Other Inherited Leukemias

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Many Names for this Group of Disorders

- Inherited leukemia
- Familial leukemia
- Leukemia susceptibility
- Hereditary hematopoietic malignancies
- Hematological malignancy predisposition

- GATA2 Deficiency and Familial Platelet Disorder (*RUNX1*) being key examples of this group
Connection to Inherited Bone Marrow Failure Syndromes (IBMFS)

- IBMFS are rare disorders with inherited germline cause of bone marrow failure in childhood/young adulthood with predisposition for cancer, particularly AML often associated with congenital abnormalities.

- Previously hematological malignancy predisposition was thought to be isolated to the IBMFS.

- Last ~15 years have made it clear that this is not so.
  - Significant overlap with primary immunodeficiencies.
  - Significant overlap with solid tumor predispositions.
  - Can be isolated hematological malignancy predisposition.
Large Heterogeneous Group
Can be divided by several characteristics

- Underlying biology
- MDS prodrome or not
- Those with or without congenital abnormalities
- Lineage of leukemia
- Those also associated with solid tumor risk

Tawana et al. Leukemia 2018
IBMFS and Hematological Malignancy Predispositions

Hematopoietic Transcription Factor Biology

Cell Signaling

DNA Repair

Telomere Biology

Ribosome Biology
The *Other* Inherited Leukemias

**IBMFS (MDS->AML)**  
FA, DC, SDS, DBA, TAR, CAMT

Present with MDS and Can Evolve to AML  
*RUNX1, GATA2*  
*TP53, SCNs*  
*SAMD9/L, DDX41, ANKRD26, MECOM*

Present with AML  
*CEBPA*  
*TP53*

**ALL associated**  
*PAX5, ETV6*  
*NBN, ATM, BLM, Turcot*

**JMML**  
*NF1*  
*Noonan*
Who Should be Evaluated for a Hematological Malignancy Predisposition

- Pediatric or <40yo patient with MDS or aplastic anemia
- Patients <40yo with cytopenias and FMH of cancer or lung disease
- Patients with cytopenias and notable infectious history or dysmorphology
- Patients with new cytopenia or leukemia with a history of *ITP*
- Patients with leukemia and biallelic *CEBPA* or *RUNX1* mutations
- Patients with hypodiploid ALL
- Patients with unusual radiation or chemotherapy sensitivity
- **More common than suspected- Look for it**
Why is it important to recognize inherited predisposition?

- Genetic counseling and family planning
- HCT donor and regimen choice
- Treatment optimization
- Cancer surveillance and syndrome specific disease monitoring
- More research is needed to fully understand this group of disorders

Sud et al. Blood 2018
Studying MDS and AML in the IBMFS

- The “classic” IBMFS have been extensively studied, and the risk of cancer in these patients is now well documented.
- Much of this work comes from the long standing NCI IBMFS study

The NCI IBMFS Study

Opened in January 2002 by Dr. Blanche Alter

- Family Study
  - > 500 families > 2000 individuals
Family Predisposition Study Process

**Participant Accrual**
- Calls referral nurse
- Study team reviews

**Questionnaires**
- Family History
- Individual History
- Pedigree

**Field Cohort**
- Medical record review
- Genetic counseling & testing
- Biospecimens

**Clinic Cohort**
- Evaluation at CC
- Subspecialists
- Biospecimens

**Phenotyping**
- Epidemiology
- Genetics
- Psychosocial research
- Biospecimen collection
Findings from the NCI IBMFS study

- Cancer types, rate, and survival in IBMFS patients
  - MDS: in FA $\uparrow 5000X$, in DC $\uparrow 500X$
  - AML: in FA $\uparrow 20X$, in DC $\uparrow 70X$
- Seven novel genes identified
- Identification of new phenotypes
- Descriptive epidemiologic studies of gynecologic, pulmonary, vascular, dermatologic, endocrine, ENT, neurologic, and dental complications of IBMFS

Planned Protocol to Study Hematological Malignancy Predispositions

- Joint DCEG-CCR Protocol with the NIH Myeloid Malignancy Scientific Interest group
- Natural history protocol for patients on NIH treatment protocols and those treated elsewhere
- Not enrolling *RUNX1*, *GATA2*, LFS patients, refer to disease specific protocols
- Family history questionnaires, genetic counseling, exome sequencing
- Identify families with known genes and novel gene discovery
- Longitudinal follow-up
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Patients & Families

Have a patient with a suspected hematological malignancy predisposition or IBMFS? Please refer them.

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