National Cancer Institute

Fanconi Anemia 101

FA Camp 2010

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National Institutes of Health

When You Hear …., Think …., Or ….

Open Minds

"I've never seen this before."

should be

"I've never ***recognized*** this before."

Question

- How many think that the diagnosis of FA was missed by one or more physicians prior to being made?

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

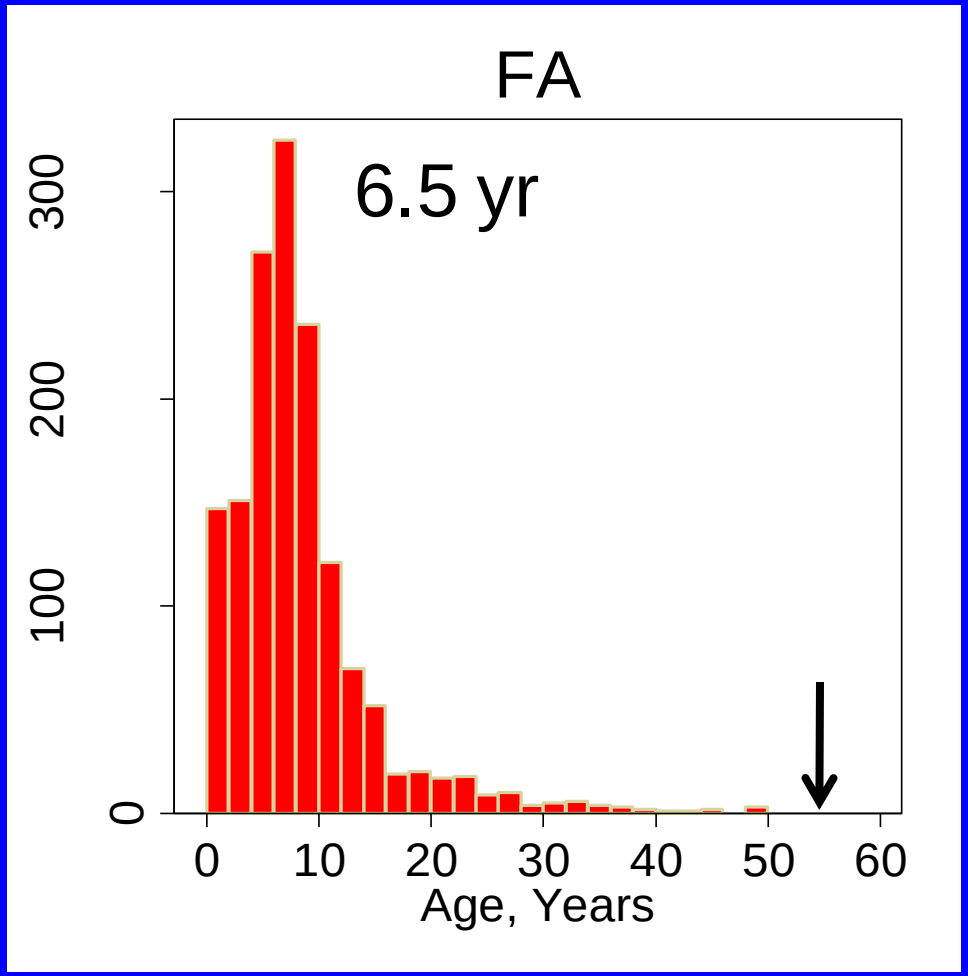
Fanconi Anemia: Children

Photos with permission

Fanconi Anemia: Adults

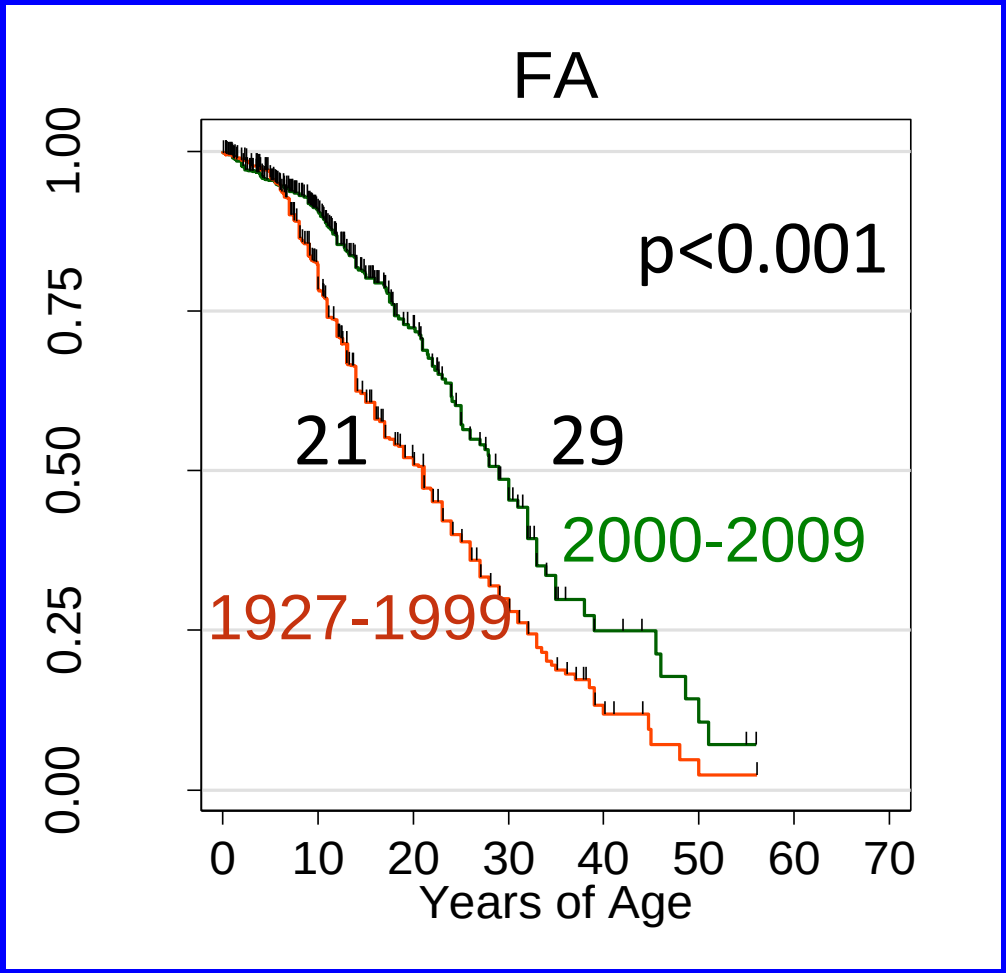
Photos with permission

FA: Age at Diagnosis



Shimamura and Alter, Blood Reviews, 2010

Fanconi Anemia Literature Survival



Recent better survival:

- better treatment
- older diagnoses

Shimamura and Alter, Blood Reviews, 2010

Literature: Physical Findings

Finding	%
Low Birth Weight	52
Short	45
Skin hyperpigmented	31
Skin café au lait	18
Thumbs	32
Radii	7
Gonads male	26
Gonads female	1
Microcephaly	22

Finding	%
Eyes	20
Renal	20
Developmental delay	10
Ears, deaf	8
Legs, hips, feet	6
Cardiopulmonary	6
Gastrointestinal tract	5
Brain/pituitary	3
Short or skin only	7

All findings biased by under- or over-reporting!

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

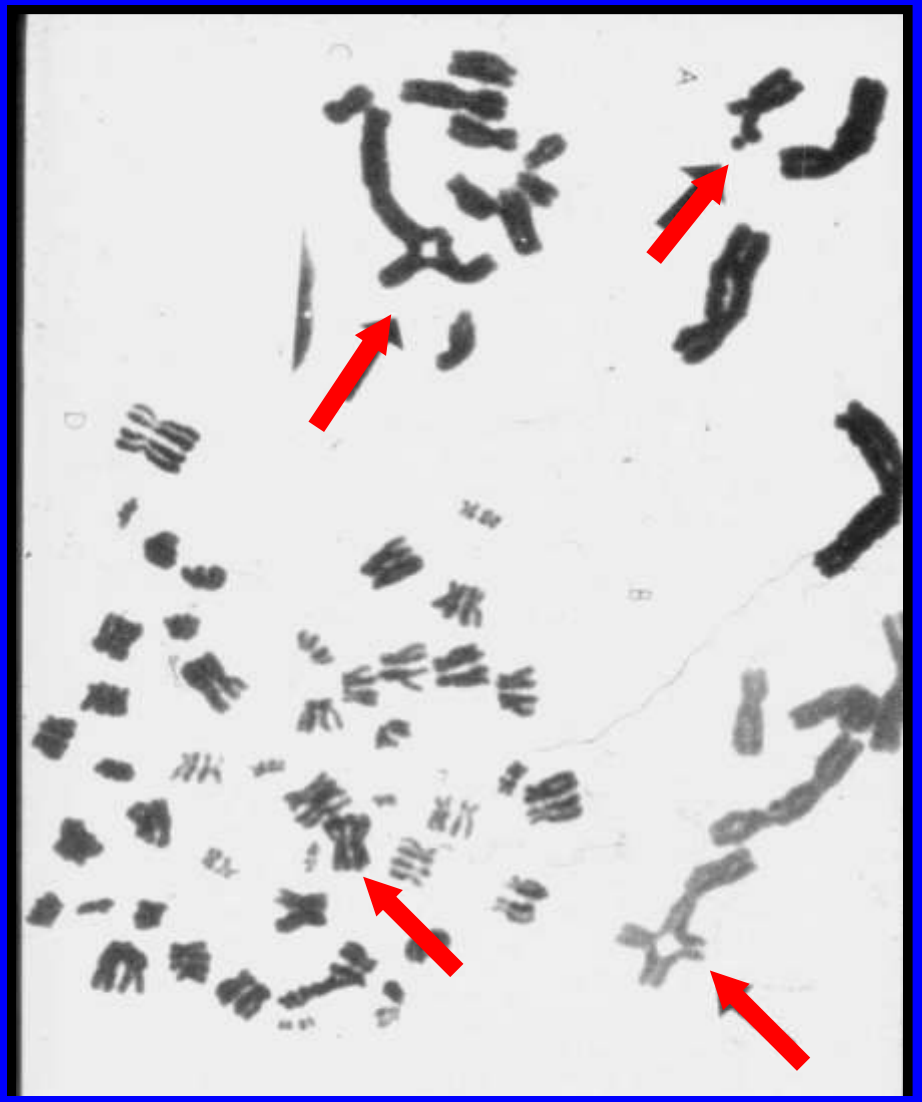
- Low blood counts (pancytopenia)
- Large red cells (macrocytosis)
- Increased fetal hemoglobin (Hb F)
- Chromosome breakage in lymphocytes or fibroblasts cultured with a DNA crosslinker, e.g. diepoxybutane (DEB) or mitomycin C (MMC)

FA: Hands

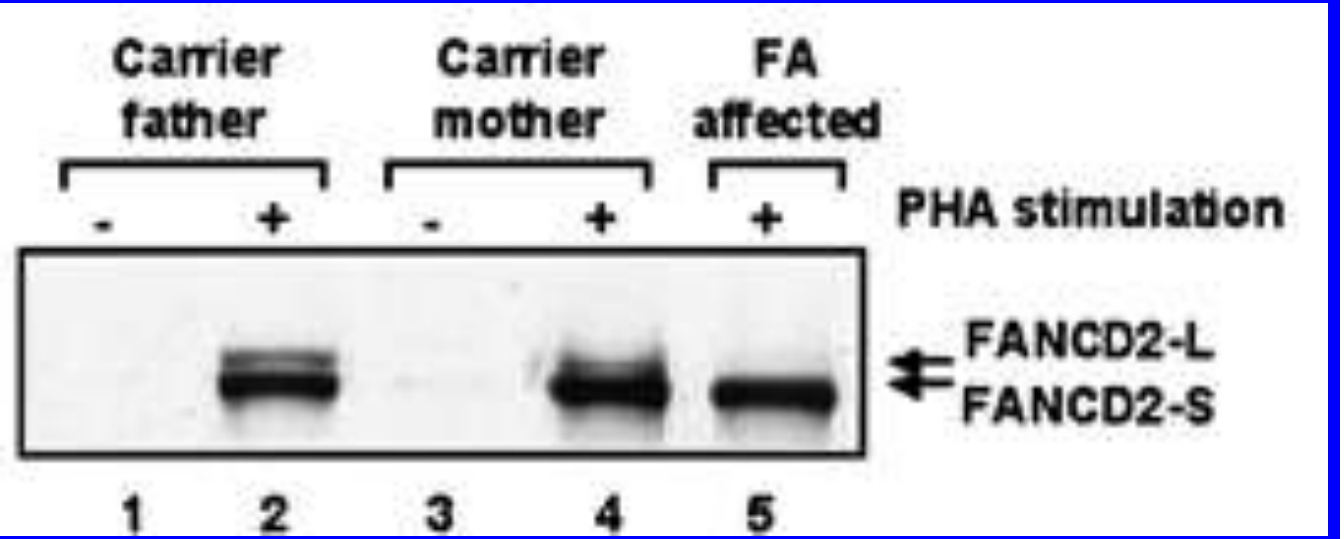
Right

Left

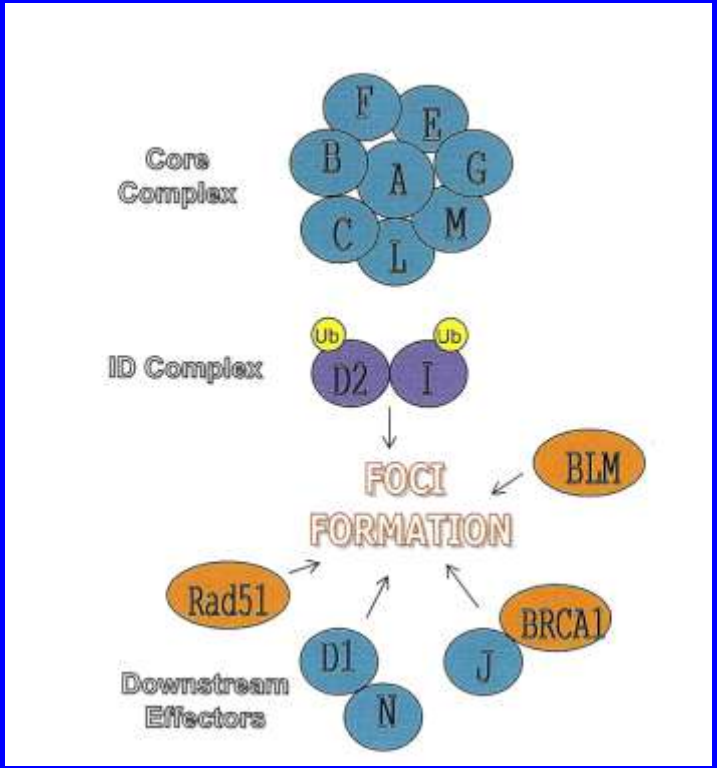
Chromosomes



FA: D2 Ubiquitination

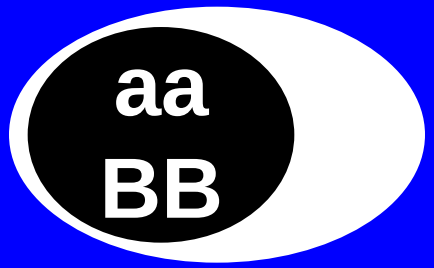


Shimamura et al, Blood, 2002

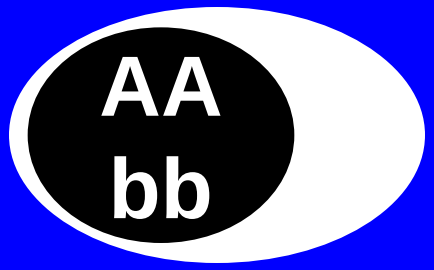


Green and Kupfer,
HemOnc Clin NA, 2009

Complementation Analysis

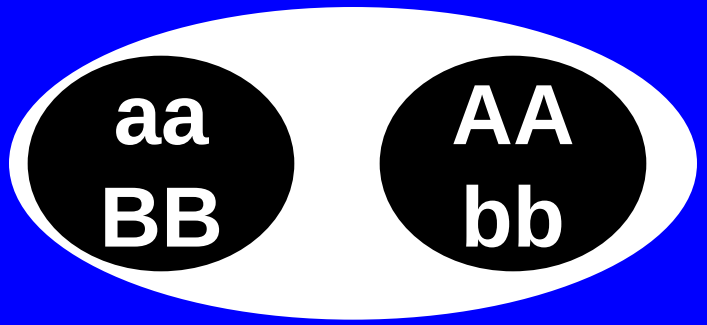


DEB → **BREAKS**



DEB → **BREAKS**

CELL FUSION:

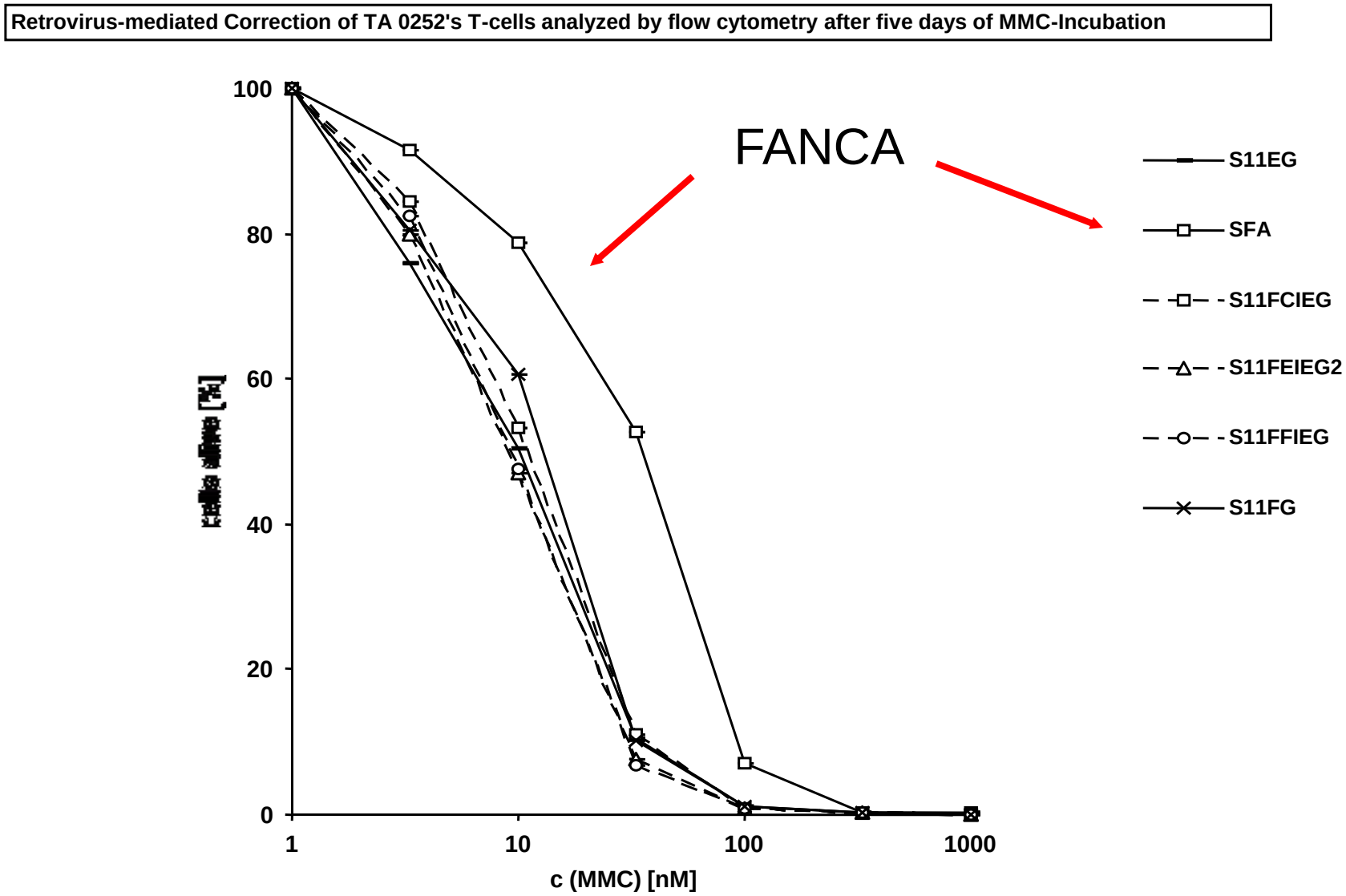


DEB → **NO BREAKS**

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



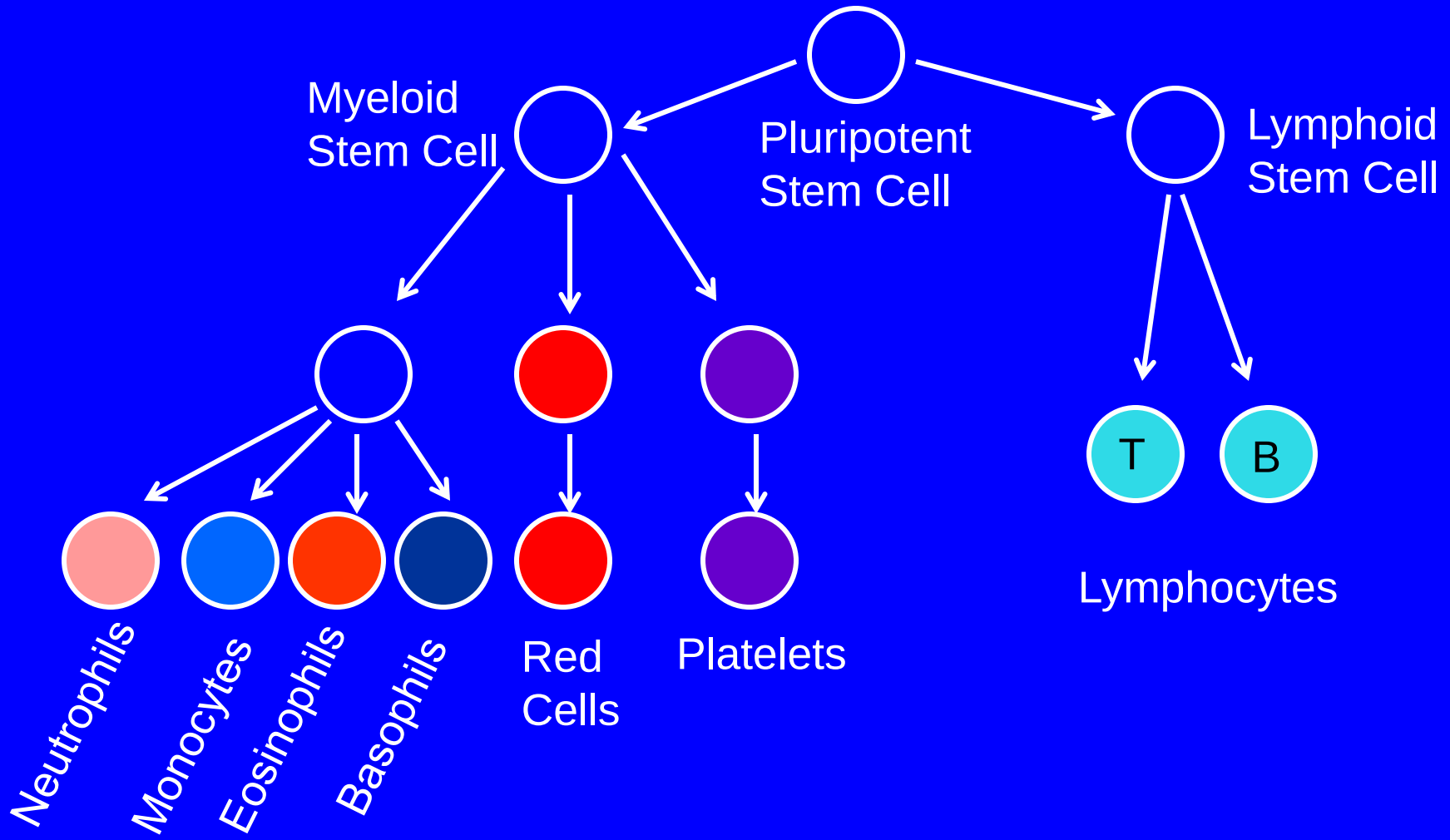
Benefits of Genetic Testing

- Improved medical management
- Relief from uncertainty and anxiety about FA-associated problems
- Information for individual and family members
- Lifestyle decision-making

Limitations of Genetic Testing

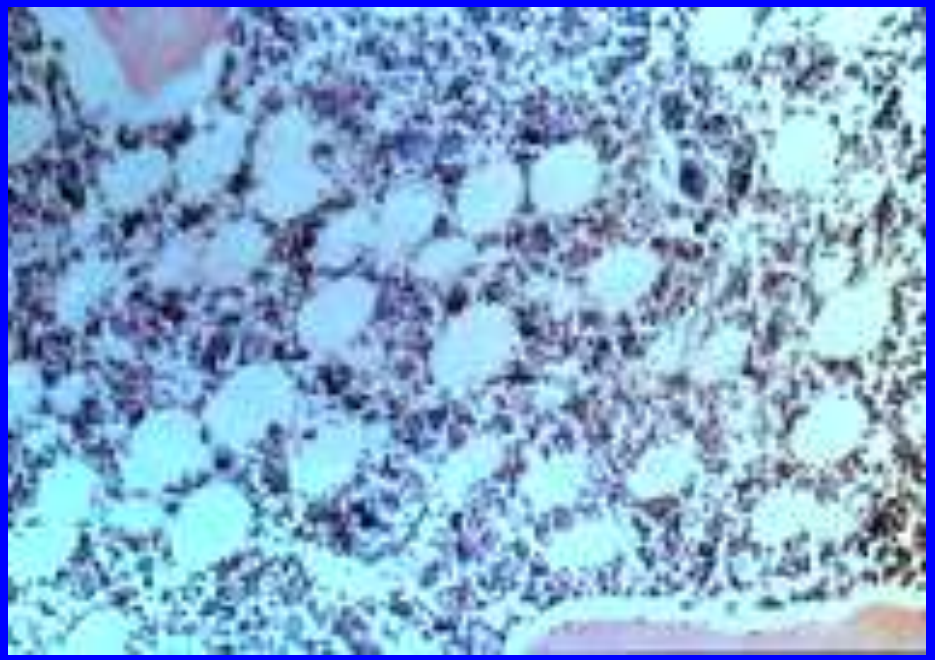
- Not all mutations are detectable
- Negative molecular genetics test result is fully informative *only* if mutation has been identified in family
- Diagnosis of FA indicates an *increased risk*, not certainty, of developing aplastic anemia, leukemia, or cancer

Blood Production (Hematopoiesis)

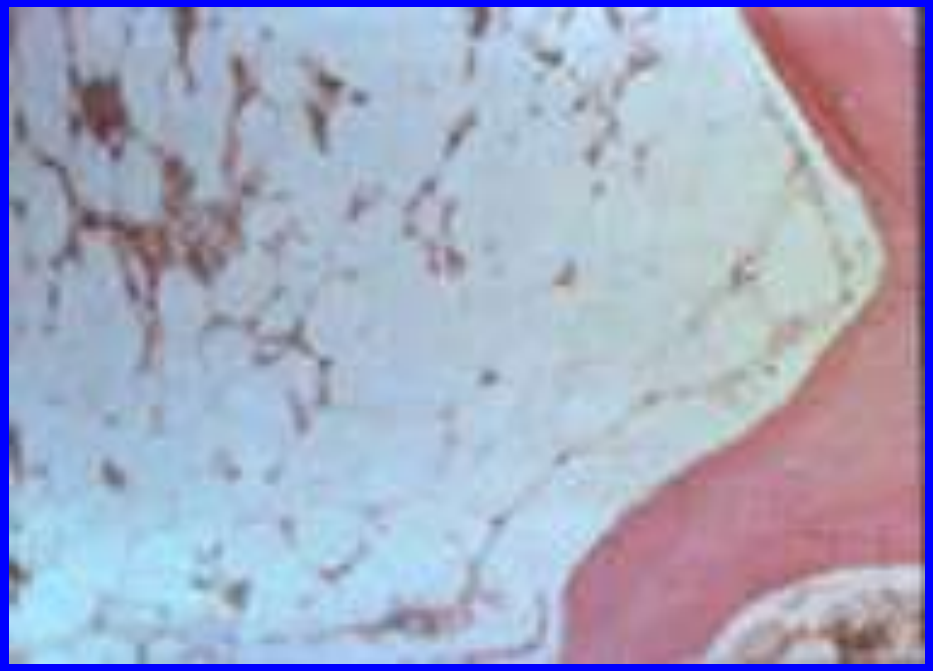


Bone Marrow Biopsy

Normal



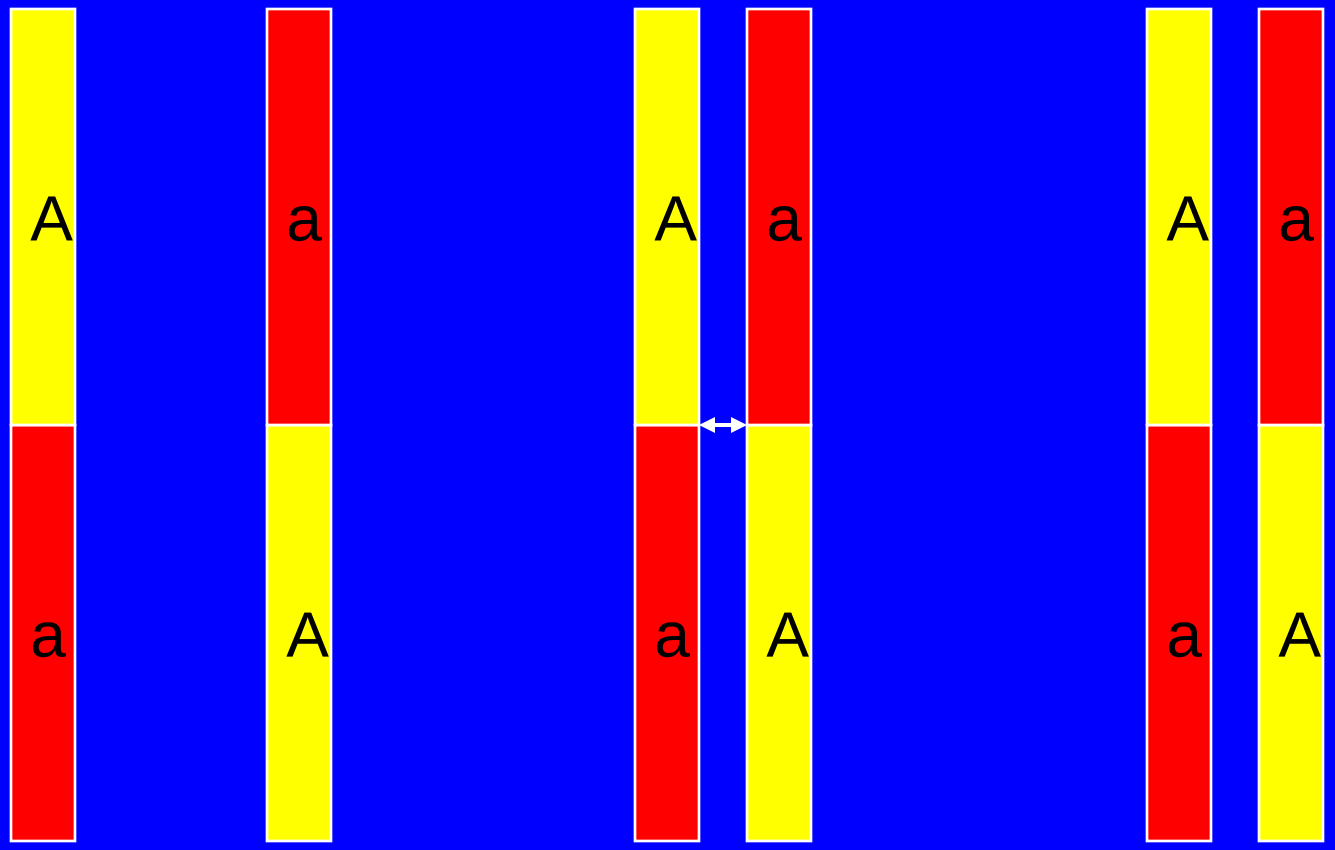
Aplastic



Proof of Mosaicism in FA

- Peripheral blood lymphocyte chromosome breakage test normal
- Skin fibroblast chromosome breakage test abnormal
- One mechanism is recombination during mitosis

Mosaicism from Recombination



Definitions

- Aplastic Anemia (AA)
  - Pancytopenia (low blood counts)
  - Hypocellular bone marrow (decreased cells)
- Myelodysplastic Syndrome (MDS)
  - Cytopenias with hypercellular bone marrow (increased cells)
- Acute Leukemia (AL)
  - Malignant proliferation of immature cells

FA: Complications

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

Aplastic Anemia: Signs and Symptoms

- Thrombocytopenia
  - bruises, petechiae
- Anemia
  - fatigue, lassitude, dyspnea
- Neutropenia
  - infections

Criteria for the Diagnosis of MDS

- Dyspoiesis (abnormal appearance) in at least 20 % of cells in 2 or 3 cell lineages
- Lineages
  - Erythroid, red cells
  - Myeloid, white cells
  - Megakaryocytic, platelets

Bone Marrow Clone

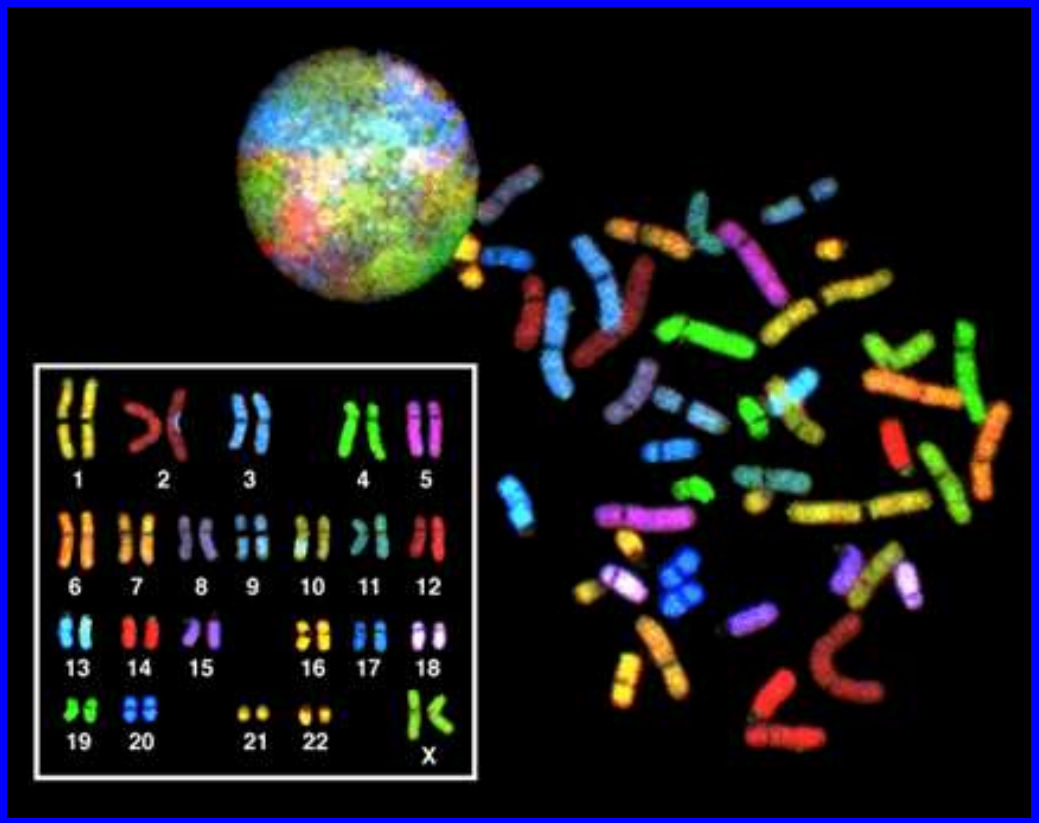
- Count at least 20-30 metaphases (dividing cells)
- Abnormal finding in at least 2 cells
- If loss of chromosome, must be in at least 3 cells

D Arthur, NCI

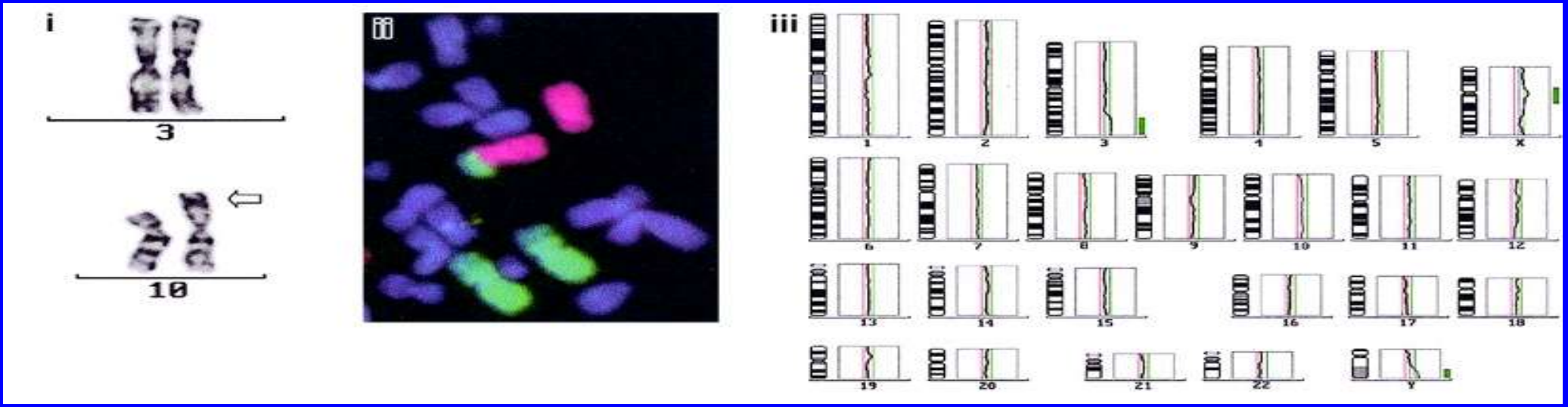
Metaphase

G-banding

SKY: Spectral karyotyping



Gain of Chromosome 3q Material



(i) Partial karyotype of chromosomes 3 and 10 after GTG banding of a bone marrow cell. The arrow points to the translocated material of chromosome 3 onto chromosome 10. (ii) Whole chromosome paints for chromosome 3 (green) and chromosome 10 (red) on a BM metaphase plate for the validation of CGH results. (iii) Averaged CGH copy number karyotype indicating the gain of chromosome 3q25qter material (green bar right of chromosome 3). Tonnies et al, Blood 101:3872, 2003

“MDS” in FA

- Clone alone does *not* have a bad prognosis.
- Morphologic MDS + significant cytopenias require treatment. Alter et al, Ca Genet Cytogenet, 2000.
- Accumulation of cells with gain of 3q. Tonnies et al, Blood, 2003.

Clone alone does not define MDS in FA.

FA: When to Treat Bone Marrow

- Cytopenias
  - Hb <8 g/dL or symptoms
  - Platelets <30,000/mm^3
  - WBC <500/mm^3
- Leukemia
  - Blasts in blood
  - >20% blasts in marrow
- MDS
  - Morphologic + cytopenias
  - Not for clone alone

FA: Treatment for Bone Marrow

- Transplant
- Androgen +/- corticosteroid
- Hematopoietic growth factors
- Gene therapy?

FA: Treatment with Transplant

- Bone marrow, cord blood, or peripheral blood stem cells
- HLA-matched 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 mg/day oral
- Folic acid
  - 1 mg/day oral