Familial Platelet Disorder with Associated Myeloid Malignancy

MDS Symposium
July 12, 2019

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Many Genes Mutated in Myeloid Neoplasms with Germline Predisposition

• Associated with platelet dysfunction
  • **RUNX1**, ANKRD26 & ETV6

• Associated with other organ dysfunction
  • ATG2P, ATM, BLM, BRCA1, BRCA2, GATA2, GSKIP, NF1 & SBDS

• Not Associated with other organ dysfunction
  • CEBPA, DDX41 & RBBP6

Adapted from Brown et al, Semin Hematol. 2017 54(2):60-68
**Familial Platelet Disorder with Associated Myeloid Malignancy (FPDMM) OMIM 601399**

**INHERITANCE**
- AD germline mutated RUNX1 (21q22.12) (first hit) -> FPDMM (1999)

**HEMATOLOGY**
- Quantitative platelet defect (mild to moderate thrombocytopenia)
- Qualitative platelet defect (dense granule secretion defect - EM)
- Mild to moderate bleeding/bruising
- Variable clinical phenotypes (same mutation/same family)
- Some families exhibit ‘genetic anticipation’

**NEOPLASIA**
- 25-55% patients develop AML or MDS; Median age 33 years
- T-cell acute lymphoblastic leukemia (T-cell ALL) also reported
>78 Germline RUNX1 Mutations Identified

Adapted from Brown et al, Semin Hematol. 2017 54(2):60-68
Normal hematopoiesis tightly-regulated

Adapted from Ichikawa et. al, 2013.
Leukemogenesis in FPD occurs through clonal expansion of acquired mutations

Modified from Churpek et al, Blood, 2015
Potential Second Hits for FPDMM Leukemogenesis

<table>
<thead>
<tr>
<th>Pathway:</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III?</th>
<th>Other</th>
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<tbody>
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<td></td>
<td>Signal Transduction</td>
<td>Differentiation</td>
<td>Epigenetic regulation</td>
<td>Tumor suppressor</td>
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<td>Genes:</td>
<td>FLT3</td>
<td>RUNX1</td>
<td>TET2</td>
<td>WT1</td>
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<td>KIT</td>
<td>CBFβ</td>
<td>IDH1, IDH2</td>
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<td>PTPN11</td>
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Adapted from Dumbret/Shen et al Blood 2011
Pedigree Analysis & Clonal Expansion with Age

Germline RUNX1 R320* asymptomatic carrier

➢ Is early clonal haematopoiesis a trigger for malignancy in germline RUNX1 mutation carriers?

➢ Can pre-leukemic cells be identified & targeted to prevent frank leukemia?
Pedigree analysis of whole exome sequencing to identify secondary germline mutations

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<tr>
<th>Gene</th>
<th>I:1</th>
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- **Wild-type**
- **Mutant**
Purpose of FPDMM/RUNX1 Clinic at NIH

**NCT03854318**

• *Natural History Protocol for infants-adults*
• Patients/families can’t easily access sequencing via insurance
• Discover true prevalence of germline RUNX1 mutations (somatic RUNX1 mutations ~10% of de novo MDS/AML)
• Provide Clinical/Research labs-WES, RNAseq, SNP array
• Learn how to monitor identified patients
Patient Monitoring

- Identify individuals at higher risk of developing leukemia earlier to improve outcomes
- Dominant negative RUNX1 mutations associated with higher incidence of malignancy than haploinsufficiency
- Expectant management/counselling avoidance of platelet inhibitors, use of HLA matched platelets (prevention of alloimmunization)
MDS/Acute Leukemia Therapy for FPDMM

• No difference from usual best practice for the specific malignancy identified (at this time)

• Patients with somatic RUNX1 mutated AML are ‘intermediate risk’
  • BUT- mutated RUNX1 associated with higher risk CN, lower EFS & RFS, 30% refractory to chemotherapy & have better outcomes with HSCT (Gaidzik et al 2011)

• Careful evaluation/sequencing of potential HSCT familial donors

• Transplantation offered to those with MDS or AML (NIH or home)

• Relapse post transplantation is not higher unless (HR CN or no CR)

• CIBMTR data for RUNX1 germline vs somatic mutation/outcomes
Blood and Inherited Diseases
Cellular Therapy Program (BID-CTP)

NHGRI
RUNX1
GATA2
DOCK8
Heme malignancies
Primary Immunodeficiency

NHLBI
Sickle cell Transplant
Sickle Cell Gene Therapy
Severe Aplastic Anemia

NIAID
CGD BMT
X-SCID Gene therapy

National Institutes of Health
National Heart, Lung, and Blood Institute
National Cancer Institute
National Institutes of Health Clinical Center
National Human Genome Research Institute
Runx1 Transplantation Protocol

**Preparative Regimen for 10/10 MRD & MUD**
- Fludarabine 40 mg/m$^2$ IV once daily x 4 days on Day’s -6, -5, -4, and -3
- Busulfan 3.2 mg/kg IV once daily x 4 days on Day’s -6, -5, -4 and -3

**Preparative Regimen for Haploidentical**
1) Fludarabine 30 mg/m$^2$ IV once daily x 5 days on Day’s -6, -5, -4, -3, -2
2) Total Body Irradiation (TBI) 200 cGy, Day -1
3) Cyclophosphamide 14.5 mg/kg IV once daily x 2 days on Day’s -6, -5
4) Busulfan 3.2 mg/kg IV on Day’s -4, -3 (and day -2 if clonal chromosomal abnormalities)
Runx1 Sequencing Pt/Family

Genetic Counseling Pt/Family

Treatment as Indicated or New Therapies

Clinical Monitoring

Natural History Protocol/Pt Samples (WES, RNAseq, SNP)

New Models
Conclusions/Future Directions

• Discover new cooperating genes/new mechanisms (single cell seq/microenvironment)
• Develop new biomarkers /risk score for MDS/AML development
• Develop preventive therapy (small molecule screen restore Runx1 function)
• Develop Gene (CRISPR) or cellular therapy (iPS)
• Enhance patient engagement/patient experience
• Enhance communication with all stakeholders
NIH

Consortium

Communication/Infrastructure

Patient & Family

Local provider
Acknowledgments

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The Liu lab
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David McKellar

NHGRI Collaborators
Nancy Hansen (CBCBB)
Jim Mullikin (CGCGB/NISC)
Niraj Trivedi (Bioinformatics Core)
Abdel Elkahloun (Microarray Core)
Stephen Wincovitch (Microscope Core)
Marypat Jones (Genomics Core)

*FPD Patients and their families*

NCI
Dennis Hickstein & GATA2 team

Clinical Center
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NIAID
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University of Chicago
Lucy Godley

Johns Hopkins
Linzhao Cheng
Yongxing Gao

Other Project Advisors
Anna Brown
Marshall Horowitz
Proposed criteria for diagnosing MDS in individuals with FPDMM and germline RUNX1 mutations.

**Major criteria**
1. Germline RUNX1 mutation
2. Cytopenia in ≥1 hematopoietic lineage, other than thrombocytopenia
3. Exclusion of non-neoplastic causes of cytopenias
4. Bone marrow and peripheral blood blasts <20%

**Minor criteria**
A. Morphologic features of myelodysplasia in ≥2 hematopoietic lineages
B. Acquired clonal cytogenetic or molecular genetic abnormality

*All major criteria and one of the minor criteria are required to make a diagnosis of myelodysplastic syndrome*

Kanagal-Shamanna et al 2017