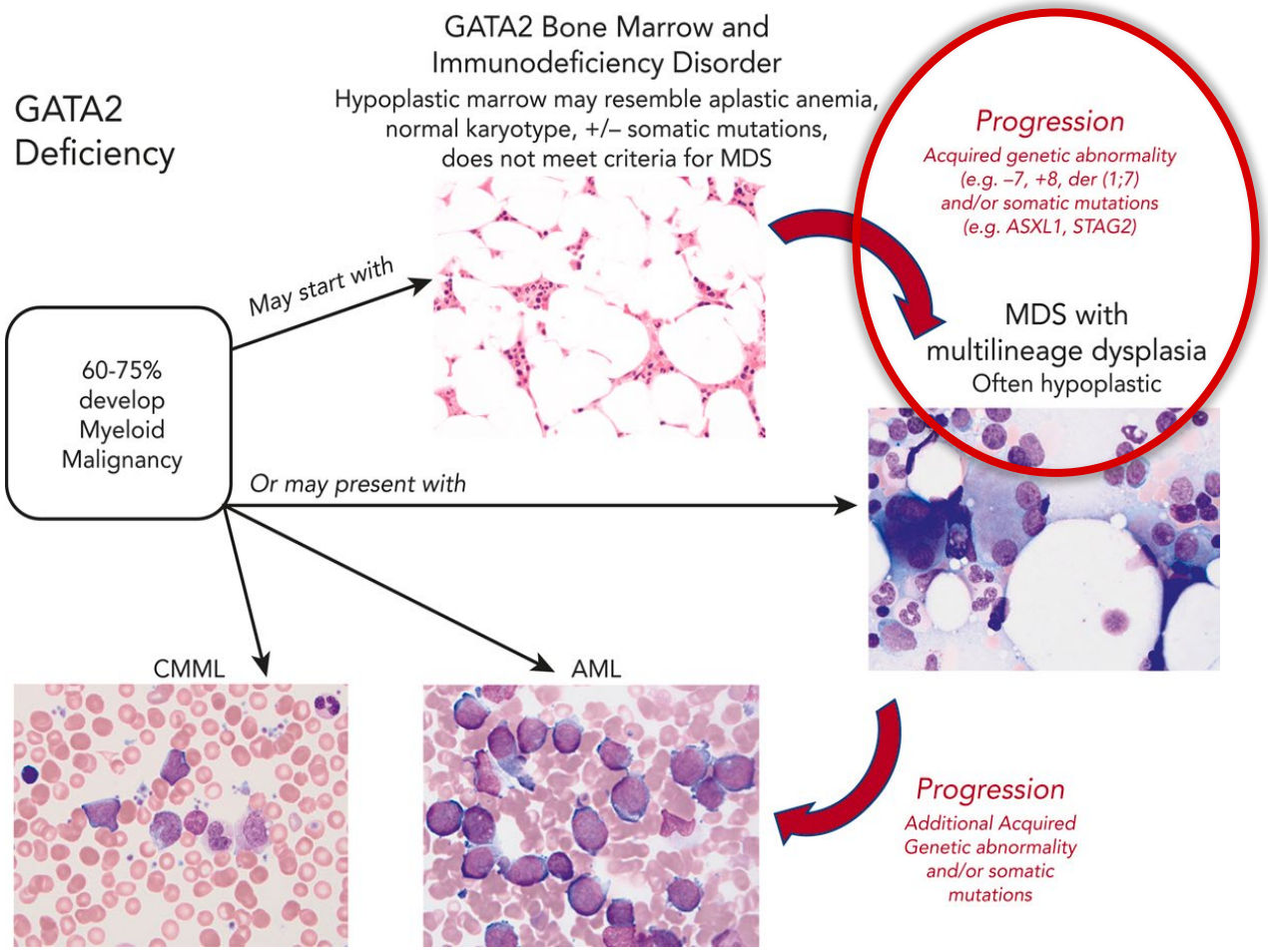
(Blood Adv. 2023 Oct 24;7(20):6092-6107)

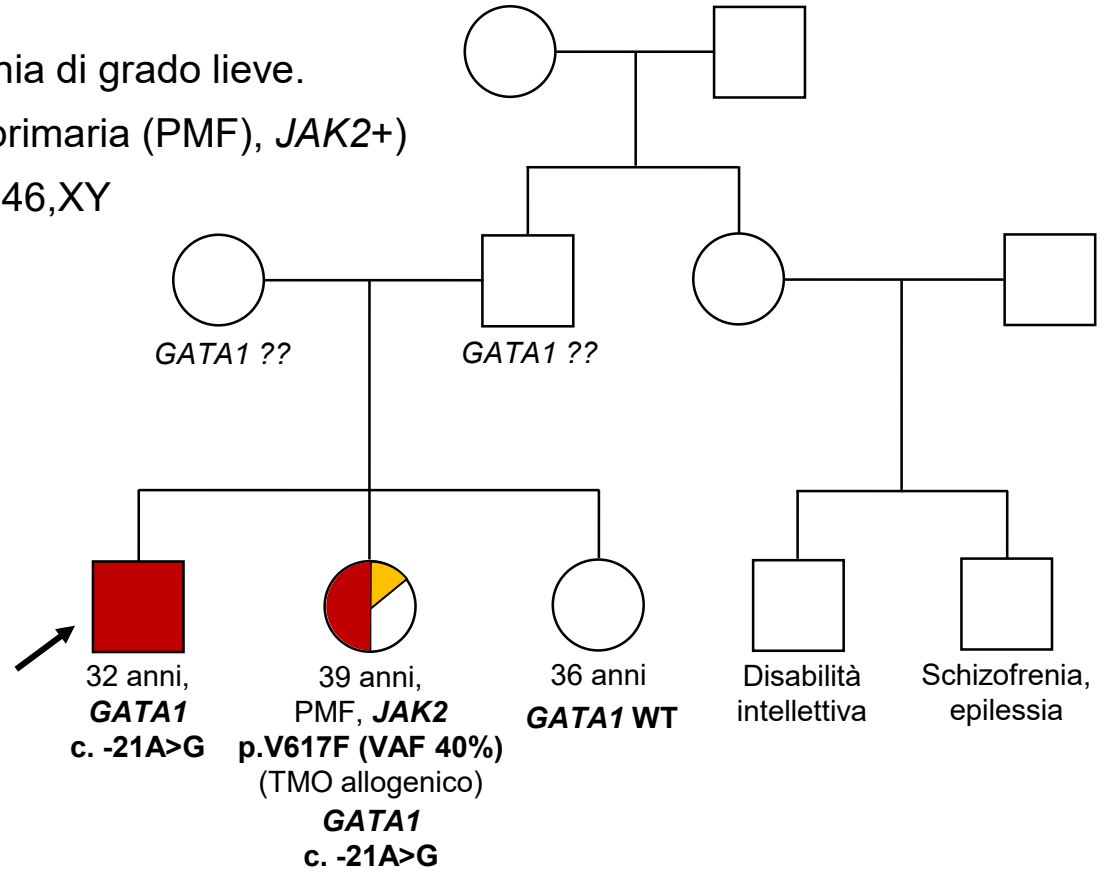


(Blood. 2023 Mar 30;141(13):1524-1532)

Predisposizione germinale alle neoplasie mieloidi: caso clinico (3)

Uomo di 32 anni

- **2006-2017**: pancitopenia di grado lieve stabile
- **2017**: prima visita Ematologia Policlinico San Matteo Pavia per citopenia di grado lieve.
  Familiarità per neoplasia ematologica (sorella con mielofibrosi primaria (PMF), *JAK2*+)
- **2018**: BOM: cellularità 40% (ridotta per l'età), blasti 3%. Citogenetica: 46,XY
  Fibrosi midollare. Note displastiche.
  Citopenia di incerto significato → ICUS
- **2020**: rivalutazione con stabilità del quadro



NGS SOMATICO: wild type (WT)

NGS GERMINALE

***GATA1* c. -21A>G in emizigosi (X-linked)**

PATOGENETICA

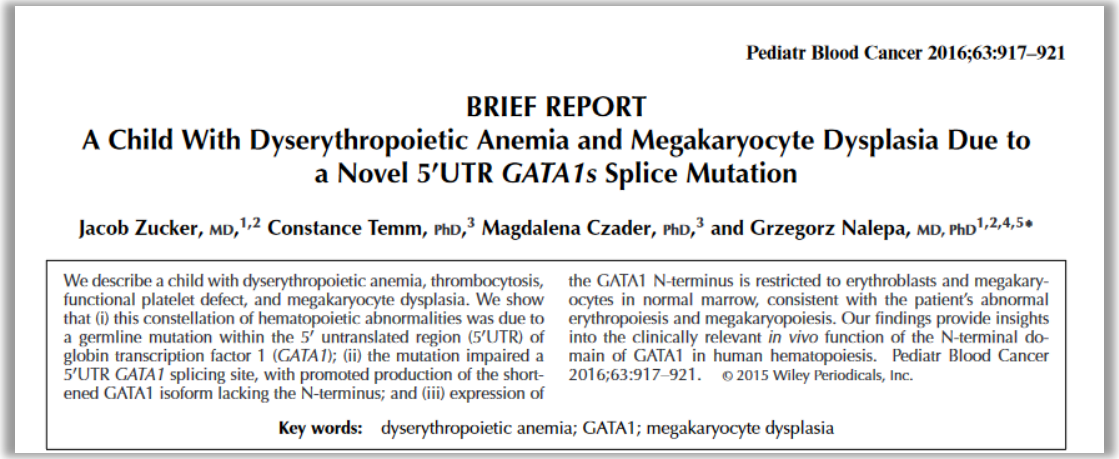
NGS GERMINALE della fratria:

- 1 sorella con mielofibrosi primaria (PMF), *GATA1* c. -21A>G in eterozigosi (X-linked)
- 1 sorella *GATA1* WT

Disordini da difetti germinali di GATA1

Le mutazioni germinali a carico del gene *GATA1* si associano ad uno spettro di disordini ematologici caratterizzati da insufficienza midollare e aumentato rischio di neoplasia ematologica, con ereditarietà recessiva legata al cromosoma X:

- Anemia diseritropoietica con/senza neutropenia e/o anomalie piastriniche
- Trombocitopenia con o senza anemia diseritropoietica
- Anemia diseritropoietica congenita
- Beta talassemia legata all'X con trombocitopenia
- Anemia di Diamond-Blackfan (DBA)



Pediatr Blood Cancer 2016;63:917–921

BRIEF REPORT

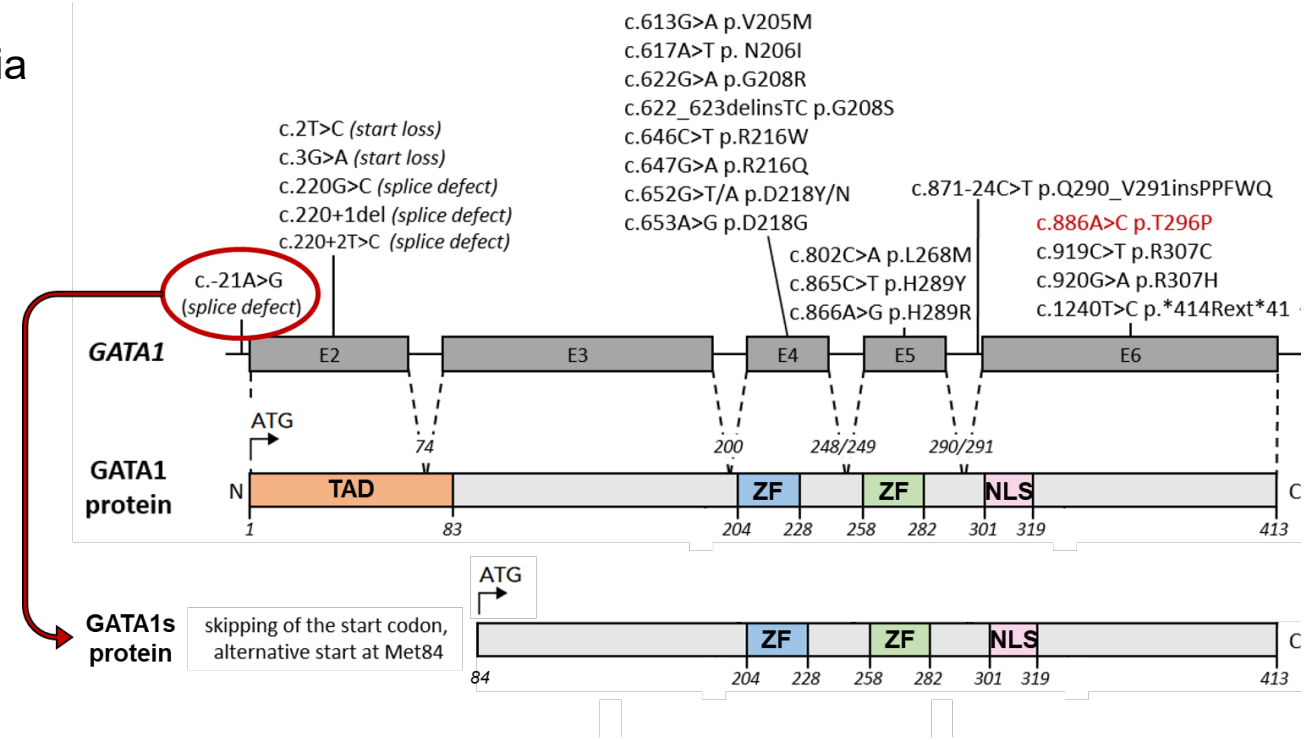
A Child With Dyserythropoietic Anemia and Megakaryocyte Dysplasia Due to a Novel 5′UTR *GATA1s* Splice Mutation

Jacob Zucker, MD,[1,2] Constance Temm, PhD,[3] Magdalena Czader, PhD,[3] and Grzegorz Nalepa, MD, PhD[1,2,4,5]*

We describe a child with dyserythropoietic anemia, thrombocytosis, functional platelet defect, and megakaryocyte dysplasia. We show that (i) this constellation of hematopoietic abnormalities was due to a germline mutation within the 5′ untranslated region (5′UTR) of globin transcription factor 1 (*GATA1*); (ii) the mutation impaired a 5′UTR *GATA1* splicing site, with promoted production of the shortened GATA1 isoform lacking the N-terminus; and (iii) expression of the GATA1 N-terminus is restricted to erythroblasts and megakaryocytes in normal marrow, consistent with the patient's abnormal erythropoiesis and megakaryopoiesis. Our findings provide insights into the clinically relevant *in vivo* function of the N-terminal domain of GATA1 in human hematopoiesis. Pediatr Blood Cancer 2016;63:917–921. © 2015 Wiley Periodicals, Inc.

Key words: dyserythropoietic anemia; GATA1; megakaryocyte dysplasia

(Pediatr Blood Cancer. 2016 May;63(5):917-21)



GATA1: fattore trascrizionale che lega il DNA a livello delle sequenze consenso (A/T)GATA(A/G) tramite i due domini Zinc finger

Conclusioni

- Significativa prevalenza di mutazioni germinali associate a sindromi predisponenti in pazienti adulti con neoplasia mieloide.

- L'analisi di mutazioni germinali può contribuire a spiegare le basi molecolari delle citopenie di incerto significato.

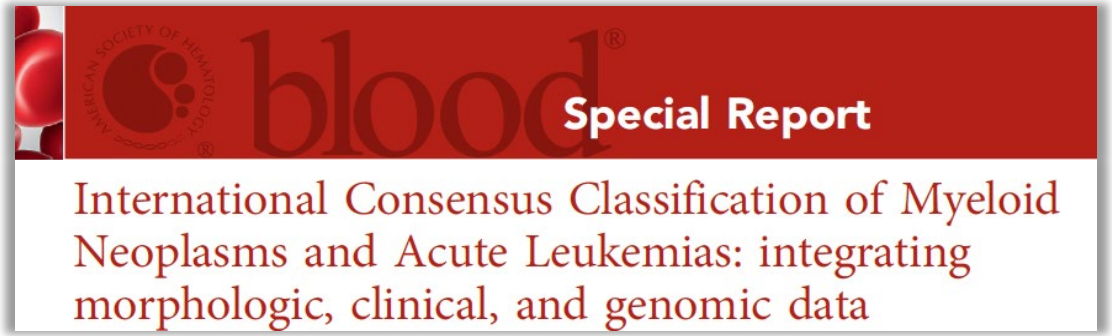
- La presenza di mutazioni germinali si associa ad un quadro clinico più aggressivo; la loro identificazione indirizza lo studio dei membri della famiglia ed è fondamentale per la scelta dell'eventuale strategia trapiantologica.

- Il monitoraggio molecolare somatico nei pazienti con mutazioni germinali consente un'identificazione precoce dell'evoluzione neoplastica.

- Il test germinale può essere richiesto in base al quadro clinico del paziente anche se alcune condizioni predisponenti sono caratterizzate da ridotta o assente espressività clinica.

Grazie per l’attenzione

Predisposizione germinale alle neoplasie mieloidi: caso clinico (1)



(Blood. 2022 Sep;140(11):1200-1228)

Diagnosis of MDS in the setting of germline predisposition

The ICC recognizes that many of the genes predisposing to myeloid malignancy also predispose to baseline changes in BM cells that overlap with dysplastic features. These dyspoietic changes may be present irrespective of whether the patient has a myeloid malignancy. For this reason, a germline predisposition should be considered for cases with morphologic atypia in the absence of additional factors supporting a diagnosis of MDS or other myeloid malignancy. In general, the development of MDS in patients with germline predisposition is associated with new or progressive cytopenia(s) often in the setting of rising marrow cellularity, overt multilineage dysplasia, increased blasts, and/or acquired pathogenic genetic alterations. Emergence of del(5q), −7/del(7q), complex karyotype, multihit *TP53* mutations (VAF > 10%), or *SF3B1* mutation (VAF > 10%) is considered MDS defining. Acquired genetic changes must be interpreted in the context of the specific germline genetic mutation: for example, patients with Shwachman Diamond syndrome frequently develop small stable clones with monoallelic *TP53* mutations, and in isolation, these are not considered to represent development of MDS; however, biallelic *TP53* mutations in this context are associated with myeloid malignancy.[181]

GATA1

The GATA1 gene encodes a zinc finger DNA-binding transcription factor that plays a critical role in the normal development of hematopoietic cell lineages. The protein contains an N-terminal region that confers transcriptional activity and a C-terminal domain that mediates binding to DNA and other factors

Donna di 29 anni, 81kg

2021: Pancitopenia grado lieve-moderato → **ICUS**

Consulenza genetica Azienda Ospedale - Università Padova
GATA2 c.988C>T; p.R330* PATOGENETICA
Sindrome da deficit di GATA2 AD

Maggio: Aborto spontaneo primo trimestre

Ottobre: Gravidanza

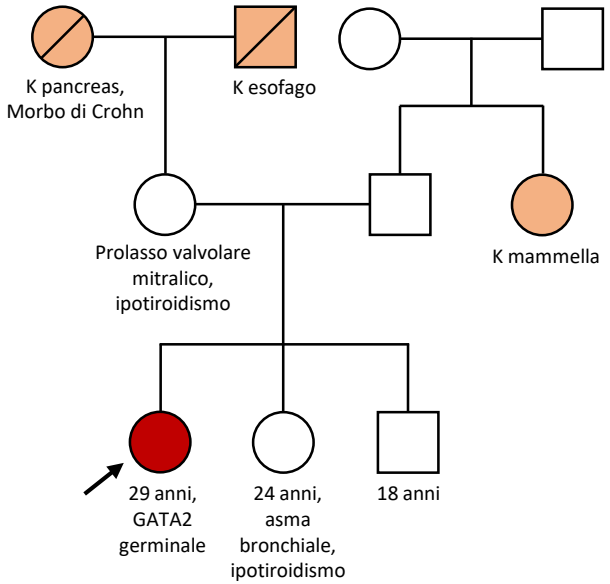
NGS SOMATICO: WT

2022: Pancitopenia grado lieve-moderato → **ICUS**
Parto

2023: Consulenza genetica Genetica Medica Ospedale San Matteo.
Figlia non testata per GATA2.
NGS SOMATICO: ASXL1 c.2077C>T; p.R693* VAF 4,4%
PATOGENETICA
Pancitopenia grado lieve-moderato clonale→ **CCUS**

Counseling genetica medica familiari primo grado

Familiarità per neoplasia solida



Predisposizione germinale alle neoplasie mieloidi: case report

Donna di 29 anni, 81kg

- Cistiti ricorrenti fino a 3 anni
- Menarca precoce (9 anni)
- Prolasso valvolare mitralico
- Mutazione del gene *MTHFR* c.677C>T in eterozigosi
- Dal 2015: gastrite cronica
- Dal 2016: extrasistolia in terapia con betabloccante
- 2019: tiroidite di Hashimoto; tiroidectomia totale per carcinoma papillare

- **2007**: primo riscontro di pancitopenia di grado lieve-moderato
- **2016**: prima valutazione ematologica (Ferrara)
  → mieloaspirato nella norma; citogenetica 46,XX
- **2017**: peggioramento pancitopenia.
  Biopsia osteo-midollare (BOM): cellularità ridotta 20-25%, blasti 1%.
- **2020**: prima visita Ematologia Policlinico San Matteo Pavia.
  BOM: cellularità ridotta per l'età 40%, blasti 1%. Citogenetica: 46,XX
  Pancitopenia di grado lieve-moderato → ICUS

Familiarità per neoplasia solida