Evaluation and care of patients and families with inherited predisposition to develop MDS

MDS Foundation’s Educational Patient-Caregiver Forum
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Sioban Keel, MD
Associate Professor of Medicine
Bone marrow failure definition -

Bone marrow is unable to keep up with the body’s need for healthy blood cells

1. Acquired
   - Myelodysplastic syndromes (MDS)
   - Aplastic anemia
   - PNH
   - Toxins (e.g., drugs, irradiation, infections)

2. Inherited*

* Are at risk for developing MDS or leukemia
From the Cell to DNA

- chromosome
- DNA
- Genes
- Basepairs
- Nucleosome
- Histone
- Nucleotide
  - Guanine
  - Cytosine
  - Adenine
  - Thymine
Mutations – changes in the DNA

- Mutations can be *inherited* or *acquired* during a person’s life.
Mendelian Inheritance

Example - Autosomal dominant

<table>
<thead>
<tr>
<th>Wild-type</th>
<th>Wild-type</th>
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<tbody>
<tr>
<td>*</td>
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Wild-type Wild-type

Parents

Affected

Unaffected

Children

Affected

Affected

Unaffected

Unaffected
Genetic predisposition to cancer

1866


1999 1st reported inherited acute leukemia and MDS predisposition syndrome - Familial platelet disorder with associated myeloid malignancy due to mutations in RUNX1.²

# Genetic laboratory testing

<table>
<thead>
<tr>
<th></th>
<th>Karyotype</th>
<th>FISH</th>
<th>Microarray</th>
<th>Next-gen sequencing</th>
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</thead>
<tbody>
<tr>
<td><strong>Coverage</strong></td>
<td>Genome</td>
<td>Targeted</td>
<td>Genome</td>
<td>Exome/genome</td>
</tr>
<tr>
<td><strong>Resolution</strong></td>
<td>Low</td>
<td>High</td>
<td>Higher</td>
<td>Highest</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Living cells</td>
<td>Living/fixed cells</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Detect balanced rearrangements?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Sometimes</td>
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Inherited bone marrow failure & inherited MDS/leukemia predisposition syndromes

- Marrow failure
  - Often hypocellular

- ± Cancer predisposition

- ± Findings on exam

Inherited MDS predisposition syndromes

- Classical inherited bone marrow failure syndromes
- Germline predisposition for hematopoietic malignancy
  - CEPBA
  - DDX41
  - 14q32.2 genomic duplication (ATG2B/GSKIP)
- Germline predisposition for hematopoietic malignancy with pre-existing cytopenia(s) and/or other organ dysfunction prior to hematopoietic malignancy presentation
  - ANKRD26
  - ETV6
  - GATA2 Deficiency Syndrome
  - RUNX1 - Familial platelet disorder with associated myeloid malignancy
  - SAMD9 - MIRAGE syndrome; SAMD9L - Ataxia Pancytopenia Syndrome
  - SRP72
- Germline predisposition for myeloid neoplasms and solid tumor cancers
  - Constitutional mismatch repair deficiency
  - Hereditary breast and ovarian cancer (e.g., BRCA1, BRCA2)
  - Li-Fraumeni syndrome
  - RASopathies
  - Other rare DNA repair syndromes (e.g., BLM)

Modified from 2019 NCCN MDS Guidelines
Cumulative incidence of MDS by age 50 were 5% in DBA, 20% in DC, 50% in FA, and 65% in SDS.
Why do we need to recognize these inherited syndromes?
1. Some syndromes are associated with a risk of developing MDS or leukemia
   • Allows surveillance *prior* to development of MDS/leukemia.
   • Informs hematopoietic stem cell transplant donor selection, timing, and preparatory regimen for patients who develop MDS/leukemia.

2. Follow-up and care for non-blood related complications
GATA2 deficiency syndrome

Surveillance and treatment considerations (before development of MDS)
- CBC and blood count monitoring
- HPV vaccination
- Prophylactic antibiotics for certain infections (NTM)
- Family counseling and follow-up
3. Appropriate family counseling and follow-up
Patients Pursuing a Genetic Consultation

- Medical Evaluation
- Psychosocial Counseling
Hematologic Malignancy Genetics Clinic

Services offered to individuals and families

• Hematologic malignancies cancer risk assessment and genetic testing
• HSCT planning
• Surveillance Program
• Family counseling
• Research opportunities to improve patient care
How do you distinguish between acquired & inherited marrow failure?

- Clinical History
- Physical Exam
- Laboratory Evaluation
- Family History
  - Other members with similar disease
  - Malignancy

Lack of a concerning family history or physical exam findings DOES NOT exclude the possibility of an underlying inherited cause.
Pediatric & young adult patients transplanted for “acquired disorders” had underlying inherited disorders

Study Design
- Fred Hutchinson Cancer Research Center Cell Bank Repository of pre-hematopoietic stem cell transplant DNA
- MDS patients ≤ 40 years-old and transplanted 2001-2011 or MDS or AML with monosomy 7 patients <20 years-old and transplanted 1991-2001

Findings
- 12.7% (14/110) MDS/AML carried pathologic mutations
- Absence of a family history or congenital anomalies does not exclude a genetic cause

Which patients are we currently testing?

- Patient with a suggestive personal and/or family history
- Younger patients presenting with marrow failure, MDS, or leukemia
- Family member in a known inherited predisposition family (mutation-directed sequencing)
- Potential sibling allogeneic stem cell donor in a known inherited predisposition family
- Patient with potential inherited mutation found on testing cancer cells
Complexities of genetic testing: inherited vs. acquired mutations

Inherited mutations

- Parent
  - Mutation in egg or sperm
  - Heritable - can pass mutation on to children

Child
- Mutation in all cells in affected child

Acquired mutations

- Mutation in a cancer (e.g., lung cancer)
  - Not heritable
  - Present only in the cancer

In MDS, cancer is in the blood – so testing blood can be confusing.
Other complexities of genetic testing

- Limitations of different sequencing methods
- Interpretation of sequencing results is complicated
- Evolving field (new genes, new mutations)
Treatment options

• Depends on specific underlying syndrome
• Cancer surveillance
• Supportive care
• Other therapies depending on disease
  – Androgens (Fanconi anemia)
  – Steroids (DBA)
• Bone marrow transplantation
Concluding thoughts

• Recognition of an underlying inherited predisposition to develop MDS guides medical care.

• Goal of diagnosis and follow-up is to keep people healthy.
Questions?
Example pedigree: Autosomal dominant disease
Defined inherited bone marrow failure or MDS/AML predisposition syndromes – 74 patients

- Diamond-Blackfan anemia (15)
- Telomere disorders (13)
- Fanconi anemia (4)
- GATA2 disorders (9)
- Shwachman-Diamond syndrome (7)
- RUNX1 disorders (21)
- DDX41 disorders (1)
- Congenital neutropenia (3)

Other (1)