When and How Genetic Predisposition to MDS Should be Taken into Account in Clinical Decision Making

Luca Malcovati, MD
Department of Molecular Medicine, University of Pavia Medical School;
Unit of Precision Hematology Oncology, IRCCS S. Matteo Hospital Foundation, Pavia, Italy.
DISCLOSURE
Luca Malcovati, MD

I have no financial relationships to disclose.
The case of Mr. H.C.

• 65 year-old male
• Negative family history
• Smoker
• Incidental finding of mild-to-moderate pancytopenia (Hb 12 g/dL, MCV 98 fL, WBC 3.54x10^9/L [ANC 1.38x10^9/L], Plt 64x10^9/L)
• BM biopsy: cellularity 10%, CD34+ cells 2%
• Conventional cytogenetics: 46,XY
• Myeloid somatic mutation analysis (54 genes): absence of P/LP variants

C: non-severe aplastic anemia

• Worsening of cytopenia (Hb 9.4 g/dL, MCV 100 fL, WBC 1.65x10^9/L [ANC 0.9x10^9/L], Plt 23x10^9/L)
• BM biopsy: cellularity 20%, CD34+ cells 10%
• Conventional cytogenetics: 46,XY

C: MDS-EB-2

• Germline DDX41 I207T
• Somatic mutation analysis: DDX41 R525H
The case of Mr. H.C.

- HLA testing: 4 haploidentical relatives (germline testing in progress)
- Matched unrelated donor search
- Treatment: azacitidine with achievement of mCR
## Myeloid neoplasms with germline predisposition

### Myeloid neoplasm classification

<table>
<thead>
<tr>
<th>Myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML with germline CEBPA mutation</td>
</tr>
<tr>
<td>Myeloid neoplasms with germline DDX41 mutation*</td>
</tr>
</tbody>
</table>

| Myeloid neoplasms with germline predisposition and preexisting platelet disorders            |
| Myeloid neoplasms with germline RUNX1 mutation*                                            |
| Myeloid neoplasms with germline ANKRD26 mutation*                                          |
| Myeloid neoplasms with germline ETV6 mutation*                                            |

| Myeloid neoplasms with germline predisposition and other organ dysfunction                  |
| Myeloid neoplasms with germline GATA2 mutation                                               |
| Myeloid neoplasms associated with BM failure syndromes                                     |
| Myeloid neoplasms associated with telomere biology disorders                               |
| JMML associated with neurofibromatosis, Noonan syndrome or                                 |
| Noonan syndrome-like disorders                                                             |
| Myeloid neoplasms associated with Down syndrome*                                           |

---

### Open questions

- Prevalence in adult patients with suspected MDS
- Clinical implications
- Selection of candidates to screening
- Methods for assessment:
  - Control tissue
  - Interpretation of variants
Germline predisposition in adult patients with apparently sporadic MDS

N. of patients: 107
Age: 18-40 yrs
Diagnosis:
- MDS/AML-MDS: 68
- AA: 39
P/LP germline variants:
- MDS/AML-MDS: 19%
- AA: 15%

Feurstein et al. Leukemia. 2021;35:2439-2444

N. of patients: 1514
Age (yrs):
- 0-18: 97
≥18: 1417
Diagnosis:
- Primary MDS: 1203
- t-MDS: 311
Germline variants:
- GATA2: 11%
- Biallelic SBDS: 2%

Clinical implications of germline predisposition: *why seeking predisposing germline variants*

- Interpretation of the hematologic phenotype (correct diagnosis)
- Canalization of somatic progression
- Effect on clinical outcomes
- Effect on disease modifying treatments
- Hematopoietic stem cell donor selection
- Genetic counseling
Germline predisposition to myeloid neoplasm in adults with hypoplastic bone marrow

402 adult patients with unexplained cytopenia and age-adjusted BM hypocellularity

- MN=173
- AA=187
- ICUS=187

74 / 402 (18%) P/LP germline variants in 18 genes

328/402 (82%) wild-type / VUS

50/402 (12%) GL genotype causative of inherited disorder

- 74 / 402 (18%)
- 328/402 (82%)
- 50/402 (12%)

50/402 (12%) GL genotype causative of inherited disorder

74 / 402 (18%)
P/LP germline variants in 18 genes

328/402 (82%) wild-type / VUS

50/402 (12%) GL genotype causative of inherited disorder

- MN
- AA/ICUS

MN
- 30/50 (60%)

AA/ICUS
- 20/50 (40%)

75% Somatic mutation(s) consistent with MN

25% No somatic mutation

Molteni E, Bono E et al. Manuscript in preparation
Canalization of somatic progression

Revertant mosaicism in SAMD9/SAMD9L mutation

Inaba et al. Blood. 2018;131:2891-2898

Second DDX41 somatic hit in germline DDX41 mutation

Effect on clinical outcomes and disease modifying treatments

**Overall survival of germline DDX41-mutated MDS/AML compared with matched controls**

![Graph showing overall survival over time with different mutation statuses.](image_url)

**Survival after Allo-SCT according to germline mutation status**

![Graph showing survival probability over time with different mutation statuses.](image_url)


Potential clinical indicators of germline mutations in adults

- Age
- Hypocellular bone marrow
- Extra-hematologic signs
- Family history of hematologic and/or non-hematologic cancer
- Personal history of multiple tumors
Potential clinical indicators of germline mutations in adults
Effect of germline predisposition on clinical phenotype

- Germline predisposition without pre-existing disorder or organ dysfunction (or very mild phenotype other than myeloid neoplasm)

- Germline predisposition with hematologic and/or extra-hematologic phenotype
  - Late diagnosis in adulthood
  - Selection of disorders / variants with incomplete penetrance and/or mild clinical expressivity
    - Molecular heterogeneity
    - Influence of the sex
    - Influence of the allele in \textit{trans}
    - Influence of a polymorphism present in \textit{cis}
    - Influence of a modifier gene
    - Anticipation
    - Somatic mosaicism
Interpretation of germline variants: the ACMG-AMP recommendations

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD¹, Nazneen Aziz, PhD²,¹⁶, Sherri Bale, PhD³, David Bick, MD⁴, Soma Das, PhD⁵, Julie Gastier-Foster, PhD⁶,⁷,⁸, Wayne W. Grody, MD, PhD⁹,¹⁰,¹¹, Madhuri Hegde, PhD¹², Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelkerding, MD¹³ and Heidi L. Rehm, PhD¹⁵; on behalf of the ACMG Laboratory Quality Assurance Committee

Functional classification of germline variants: a journey of a thousand miles

---


ClinGen: a central resource to define the clinical relevance of genes and variants

**Key Goals**

- Share genomic and phenotypic data between clinicians, researchers, and patients through centralized and federated databases for clinical and research use.

- Develop and implement standards to support clinical annotation and interpretation of genes and variants.

- Develop data standards, software infrastructure and computational approaches to enable curation at scale and facilitate integration into healthcare delivery.

- Enhance and accelerate expert review of the clinical relevance of genes and variants.

- Disseminate and integrate ClinGen knowledge and resources to the broader community.

https://www.clinicalgenome.org/

Conclusions

• Emerging evidence is suggesting that germline predisposition has a prevalence higher than expected in adult patients with apparently sporadic MDS.

• Absence of pre-existing disorder or organ dysfunction and selection of disorders / variants with incomplete penetrance and mild clinical expressivity complicate the identification of patients candidate to screening for germline variants.

• Germline predisposition has major clinical implications in adult patients with MDS, affecting hematologic and extra-hematologic phenotype, response to treatment and clinical outcome.

• Germline predisposition appears to be critical to clinical decision-making in patients with MDS/AML and should be taken into account in diagnosis, treatment and transplantation strategies.

• Classification of variants is problematic, and international collaborative efforts are critical to develop and implement standards to support clinical annotation and interpretation of genes and variants.