Fanconi Anemia 101

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FA Adult Meeting, 2012
Questions

1. How many are new to an FA meeting?
2. How many have been to one before?
3. How many have FA?
4. How many are a relative or support person?
5. How many think that the diagnosis of FA was initially missed by one or more physicians?
Learning Objectives

1. FA is no longer a pediatric diagnosis; the majority of the patients are adults.
2. Many patients are now post-BMT.
3. Some patients are only diagnosed as adults; mosaicism may be relevant.
4. Patients with FA have an increased risk of cancer (leukemia, head and neck and gyn cancers).
5. HPV may not be the sole cause of cancer.
History: Guido Fanconi

- **Fanconi Anemia** (Fanconi pancytopenia syndrome): 1927, 3 brothers with pancytopenia and physical abnormalities, “perniziosiforme”

- **Fanconi Syndrome** (renal Fanconi syndrome): 1936, proteinuria, glucosuria, phosphaturia, aminoaciduria, citraturia, and proximal renal tubular acidosis
Fanconi Anemia: Children
FA Literature: Physical Findings, 66%

- Any PE
- Short
- Thumbs
- Skin hyperpigmented
- Gonads male
- Head, face
- Renal
- Eyes
- Skin café au lait
- Developmental delay
- Ears, deaf
- Radii
- Cardiopulmonary
- Gastrointestinal tract
- Legs, hips, feet
- Brain/pituitary
- Gonads female

M:F 1.3:1
Fanconi Anemia: Adult Examples

- Diagnosed at birth due to absent radius
- Aplastic anemia, age 5; BMT age 9
- Aplastic anemia, age 16; BMT age 18
- Aplastic anemia, age 42
- Tongue cancer, age 30
- BMT donor, age 55

Look around you….
FA Literature: Age at Diagnosis

Shimamura and Alter, Blood Reviews 2010
FA Literature:
Survival before and after 2000

~80% survival ≥ age 18

Biases: reporting, ascertainment, survival, time trend
Characteristics of Persons with FA

- Physical findings described in the literature may not be found in all persons with FA
  - 11% had short stature and skin findings only
  - At least 25% of those reported had no physical findings
- Some persons without physical findings may be diagnosed at a later age
FA: Laboratory Findings

- Low blood counts (pancytopenia)
- Large red cells (macrocytosis)
- Increased fetal hemoglobin (Hb F)
- Chromosome breakage in lymphocytes or fibroblasts cultured with a DNA crosslinker, e.g. diepoxybutane (DEB) or mitomycin C (MMC)
FA: Carrier Frequency

- 1:300 in New York State in 1971 (Swift, 1971)
- ~1:100 in Ashkenazi Jews, Afrikaners, Spanish Gypsies, black sub-Saharan Africans
- 1:181 in US in 2010
- 1:93 in Israel in 2008 (Rosenberg et al, 2010)
Fanconi Anemia: Definition

- Autosomal recessive
  - 1 X-linked recessive gene
- Physical findings
- Aplastic anemia
- Leukemia
- Solid tumors
- Chromosome instability
- DNA repair defect
- >15 genes
FA Inheritance

- Persons with FA:
  - Unaffected parents carry one FA gene and one normal gene (carriers)
  - Affected offspring get one FA gene from each parent

- Children of persons with FA:
  - Each child will have one FA gene (carriers)
Autosomal Recessive Inheritance
Autosomal Recessive Inheritance

Child of affected and unaffected
Disease-Associated Mutations

A *mutation* is a change in the normal base pair sequence

Commonly used to define DNA sequence changes that alter protein function
15 FA Genes (?)

Data from Leiden Open Variation Database, http://chromium.liacs.nl/LOVD2/FANC/home.php
## FA: Complementation Groups/Genes

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<th>Group</th>
<th>Locus</th>
<th>cDNA</th>
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*Breast cancer genes in carriers
FA/BRCA DNA Repair Pathway

Courtesy of Akiko Shimamura, 2012
Who Should be Tested for FA?

- Characteristic birth defects (e.g., thumbs, kidneys, poor growth, etc)
- Aplastic Anemia (AA)
- Myelodysplastic Syndrome (MDS)
- Acute Myeloid Leukemia (AML)
- Decreased fertility
- Early characteristic cancer
- Siblings of persons with FA
What are the FA Tests?

- Chromosome breakage, DEB or MMC
- D2 ubiquitination (Western blot)
- BRCA2 (Western blot)
- Complementation with cell lines
- Complementation with retroviruses
- Sequencing of candidate genes (e.g., FANCC IVS4+4 A->T)
- Sequencing of all cloned genes

*Blood lymphocytes, skin fibroblasts*
Chromosome Breakage
FA: D2 Ubiquitination (Western Blot)

Shimamura et al, Blood, 2002

Green and Kupfer, HemOnc Clin NA, 2009
Complementation Analysis, Cloned FANC Genes

- FA cells are sensitive to DEB or MMC
- Introduce specific cloned FA genes
- Cells no longer sensitive
  - Normal gene ‘complemented’ patient cells, defining the complementation group
- Cells still sensitive
  - Normal gene not identified for patient cells
Retrovirus-mediated Correction of FA Cells

Retrovirus-mediated Correction of TA 0252’s T-cells analyzed by flow cytometry after five days of MMC-Incubation

FANCA

- S11EG
- SFA
- S11FCIEG
- S11FEIEG2
- S11FFIEG
- S11FG
Blood Production (Hematopoiesis)

- Pluripotent Stem Cell
  - Myeloid Stem Cell
    - Neutrophils
    - Monocytes
    - Eosinophils
    - Basophils
    - Red Cells
  - Platelets
  - Lymphoid Stem Cell
    - T Lymphocytes
    - B Lymphocytes
Bone Marrow Biopsy

Normal

Aplastic
Proof of Mosaicism in FA

- Peripheral blood lymphocyte chromosome breakage test normal
- Skin fibroblast chromosome breakage test abnormal
Mosaicism from Recombination
Gastroenterology

- Anatomical
  - Esophageal atresia, tracheoesophageal fistula, duodenal atresia, imperforate anus

- GI Symptoms
  - Reflux, gastric emptying delay, poor appetite

- Liver disease
  - Androgens: abnormal liver function, peliosis, adenomas, hepatomas,
  - Transfusions: iron overload

- Nutrition
  - Enteral supplements via NG or NJ tubes or gastrostomies
Endocrine, %

Adapted from Giri et al, JCEM, 2007
Complications

- Aplastic Anemia
- Acute Leukemia
- Myelodysplastic Syndrome
- Solid Tumors
- Liver Tumors
Definitions

- Aplastic Anemia (AA)
  - Pancytopenia
  - Hypocellular bone marrow

- Acute Leukemia (AL)
  - Malignant proliferation of immature cells

- Myelodysplastic Syndrome (MDS)
  - Cytopenias with hypercellular bone marrow
Aplastic Anemia: Signs and Symptoms

- Thrombocytopenia
  - bruises, petechiae
- Anemia
  - fatigue, lassitude, dyspnea
- Neutropenia
  - infections
FA: When to Treat Bone Marrow

- Cytopenias
  - Hb < 8 g/dL or symptoms
  - Platelets < 30,000/mm³
  - WBC < 500/mm³
- Leukemia
  - Blasts in blood
  - > 20% blasts in marrow
- MDS
  - Morphologic + cytopenias
  - Not for clone alone
FA: Treatment for Bone Marrow

- Transplant
- Androgen
- Hematopoietic growth factors
- Gene therapy?
FA: Treatment with Transplant

- Bone marrow, cord blood, or peripheral blood stem cells
- HLA-related donor
  - when meet any treatment criteria
- Alternate donor (mismatched unrelated [MUD], partial match family member)
  - Leukemia or clinical MDS (not clone alone)
  - Refractory aplastic anemia
FA: Medical Treatment

- Oxymetholone
  - 2-5 mg/kg/day oral
- Danazol
  - ~200-400 mg/day oral
- Folic acid
  - 1 mg/day oral
FA: Supportive Care

- RBCs - for Hb < 8 g/dl or symptoms
- Platelets - for platelets < 10,000/mm$^3$ or symptoms
- Blood products
  - no family member donors
  - Leukopoor, possibly irradiated
- Antibiotics
  - as needed for infections
FA Literature: Cancer Types 1927-2012

188 leukemias and 286 solid tumors in 413/2190 patients; 47 had 2-4 cancers.

Updated from Shimamura and Alter, Blood Reviews 2010
FA Risk of Adverse Events

Alter et al, BJH, 2010
Relative Risk of Cancer in FA

Data from North American Survey, Germany, Israel, and NCI
Solid tumor or leukemia preceded the diagnosis of FA in 35%.
Diagnosis of FA before Cancer

- Aplastic anemia
- Birth defects
- Family history
Diagnosis of FA after Cancer

- Clinical suspicion based on phenotype
- Family history
- FA-type cancers, atypically young, no risk factors
- Unrecognized marrow failure
- Absence of marrow involvement (e.g. somatic mosaicism)
Possible Causal Factors for Cancer in FA

- Genetics
- Stem cell transplant - GVHD, XRT
- HPV
- Immunodeficiency
- Tobacco
- Alcohol
- Dental Xrays
- Oral trauma (braces)
Hypothetical cumulative incidence curves for SCC expected if the competing risks of non-SCC death could be removed. BMT would increase risk of HNSCC 4-fold, and 16 years earlier. All had GVHD.

Rosenberg et al, Blood 2005
FA: Adult Females

- Late onset of menses (14-16)
- Heavy periods if platelets low
- Early onset of menopause (30s)
- Decreased fertility
- Increased need for Caesarean sections
- Worsening bone marrow function during pregnancy
- Osteoporosis
- Cancer
  - AML
  - HNSCC
  - Vulva, vagina, cervix
  - HPV Vaccine
FA: Adult Males

- Short stature
- Infertility
- Endocrine problems: cholesterol, thyroid, growth hormone, metabolic syndrome, small pituitary, osteopenia
- Cancer
  - AML
  - HNSCC
- HPV vaccine
FA Surveillance

- Every 4-6 months (or more as needed): CBC
- Annual:
  - BM aspirate/biopsy/chromosomes
  - Liver enzymes, chemistries, lipids, thyroid
  - Liver ultrasound
  - Dental
  - Head and neck with laryngoscopy
  - Gyn exam
  - Skin exam
  - Consider esophageal endoscopy?
- HPV vaccine
ABOUT THE RESEARCH TEAM

Blanche P. Alter, M.D., M.P.H., is the lead investigator for this study. A cancer expert in the NCI Clinical Genetics Branch, she has been caring for and studying patients with bone marrow failure disorders for more than 25 years.

Regarded as one of the leading investigators for these diseases, both in the United States and abroad, she came to the National Institutes of Health in September 2000 with the purpose of developing this study.

Dr. Alter has teamed with a large number of associate investigators in all specialties at the NIH and other medical centers, to provide comprehensive evaluation for people with these complex, multi-system disorders.

FOR MORE INFORMATION

Phone: 1-800-518-8474 to speak with a member of the research team.

Email: LisaLeathwood@westat.com

Web site: www.marrowfailure.cancer.gov

For more information, please visit the National Cancer Institute's website at www.cancer.gov.
Inherited Bone Marrow Failure Syndromes (IBMFS) are rare disorders in which there is usually some form of aplastic anemia (failure of the bone marrow to produce blood), associated with a family history of the same disorder. Some of these conditions have typical changes in physical appearance or laboratory findings which suggest a specific diagnosis. There are several well-described syndromes which can be recognized by healthcare experts. There are also patients who are harder to classify, but who appear to belong in this category.

Patients with these syndromes have a very high risk of development of cancer (either leukemia or certain solid tumors). At the moment we cannot predict which specific patient with an IBMFS is going to develop cancer. The NCI’s IBMFS Cohort Study will enroll North American families in which at least one member has or had an IBMFS. We plan to:

- include individuals known to have an IBMFS as well as their first degree relatives (brothers, sisters, parents, and children);
- collect clinical information from study participants and their physicians;
- perform detailed physical examinations, x-rays and routine laboratory tests on those who are interested in traveling to the NIH to be seen in person by our team;
- attempt (on a research basis) identification of the specific genetic mutation that is associated with each family’s disease;
- screen participants for early changes related to the specific cancers that occur in each syndrome;
- perform detailed research laboratory studies on blood and tissues collected from study participants, in an effort to understand the process by which cancers develop;
- monitor study participants in an ongoing fashion to determine the rate at which complications develop related to each disease, and to identify those complications more precisely;
- provide suggestions to study participants and their physicians regarding how to best take care of family members who are affected with a particular IBMFS, and
- offer genetic counseling, and an opportunity to learn the results of mutation testing, for those persons who decide that this information will be of use to them.

The Principal Investigator responsible for this study is Blanche P. Alter, MD, MPH. For further information regarding her credentials and experience, please see http://www.cancer.gov/about-us/research/alter.html.

Our overall goal is to reach a better understanding of how cancers develop in persons with IBMFS, so that we may improve the health care which can be offered to persons with these disorders.

Clinical Genetics Branch: Neelam Giri, Sharon Savage
Westat: Lisa Leathwood, Maureen Risch, Ann Carr