Prevelance, Incidence and Risk of Leukemic Transformation in IBMFS

• Incidence: ~ 60 per million live births
  – Fanconi anemia > DBA > Schwachman-Diamond > DC

• Prevalence:
  – DBA > FA > Schwachman-Diamond > DC

• Risk of leukemia
  – FA and DC > DBA or Schwachman-Diamond
Clinical presentation: Fanconi Anemia

• Usually presents with physical anomalies early in life or with hematologic manifestations within the first decade.

• Cytopenias (usually thrombocytopenia followed by progressive pancytopenia; affect 90% of patients by age 40).

• Incidence: less than 1/100,000
Physical Findings in Fanconi Anemia

- Café-au-lait spots & other pigmentation changes (65%)
- Short stature (60%)
- Upper limb abnormalities (hypoplastic or bifid/supernumerary thumbs most common, 50%)
- “Fanconi facies”
Laboratory Assays in Fanconi Anemia Reflect Defect in DNA Repair

DEB = dihydroybutane
MMC = mitomycin C

Howlett laboratory website, Univ. of Michigan Medical School
Leukemic Transformation

• Fanconi anemia patients – predisposed to malignancies
  – avg. age 16 as opposed to 68 for the general population
  – head/neck and esophageal Ca more common solid tumors

• 120 of 754 registered FA patients have developed hematologic malignancies
  (60 AML, 53 MDS, and 5 ALL)

Bone Marrow Transplant in Fanconi Anemia

- BMT is the main therapeutic approach for marrow failure in Fanconi anemia
- Ideally the donor is an HLA-identical
- FA patients are hypersensitive to toxicities associated with conditioning (chemo and radiation) used in BMT.
  - Organ damage, second tumors
- Reduced intensity conditioning
Dyskeratosis Congenita
Defect in Telomere maintenance

• **Physical Triad:**
  – Hyperpigmentation of skin
  – Nail dystrophy
  – Oral leukoplakia

• **Typically presents in 1st decade of life**
  – Variable cytopenias
  – Premature graying
  – Pulmonary fibrosis
Dyskeratosis Congenita

- **Clinical Triad:**
  - abnormal skin pigmentation
  - nail dystrophy
  - mucosal leukoplakia

- **Pancytopenia with a hypocellular marrow**

- **Pulmonary fibrosis, cirrhosis, osteoporosis**

- **Genetics:**
  - short telomeres and low telomerase activity
  - X-linked recessive, autosomal dominant, or autosomal recessive

- **Genes:**
  - **DKC1** encodes dyskerin (stabilizes telomerase complex)
  - **TERC**: RNA component of telomerase (autosomal dominant)
  - **TERT**: Telomerase reverse transcriptase
  - **TINF2**: most common mutation
Structure and Function of Telomerase

TERC: RNA component
TERT: Telomerase reverse transcriptase
Dyskerin: Protein important for stabilizing telomerase complex
Anticipation in DC

- Disease gets worse in successive generations
- Applies predominantly to autosomal dominant form of disease
Dyskeratosis Congenita: Treatment

• Supportive care:
  – Transfusions
  – Avoid toxic exposures (tobacco, etoh, etc.)

• Androgens for bone marrow failure
  – Variable response

• Bone marrow transplantation
  – Only if bone marrow failure severe
  – May exacerbate other manifestations of disease (pulmonary fibrosis, liver disease etc.)
Diamond-Blackfan Anemia

• Congenital red cell aplasia

• >90% diagnosed within 1st year of life
  – Macrocytic anemia, low retic, normal wbc/Plts
  – Red cell adenosine deaminase is elevated
  – Physical findings may include facial defects, radial abnormalities

• Genetics
  – >50% due to haploinsufficiency of either a small or large ribosomal subunit (RPS19 most common)
  – Ribosomal stress increases p53 levels and increased apoptosis in red cell lineage
DBA: Treatment

• Corticosteroids
  – Majority of patients respond initially
  – Some patients achieve spontaneous remission

• Blood transfusions

• Bone marrow transplantation
## Inherited Bone Marrow Failure States Summary

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
<th>Cancer/other risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi anemia</td>
<td>DNA repair</td>
<td>High: MDS/leuk, Solid tumor</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>Short telomeres</td>
<td>High: MDS/leuk, solid tumor, pulmonary fibrosis</td>
</tr>
<tr>
<td>Schwachman-Diamond anemia</td>
<td>Ribosomopathy</td>
<td>MDS/Leuk</td>
</tr>
<tr>
<td>Diamond-Blackfan anemia</td>
<td>Ribosomopathy</td>
<td>Lower risk of leuk</td>
</tr>
</tbody>
</table>
RULING OUT CONGENITAL BONE MARROW FAILURE IN ADULTS

• History and physical
  – Get old counts
  – Family members with cytopenias, premature graying, pulmonary fibrosis
  – Short stature, physical abnormalities

• Lab tests
  – Fanconi screen
  – PNH assay
  – Telomeres?
Which of the following is true about telomeres and telomerase?

- A) Telomere length (below the 1st percentile) has been shown to reliably differentiate acquired aplastic anemia from dyskeratosis congenita (DC)
- B) Normal telomere length effectively excludes DC in a patient with bone marrow failure
- C) Small PNH populations are common in DC
- D) Telomere length reliably predicts the presence or absence of a mutation in healthy family members of DC patients
Short telomeres are not specific for DKC

Du et al, Blood 2009; 113:309-16