Familial Myeloid Diseases

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My patients and their families
Familial Cancer Predisposition Syndromes

- Study of these genes has informed mechanisms of carcinogenesis and impacts patient care

- Best characterized in solid tumors
  - Hereditary Breast/Ovarian CA: BRCA1/2 are Fanconi anemia-like genes
  - Lynch: MSH2/6, MLH1, PMS2 (Lymphomas are reported)
  - Li-Fraumeni: TP53 (6% of tumors are hematologic; CML, CLL, AML, ALL, NHL, HL are all reported)

- Emerging appreciation for the recognition of germline predisposition in hematopoietic malignancies
  - WHO 2015 classification of leukemias provisionally has a new category for germline predisposition
  - Recognition is best for myeloid hematopoietic malignancies (e.g., MDS/AML)
  - Great potential for appreciation of germline predisposition to lymphoid based diseases (e.g., PAX5, SH2B3, TP53, MKL1, MLL, ASXL1, etc.)
Brca1 is a Fanconi-like gene


<table>
<thead>
<tr>
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<tr>
<td>40,XX[13]</td>
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<tr>
<td>40,XX,chr(4)(C2)[1]</td>
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<td>40,XX,chr(2)(H1),chr(6)(B1)[1]</td>
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<td>40,XX,chr(1)(H5),chr(5)(D)[1]</td>
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<th>Patient Population</th>
<th>Specific Syndromes</th>
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<td></td>
<td>AML</td>
<td>Germline ANKRD26 mutation</td>
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<td>ALL</td>
<td>Germline DDX41 mutation</td>
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<td>Germline ETV6 mutation</td>
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<td>Familial AML with mutated CEBPA</td>
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<td>Germline PAX5 mutation (ALL only)</td>
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<td>Trisomy 8 mosaicism</td>
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<td><strong>Bone Marrow Failure Syndromes</strong></td>
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<td>MDS</td>
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<td>AML</td>
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<td><strong>Genetic Syndromes</strong></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>Wiskott Aldrich syndrome (WAS)</td>
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<td><strong>Familial MPNs</strong></td>
<td>PV, ET, PMF, CML</td>
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<td>RBBP6 mutations</td>
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<td><strong>Familial Lymphomas</strong></td>
<td>CLL</td>
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<td>HL/NHL</td>
<td>Familial Lymphoma Predisposition</td>
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<td>Germline MKL1 mutation</td>
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<td>Germline MLL mutation</td>
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<td>Cowden syndrome (PTEN)</td>
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<td><strong>Familial MM/LPL</strong></td>
<td>MM, MGUS, LPL</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)
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Platelet Dysfunction
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)
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Familial leukemia with CEBPA mutation

Phenotype:
- FAB M1/M2; numerous Auer rods; aberrant CD7 expression
- Most have normal karyotype
- Bi-allelic mutations are seen in the familial form of the disease, most often with the inherited allele having a mutation in the 5’ end of the gene and acquisition of a mutation in the second allele at the 3’ end of the gene
- Complete or near-complete penetrance
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.

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Familial leukemia with germline *DDX41* mutations

- Mean age of disease onset: 65 years (range 44-82)
- Normal karyotype in 80%
- Recurrent germline event is truncating: D140fs
- Acquired mutations
  - Second *DDX41* mutation (p.R525H) in 50%
  - 57% did not have any other recurrent AML-related mutations
- *DDX41* is located on chromosome band 5q35
  - Deletions of *DDX41* locus in 26% (35/133) of del(5q) cases
  - ? Increased responsiveness to lenalidomide

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

Germline variants

Somatic variants


Li R et al. *Haematologica* epub, 2016
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The germline R164W DDX41 mutation includes lymphoid malignancies and disease.
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Chromosome 14q32.2

- Four families from French West Indies
- Adult onset of myeloid malignancies; often ET → myelofibrosis/AML

Germline *RBBP6* mutations predispose to myeloproliferative diseases

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FPD: germline *RUNX1* mutations

- Clinically presents with: Inherited thrombocytopenia
  - Mild to moderate
  - Normal platelet size
  - Decreased expression of the thrombopoietin *MPL* receptor
  - Platelet function defect with abnormal platelet aggregation
  - Predisposition to myeloid malignancies and T-cell ALL
- *RUNX1* encodes a transcription factor critical for normal hematopoiesis on chromosome 21q22

- Lifetime risk of myeloid malignancy, ranges between 20-65%
- Acquisition of secondary mutations: in wild-type *RUNX1* allele and in other genes commonly mutated in *de novo* AML; some can be seen even in peripheral blood of asymptomatic carriers

![RUNX1 diagram]

Clonal evolution in FPD/AML

## Clonal evolution in FPD/AML

<table>
<thead>
<tr>
<th>Germline Gene Mutated</th>
<th>Encoded Mutant Protein</th>
<th>Malignancy</th>
<th>Mutated Gene</th>
<th>Somatic Mutation Identified</th>
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<tr>
<td><strong>RUNX1</strong></td>
<td>R204X</td>
<td>RAEB-1</td>
<td><strong>BCOR</strong></td>
<td>e9+1</td>
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<td><strong>PHF6</strong></td>
<td>Y301fs</td>
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<td><strong>BCOR</strong></td>
<td>R688H</td>
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<td><strong>DNMT3A</strong></td>
<td>L1673*</td>
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<td>R399C</td>
<td>RAEB-1</td>
<td><strong>BCOR</strong></td>
<td>S1077Rfs*35</td>
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ANKRD26 mutations predispose to thrombocytopenia, platelet dysfunction, and myeloid malignancies

ANKRD26
Chromosome 10p12.1

Total of 34 exons
ANKRD26 promoter mutations disrupt RUNX1 and FLI1 repression, leading to activation of MAPK and disrupted platelet development.

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Familial leukemia with germline *ETV6* mutations

- Platelet number and function defects
- Predisposition to hematologic malignancies (myeloid & lymphoid)
  - Age of onset: 7-82 years
- Risk of other cancers?
- GI dysmotility or strictures?
- All germline mutations:
  - Disrupt nuclear localization
  - Dominant negative on wild-type *ETV6*-mediated gene repression
  - Inhibit proliferation of CD34+ cells
  - Reduce expression of platelet-associated genes

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ETV6 on 12p13.2 encodes an ETS family transcription factor


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Familial leukemia with **GATA2** mutation

**Phenotype:**
- MDS/AML often with monosomy 7
- Age of onset: 10 to 53 years old
- Associated with:
  - Emberger Syndrome- primary lymphedema of lower legs/genitals; low T-cell ratio; cutaneous warts; sensorineural deafness
  - MonoMac Syndrome- severe monocytopenia and infections with non-TB mycobacteria/viruses/fungi; low NK cells; low B cells; low dendritic cells; pulmonary alveolar proteinosis. Infectious/pulmonary complications predate the development of MDS/AML. In addition to MDS/AML, CMML can be seen.
  - Acquired mutations in **ASXL1** are common.
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Autosomal dominant telomere syndromes (TERT and TERC)

Dyskeratosis congenita

- Classic triad:
  - oral leukoplakia
  - nail dystrophy
  - skin hypopigmentation
  - H&N, anogenital, MDS/AML

- 10 genes known to cause DC
  - TERT & TERC
    - Autosomal dominant
    - Lack the classic triad
    - Look like familial MDS/AML
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Familial leukemia with SRP72 mutation

Point mutations in SRP72
- T355KfsX19*
- R207H

Genomic rearrangements in SRP72
- Chromosome 4q11
- 2 bp deletion

Phenotype:
- To date, SRP72 mutations have been described in few families, limiting clinical correlations.
- Bone marrow failure may precede development of a myeloid bone marrow malignancy.
- In one family, bone marrow failure was associated with deafness.
How to Recognize these Syndromes

• Have a high index of clinical suspicion

• Know the signs and symptoms

• Ask specific personal and family history:
  - Cytopenias, MDS, AL?
  - Bleeding propensity?

• Consider results of molecular analyses performed on leukemic cells

2 or more close relatives
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
- Perform skin biopsy ➔ grow skin fibroblasts ➔ isolate gDNA
- Run NGS panel specific for inherited predisposition to hematopoietic malignancies
  - if positive: Family-based genetic counseling and clinical site-specific testing
  - if negative: Research-based whole exome sequencing
- bi-allelic CEBPA mutations
- RUNX1/ETV6/GATA2 mutation
  - if strong: Perform detailed personal bleeding/family history
Improving our clinical care

- Hematologic Malignancy-focused Cancer Risk Clinic

- 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

- Genetic counseling for family members

- Careful 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 upcoming WHO classification
Conclusions

• Family history is an important tool in hematology
• Consider Familial MDS/AL syndromes for all patients with cytopenias or MDS/AL
• Clinical phenomenon of anticipation is common.

• Both point mutations and genomic rearrangements can lead to germline predisposition, so testing should be comprehensive for both.
• Myeloid malignancies often show somatic acquired mutation of second, wild-type allele (e.g., RUNX1, CEBPA, and DDX41)
• Therefore, it is critical to test true germline DNA (e.g., skin fibroblasts). Commercial panel-based testing is now available in the US.

• Additional syndromes and pathways in leukemogenesis will be identified!
• Join the effort!