Genetic Predisposition Syndromes in Myeloid Malignancies

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Realizing the goal of precision medicine in oncology

DEFINE:
Baseline genetics
Baseline epigenetics
Acquired genetics in the tumor
Acquired epigenetics in the tumor

to devise an effective treatment strategy for a particular patient
A Hematologic Malignancy-focused Cancer Risk Clinic

• Genetic counseling for family members

• Early identification allows proper anticipatory medical care for mutation carriers, but the few surveillance guidelines that exist are based on expert experience rather than prospective data

• Careful hematopoietic stem cell transplant donor evaluation, including interdisciplinary discussions regarding donor selection for patients under consideration for a matched related allogeneic stem cell transplant

• Incorporation of genetic predisposition within the new WHO classification scheme and clinical guidelines, including NCCN MDS and European LeukemiaNet
Key aspects of pedigree review

- A high index of clinical suspicion

- Familiarity with the known predisposition syndromes

- Key features within the personal and family history:
  - Multiple cancers within a single individual (e.g., t-MN)
  - Other hematopoietic malignancies within 2 generations
  - Other hematopoietic abnormalities within the family (e.g., macrocytosis, bleeding propensity, severe anemia or anemia in men)
  - NOTE: NOT according to age of onset

- Consider results of molecular analyses performed on leukemic cells
<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Population</th>
<th>Specific Syndromes</th>
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<tr>
<td>MDS/AL Predisposition Syndromes</td>
<td>MDS, AML, ALL</td>
<td>FPD/AML</td>
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<td>ANKRD26</td>
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<td>ALL only: IKZF1 (emerging) PAX5 SH2B3</td>
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<td>Bone Marrow Failure Syndromes</td>
<td>AA, MDS, AML</td>
<td>Dyskeratosis congenita</td>
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<td>SBDS/EFL1/DNAJC21</td>
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<td>Fanconi anemia</td>
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<td>Genetic Syndromes</td>
<td>ALL</td>
<td>Ataxia Telangiectasia (ATM)</td>
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<td>Bloom syndrome (BLM)</td>
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<td>Down syndrome (Trisomy 21)</td>
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<td>Leopard/Noonan syndrome (PTPN11)</td>
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<td>Neurofibromatosis I (NF1)</td>
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<td>Nijmegen Breakage syndrome (NBS1)</td>
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<td>Wiskott Aldrich syndrome (WAS)</td>
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<td>Familial MPNs</td>
<td>PV, ET, PMF, CML</td>
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<td>RBBP6</td>
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<td>Familial Lymphomas</td>
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<td>PIK3CD</td>
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<td>Cancer Predisposition Syndromes</td>
<td>All</td>
<td>Li-Fraumeni syndrome (TP53)</td>
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<td>Hereditary breast &amp; ovarian cancer (BRCA1/2)</td>
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<td>Lynch syndrome</td>
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<td>Cowden syndrome (PTEN)</td>
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<td>Familial MM/LPL</td>
<td>MM, MGUS, LPL</td>
<td>Familial MM/LPL</td>
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An Algorithm for Patient Work-Up

Patient acquired through strong personal/family history

- ANKRD26
- ATM
- B Marrow Failure
- BRCA1/2
- CEBPA
- DDX41
- ETV6
- Fanconi anemia
- GATA2
- SAMD9
- SAMD9L
- SRP72
- RUNX1
- Telomere Biol
- TP53

Patient acquired through routine clinical testing of presenting leukemia

- bi-allelic CEBPA mutations
- RUNX1/ETV6/GATA2/TP53 mutation

- Perform skin biopsy → grow skin fibroblasts → isolate gDNA

- Run NGS panel and array analysis specific for inherited predisposition to hematopoietic malignancies

- if positive

- Family-based genetic counseling and clinical site-specific testing

- if strong

- if negative

- Research-based whole exome/genome sequencing

Family identified through evaluation of matched related allogeneic stem donor

- Perform detailed personal bleeding/family history

- if positive

- if negative
An Algorithm for Patient Work-Up

- **Patient acquired through strong personal/family history**
- **Patient acquired through routine clinical testing of presenting leukemia**
- **Family identified through evaluation of matched related allogeneic stem donor**

1. Perform detailed personal bleeding/family history
2. Perform skin biopsy → grow skin fibroblasts → isolate gDNA
3. Run NGS panel and array analysis specific for inherited predisposition to hematopoietic malignancies
   - **if positive**
     - Family-based genetic counseling and clinical site-specific testing
   - **if negative**
     - **if strong**
       - Research-based whole exome/genome sequencing
Detecting germline mutations through tumor mutational profiling

360 patients with tumor-only sequencing

74 of 360 (21%) patients had 88 pathogenic or likely pathogenic variants on tumor-only sequencing

44 patients with 52 pathogenic or likely pathogenic variants on tumor-only sequencing who also had germline tissue available

25 of 52 (48%) pathogenic or likely pathogenic variants on tumor-only sequencing had VAFs >0.4

6 of 25 (24%) pathogenic or likely pathogenic variants on tumor-only sequencing with VAFs >0.4 were germline in origin

30 patients with 36 pathogenic or likely pathogenic variants on tumor-only sequencing who did not have germline tissue available

27 of 52 (52%) pathogenic or likely pathogenic variants on tumor-only sequencing had VAFs <0.4

0 of 27 pathogenic or likely pathogenic variants on tumor-only sequencing with VAFs <0.4 were germline in origin
Detecting germline mutations through tumor mutational profiling

LF = TP53 mutation associated with Li-Fraumeni Syndrome
An Algorithm for Patient Work-Up

Patient acquired through strong personal/family history

Patient acquired through routine clinical testing of presenting leukemia

Family identified through evaluation of matched related allogeneic stem donor

Perform detailed personal bleeding/family history

Bi-allelic CEBPA mutations
RUNX1/ETV6/GATA2 mutation

Perform skin biopsy → grow skin fibroblasts → isolate gDNA

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Family-based genetic counseling and clinical site-specific testing

Research-based whole exome/genome sequencing

What will familial MDS/AL predisposition genes teach us?

Transcription Factors
- RUNX1
- CEBPA
- GATA2
- ETV6
- p53

Telomere Biology
- TERT
- TERC

DNA Repair
- ATM
- BRCA1
- BRCA2

Ribosomopathy
- SBDS
- DNAJC21

New Paradigms
- ANKRD26
- DDX41
- SAMD9
- SAMD9L

All Other Classes Commonly Mutated as Acquired Events
- Chromatin remodeling
- Splicing
- Growth factor receptors
- Metabolism
Specific considerations regarding particular cancer predisposition syndromes
Cancer is a genetic disease—‘Solid tumor’ gene syndromes do not exist

- Lynch: *MSH2/6, MLH1, PMS2*
- Li-Fraumeni: *TP53*
- Hereditary Breast/Ovarian CA: *BRCA1/2 are Fanconi anemia-like genes*

Brca1 is a Fanconi-like gene

**Cytogenetic abnormalities**

<table>
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<tr>
<th>Abnormality</th>
<th>Description</th>
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<tr>
<td>40,XX,chrB(4)(C2)[1]</td>
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<tr>
<td>40,XX,chtB(2)(H1),chtG(6)(B1)[1]</td>
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<td>40,XX,chtB(1)(H5),chrG(5)(D)[1]</td>
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<td>40,XX,chrG(2)(E2)[1]</td>
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<tr>
<td>39,XX,chtB(2)(B),chrB(3)(F1),chrG(13)(C3),chrG(15)(E),-16,chtB(17)(B)[1]</td>
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<td>40,XX,chtE(2;5)(F1;C2),chtE(9;12)(F1;E),pcd(16)(A)[1]</td>
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<tr>
<td>40,XX,t(1;17)(H4;A2)[1]</td>
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Known Familial MDS/AL Syndromes

Myeloid malignancies only
1. Familial AML with mutated CEBPA (CEBPA)
2. Familial MDS/AML due to DDX41 mutation (DDX41)
3. Familial MPNs--14q32.2 genomic duplication (ATG2B/GSKIP)
   -- germline RBBP6 mutation

Decreased Platelet Number/Function
1. Familial platelet disorder with propensity to myeloid malignancies (RUNX1)
2. Thrombocytopenia 2 (ANKRD26)
3. Thrombocytopenia 5 (ETV6)

Additional Organ Systems Affected
1. GATA2 deficiency syndromes (GATA2)
2. Autosomal dominant telomere syndromes (TERT and TERC)
3. Familial aplastic anemia/MDS due to SRP72 mutation (SRP72)
4. Ataxia-Pancytopenia Syndrome (SAMD9L mutation) and MIRAGE syndrome (SAMD9 mutation)
5. Shwachman-Diamond Syndrome (new causative genes: EFL1 and DNAJC21)
Key Management Issues

Myeloid malignancies only

1. Familial AML with mutated CEBPA (CEBPA)
   - Near complete penetrance
   - 10% AMLs with bi-allelic CEBPA mutations have germline mutation
   - Most often, the inherited allele has a mutation in the 5’ end of the gene, with acquisition of a mutation in the second allele at the 3’ end of the gene

2. Familial MDS/AML due to DDX41 mutation (DDX41)
   - Average age of diagnosis: 62yo
   - Three pedigrees now with pediatric cases of leukemia
   - Some mutations may also predispose to lymphoid malignancies; colon ca/gastric ca

3. Familial MPNs--14q32.2 genomic duplication (ATG2B/GSKIP)
   -- germline RBBP6 mutation
Familial leukemia with CEBPA mutation

Clonal Evolution in AMLs:

- “Relapses” appear to be independent leukemias, since acquired CEBPA mutation is distinct.
- Acquired mutations in GATA2 and WT1 are common and mutually exclusive.
- AMLs are chemosensitive.

Fam v CEBPαsm P=.003

Key Management Issues

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**DDX41 on 5q35.3 encodes a DEAD/H-Box helicase**


### Germline mutations
- E3K
- E7X
- R10fs*
- D140Gfs*(14)
- Ex6 SA
- M155I
- R164W
- F183I
- K187R
- Y259C(7)
- del363
- I396T
- R525H
- G530D
- T529Rfs*

### Somatic mutations
- E247K
- A225D
- P321L
- e11+1
- R525H (29)

- Frameshift mutation
- Missense mutation
- Splicing mutation

**Blue, Caucasian**
**Red, Asian**
Detecting a germline syndrome from tumor mutational profiling

71yo
T3N0M0 grade 3 gastric cancer
Rx: neoadjuvant chemo: cisplatin/5-FU → total gastrectomy → FOLFOX, completed 3/6 planned cycles due to cytopenias

73yo
t-MN
Panel testing:
DDX41 D140fs → skin biopsy confirmed germline

Northern Europe
paternal grandmother
non-smoker
no alcohol intake
head and neck cancer in 60’s
Detecting a germline syndrome from tumor mutational profiling

Middle East- Jordan

father
AML at 60yo

50yo
chronic phase CML → complete molecular response on Gleevec

53yo
‘myeloid blast’ phase CML → no detectable BCR-ABL →
Panel testing: DDX41
P78fs
R525H
Skin biopsy confirmed P78fs is a germline mutation.
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Key Management Issues

**Decreased Platelet Number/Function**

1. Familial platelet disorder with propensity to myeloid malignancies (*RUNX1*)
2. Thrombocytopenia 2 (*ANKRD26*)
3. Thrombocytopenia 5 (*ETV6*)

- Both germline *RUNX1* and *ETV6* mutations predispose to both myeloid and lymphoid malignancies; to date, germline *ANKRD26* mutations have only been associated with development of myeloid malignancies.

- Patients can bleed out of proportion to their platelet counts, since the platelets have abnormal aggregation. Therefore for surgery/childbirth, we recommend transfusion of normal platelets.
Key Management Issues

Familial platelet disorder with propensity to myeloid malignancies (*RUNX1*)
Clonal evolution in FPD/AML

ANKRD26 mutations confer a distinctive bone marrow pathology at baseline

hyposegmented and binucleated megakaryocytes
Known Familial MDS/AL Syndromes

**Myeloid malignancies only**
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The next frontier: inherited lymphoid malignancies

- Liver cancer
- 2 GATA3 intron variants homozygous

- Ph-like ALL + 4 variants
- Ph-like ALL + 4 variants

- ALL
- + 4 variants
Realizing the goal of precision medicine in oncology

**DEFINE:**
- Baseline genetics
- Baseline epigenetics
- Acquired genetics in the tumor/stem cell product
- Acquired epigenetics in the tumor

_to devise an effective treatment strategy for a particular patient_

- Family history (FHx) is an important tool in hematology.
- Consider familial syndromes for all patients with hematopoietic malignancies → *How can we test patients systematically?*
  - How can we diagnose cases without relying on FHx?
  - Special consideration at the time of allogeneic stem cell transplantation!

- Both point mutations and genomic rearrangements can lead to germline predisposition, so testing should be comprehensive for both.
- It is critical to test true germline DNA (e.g., skin fibroblasts).
- Additional syndromes and pathways in leukemogenesis will be identified!