Inherited Causes of Aplastic Anemia and Myelodysplastic Syndromes

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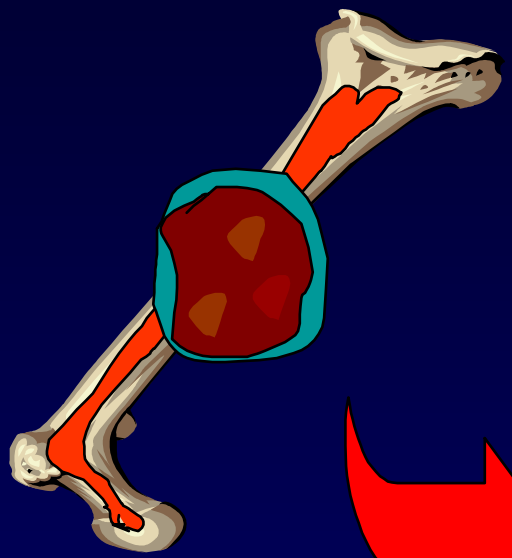
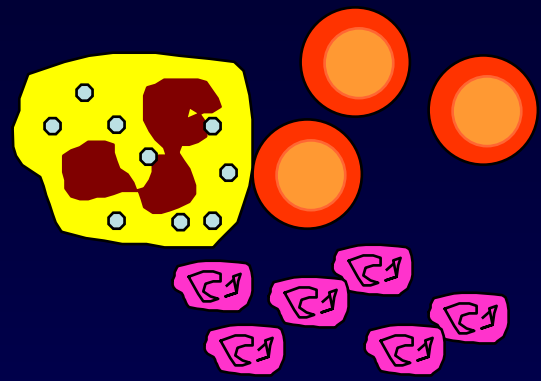
Topics for Discussion

- Genetic causes of aplastic anemia
- Medical problems
  - Blood
  - Non-blood related
- Genetic aspects
- How is the bone marrow get damaged?
- Diagnosis
- Principles of treatment

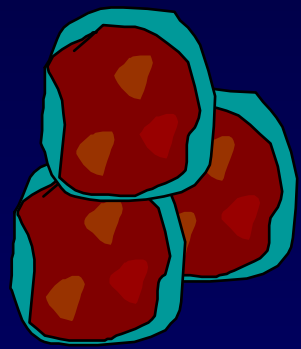
Inherited Bone Marrow Failure Syndromes



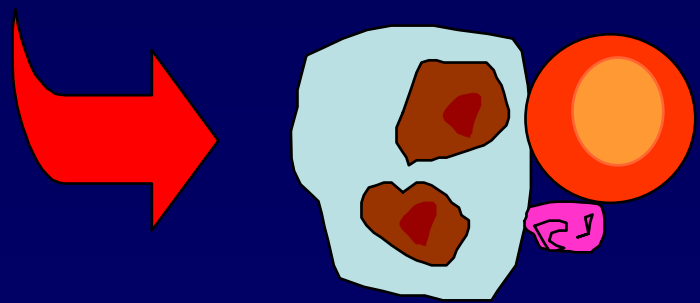
Low blood counts

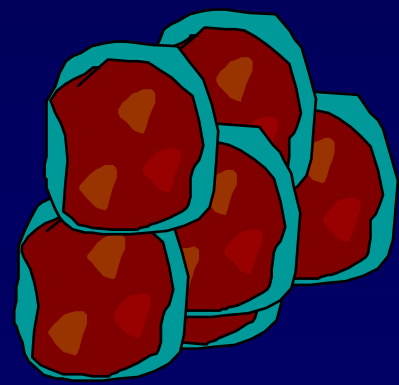


Production

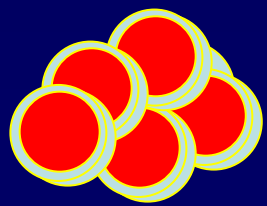


Inherited Mutation in a gene





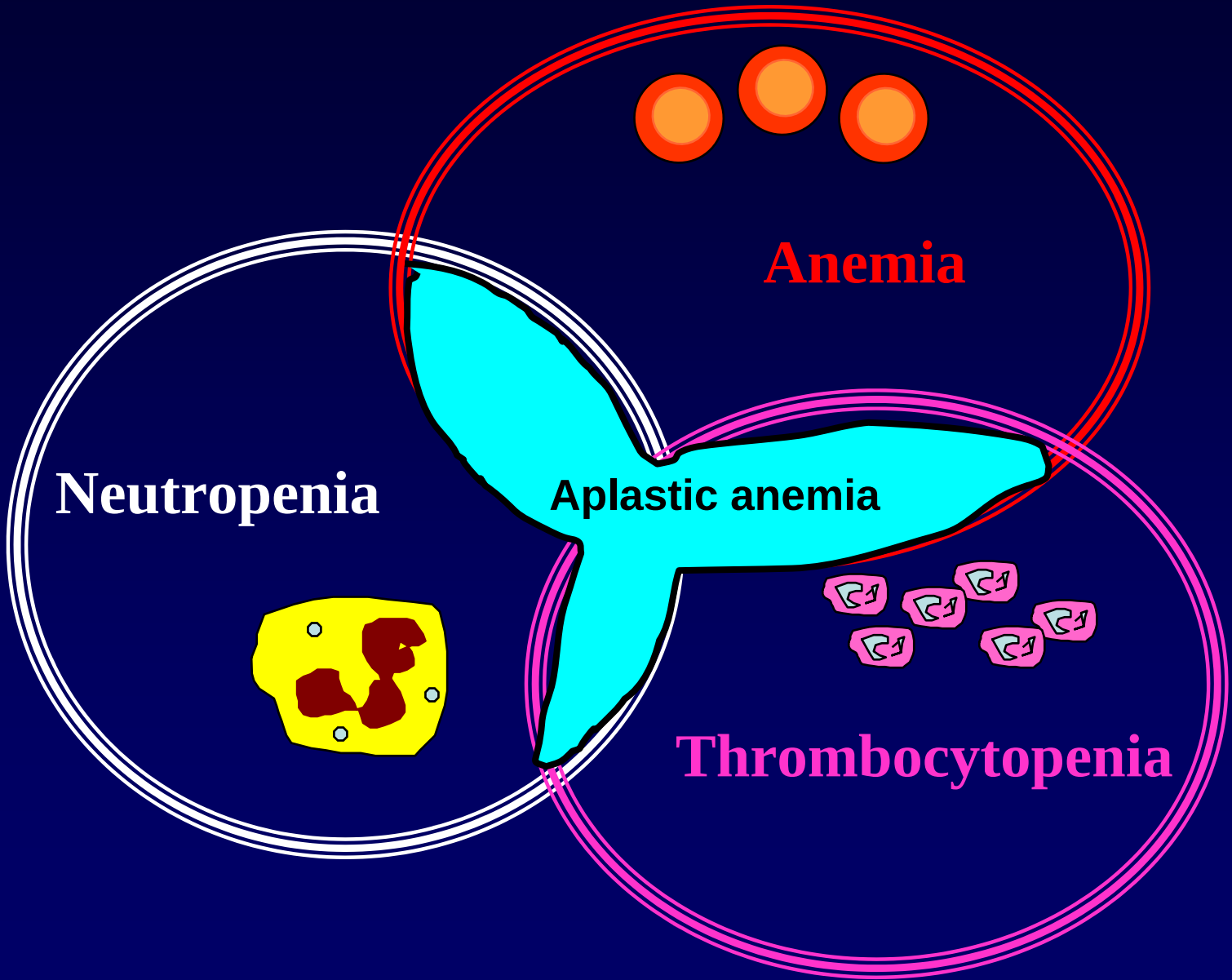
Solid tumors



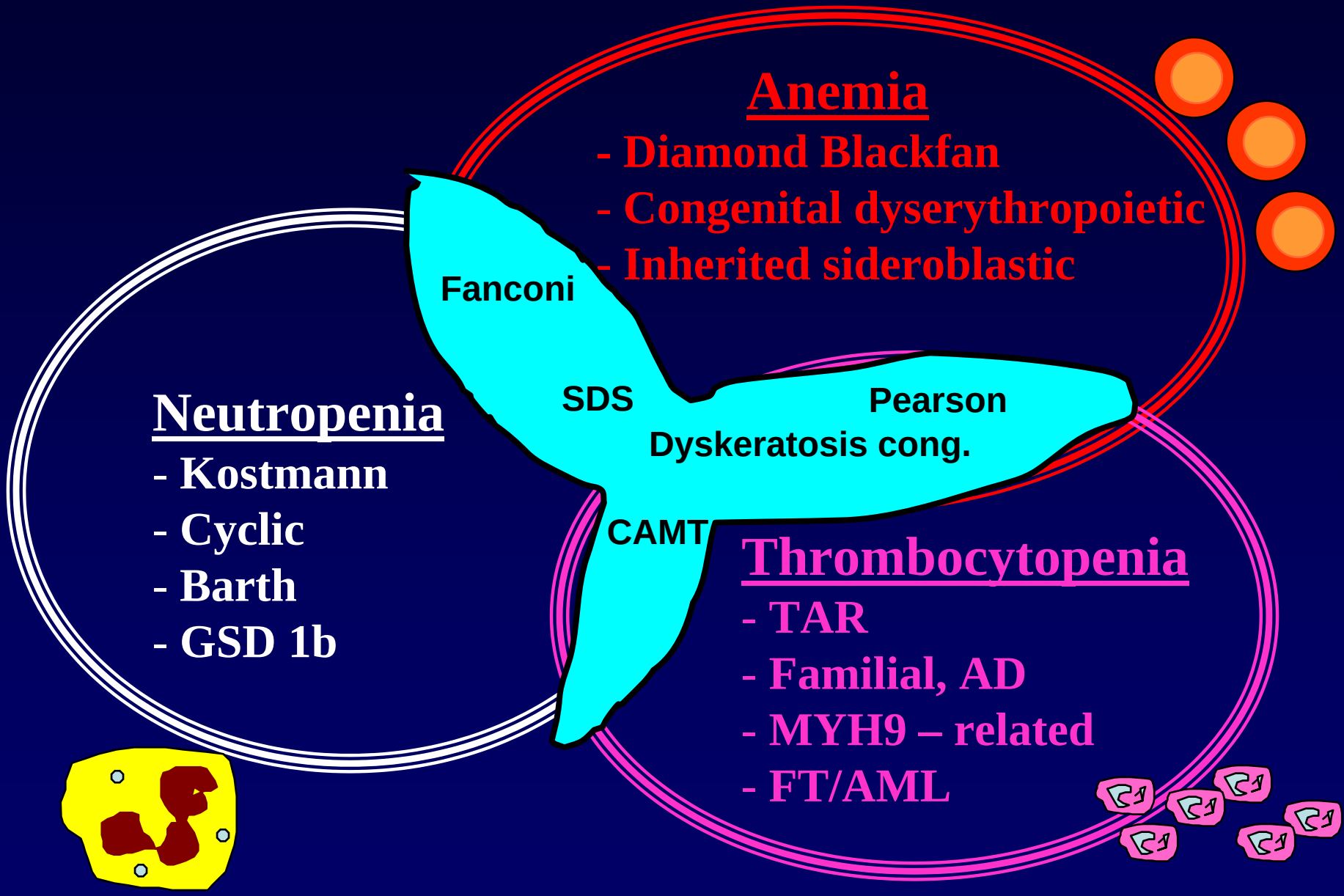
MDS

Leukemia

IMFSs - General Classification



IMFSs - General Classification



General Characteristics

- **Bone marrow dysfunction**
  - **Low blood counts, MDS, leukemia**
- **Non hematological manifestations**
  - **Skeletal (e.g. FA, SDS, DBA, TAR)**
  - **Kidneys (e.g. FA, DBA, TAR)**
  - **Cardiac (e.g. FA, DBA, TAR)**
  - **Pancreatic dysfunction (e.g. SDS)**
  - **Skin pigmentations (e.g. FA, TAR)**
  - **Nail anomalies (e.g. DC)**
  - **Solid tumors (e.g. FA, DC)**
  - **No extra-hematological changes**

Case Presentation (1)

- **16 y girl was referred to the Marrow Failure & Myelodysplasia Clinic**

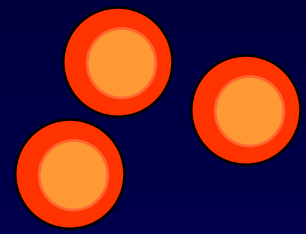
- **Family had just come to Canada from another country**

- **Age of 12 years:**
  - **Bruises**
  - **Weakness**
  - **Fever**

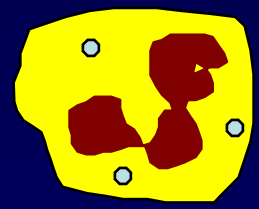
Case Presentation

Laboratory Investigation

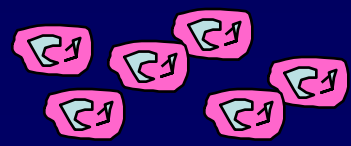
- **Hemoglobin 6.5 (normal 12-14)**



- **Neutrophils 0.48 (normal 1.5-4.5)**

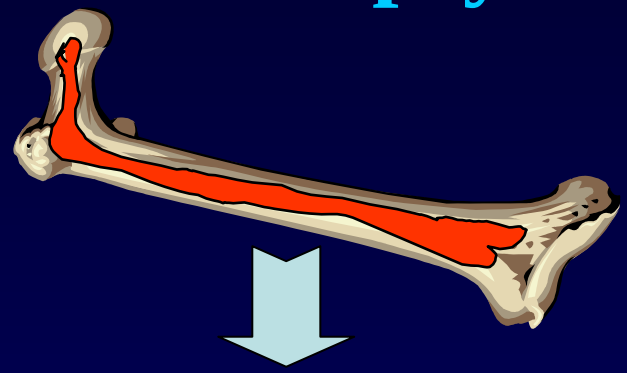


- **Platelets 12 (normal 150-450)**



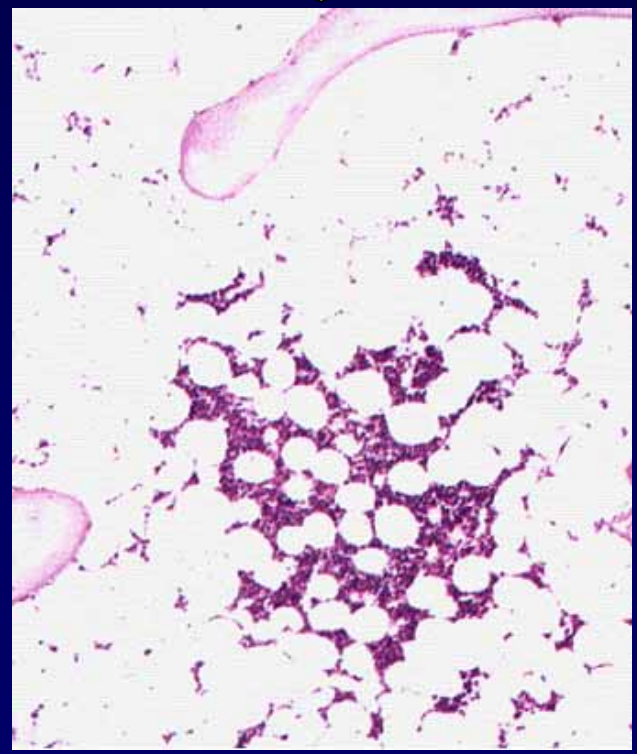
Case Presentation

Bone Marrow Aspiration & Biopsy



- **Reduced bone marrow cells (20%)**

- **No evidence of preluekemia or leukemia**
  - **No abnormal cells**
  - **Normal chromosomes**



Case Presentation

- **Diagnosed with acquired severe aplastic anemia**

- **Treated with ATG/CSA/Pred**

  → No response

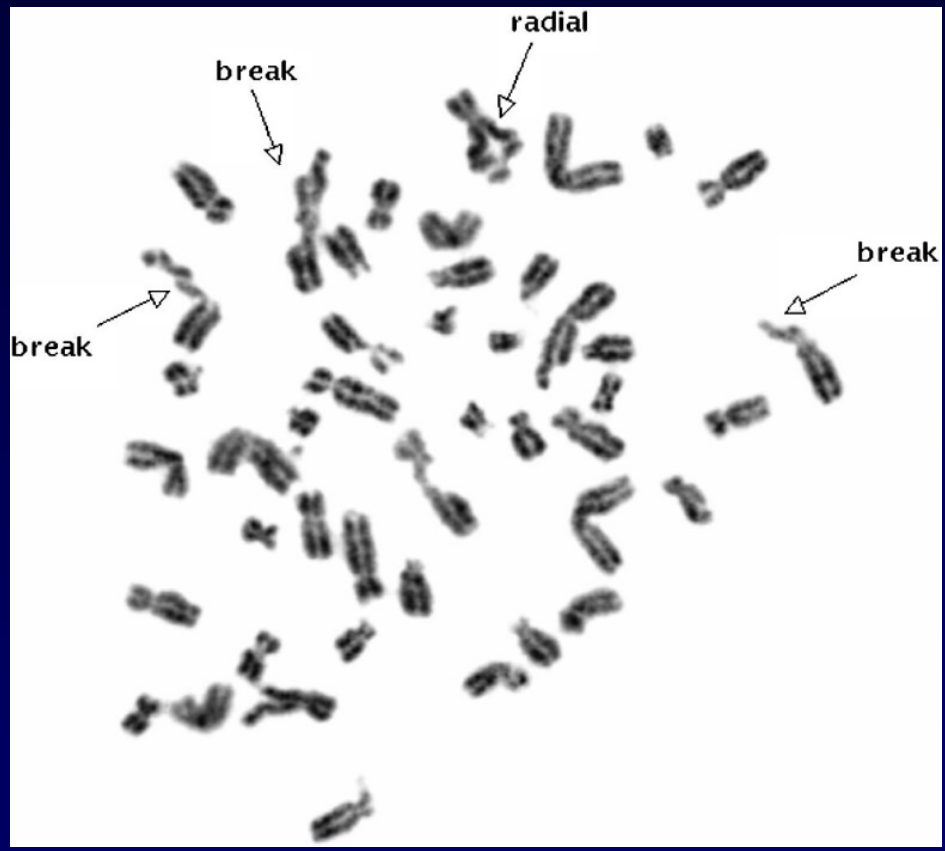
Case Presentation

- Age 14 years
  - Patient was noticed to have short stature and skin pigmentation
  - An inherited bone marrow failure syndrome was suspected

Case Presentation

- **chromosomal fragility test**

→ Chromosome breaks



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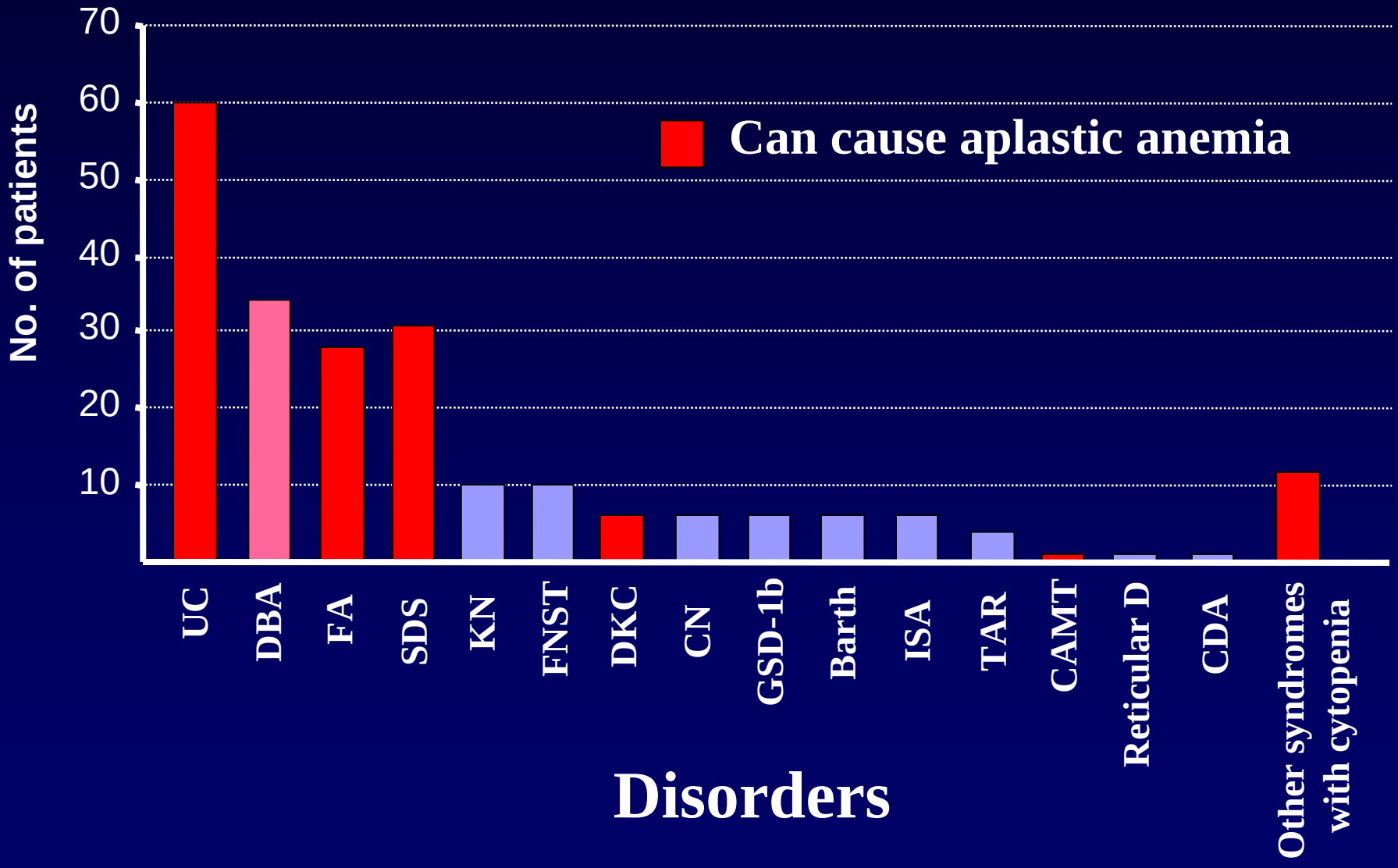
Case Presentation

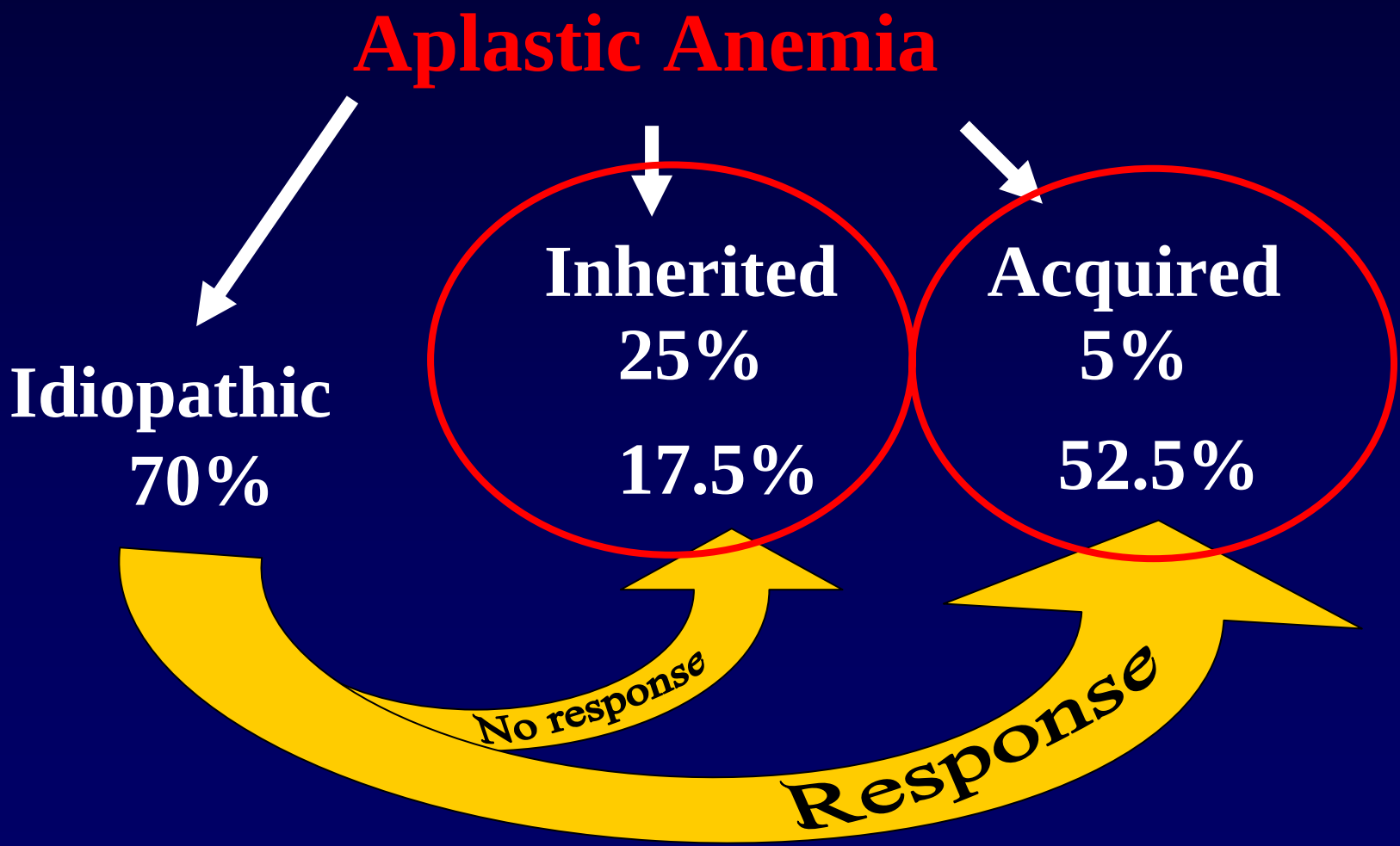
- **Revised Diagnosis**

→ **Fanconi Anemia**

Inherited Marrow Failure Syndromes - Relative Prevalence on CIMFR Data



Causes and Course of the Disease

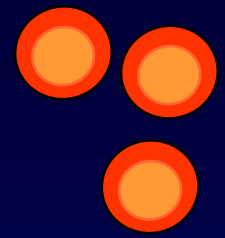


Case Presentation (2)

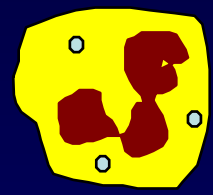
- **42 year old man presented to a family doctor with increasing pallor and weakness for several months.**

- **Family history**
  - **Unremarkable. Parents, 2 siblings and 2 children are healthy.**

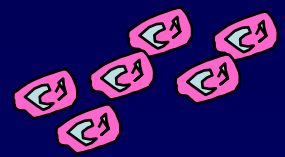
Case Presentation
Laboratory Investigation



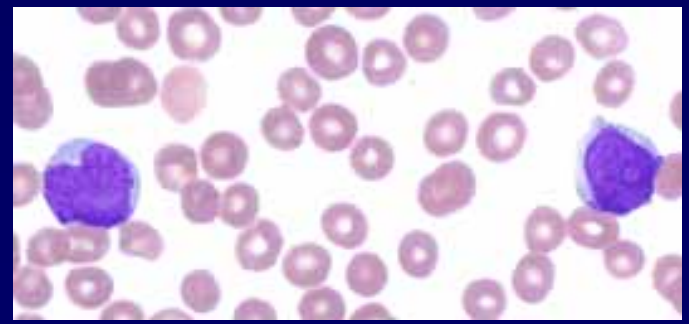
- **Hemoglobin 7.2 (normal 14-16)**



- **Neutrophils 0.6 (normal 1.5-4.5)**



- **Platelets 40 (normal 150-450)**

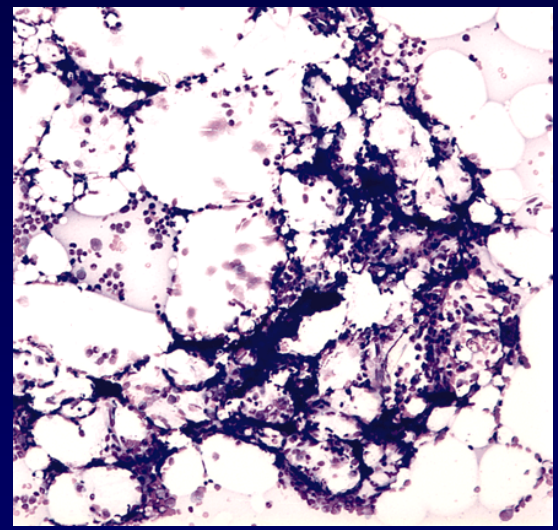


- **Smear: blasts**

Case Presentation

Bone marrow:

- Reduced cell numbers (30%)
- Fibrosis (“scar tissue”)
- 6% blasts (Normal < 5%)
- Chromosome abnormalities
  - Loss of one chromosome 3
  - Loss of one chromosome 5
  - Loss of one chromosome 20
  - translocation between chromosome 5 and 7



→ Myelodysplastic syndrome (MDS)

Case Presentation

- **Careful medical history**
  - **During childhood the patient had pancreatic insufficiency and chronic marrow failure**
  - **Was diagnosed with Shwachman-Diamond syndrome**
  - **Was well without treatment and no follow-up after childhood**

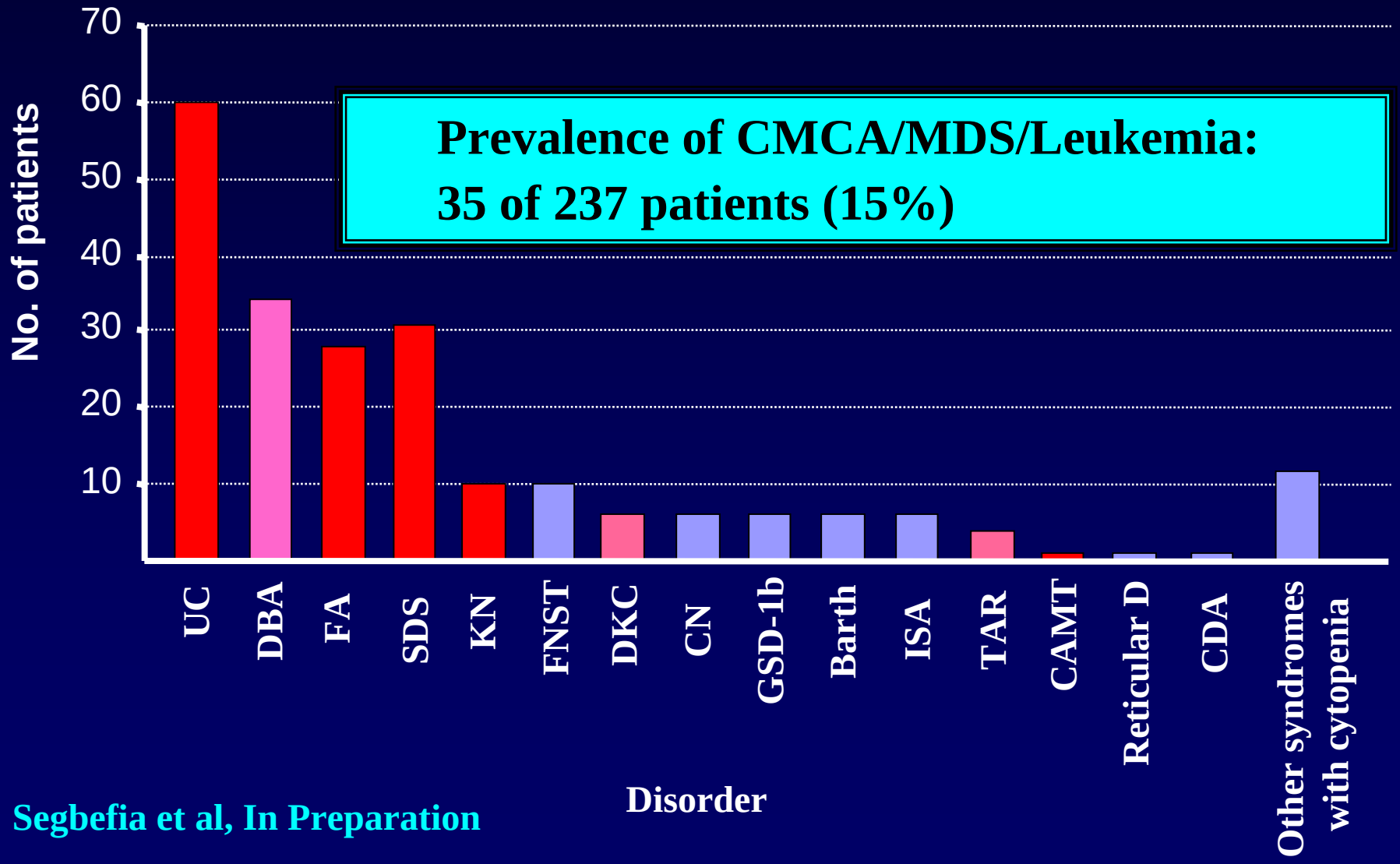
Case Presentation

Diagnosis – MDS

Type:

- **Syndrome related MDS (SDS) /**
- **Refractory cytopenia with excess blasts /**
- **Complex cytogenetic abnormalities**

Inherited Marrow Failure Syndromes Causing MDS - Relative Prevalence on CIMFR Data



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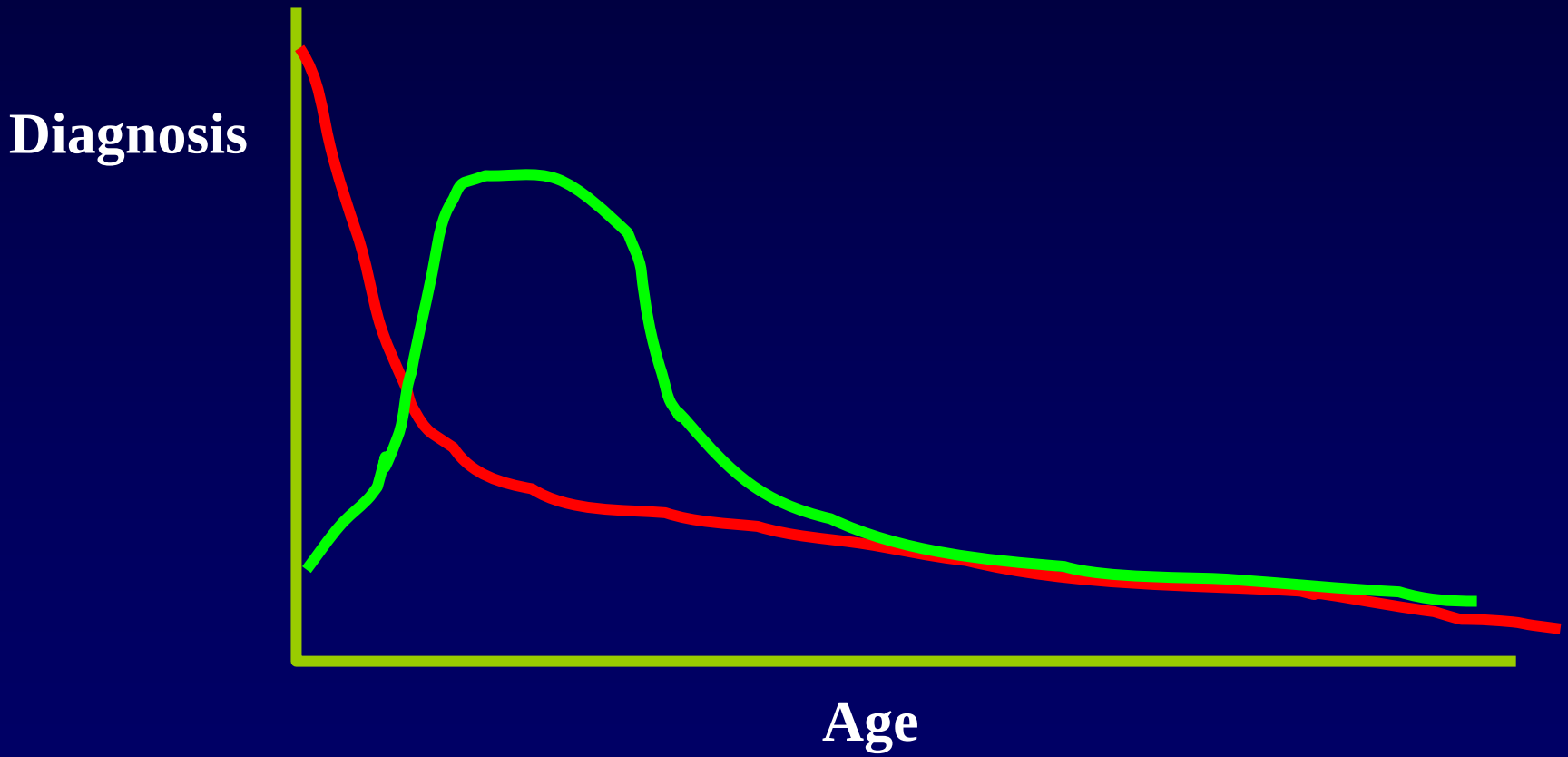
Age of Presentation of the Inherited Marrow Failure Syndromes



Incidence of the Inherited Marrow Failure Syndromes

- About 40% of the aplastic anemias in children are genetic

  ≃ 1.5 per 10^6 per year

- Inherited marrow failure syndromes with single cytopenia (one affected cell lineage)

  ≃ 1 per 10^6 per year

Total

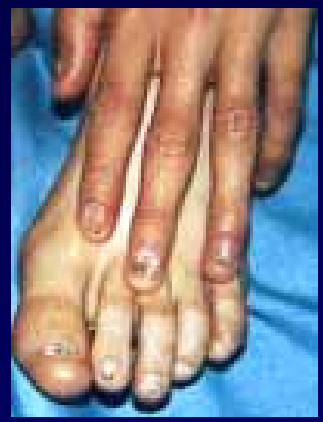
≃ 2.5 per 10^6 per year

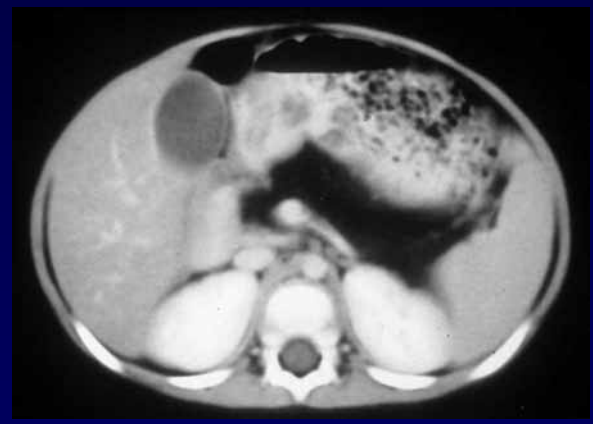
How Do We Make A Diagnosis of an Inherited Marrow Failure Syndrome?

- Establishing a diagnosis of bone marrow failure
  - Medical history
  - Family history
  - Physical examination
  - blood counts
  - Bone marrow
- Additional information for establishing a genetic diagnosis
  - Laboratory testing (e.g. adenosine deaminase, chromosomal fragility, telomere length, pancreatic enzymes)
  - Genetic work-up (e.g. for FA, SDS)

Diagnostic Clues

Aplastic anemia





Fanconi Anemia

Dyskeratosis Congenita

Shwachman-Diamond

IMFS Genes and Their Postulated Functions

Cytoplasm

Growth factor receptors
cMPL

Enzymes
ELA2

Protein Synthesis
RPS19, SBDS

Cell Survival
HAX1

Nucleus

Repair of DNA Damage
FANCA,B,C,D1,D2,E,F,G,J,L

Maintenance of the chromosome ends
TERC, DKC1, TERT, TIN2, NOP10

Transcription of genes
GATA1,CBFA2,HOXA11, GFI1

Which Patient with Inherited Marrow Failure Needs Treatment and When?

- Severely low blood counts?
- MDS with excess blasts?
- Leukemia?
- Solid tumor?

Yes → **Treatment**

No → **Surveillance**

Surveillance And Follow-Up - FA, SDS, KN, DKC

- **Periodic follow-up**
  - **Taking medical history and physical examination every 6m**
  - **Blood counts every 3m**
  - **Bone marrow testing every 1-2 years**

- **Indication for treatment:**
  - **platelets < 20-30,000**
  - **neutrophils < 0.5**
  - **hemoglobin < 7-8**
  - **MDS with excess blasts or leukemia**
  - **Solid tumors**

Treatment

	Blood replacement	Marrow stimulators	Marrow Replacement
FA	Rbc, Plat	Oxy, GFs	BMT
DKC	Rbc, Plat	Oxy, GFs	BMT
SDS	Rbc, Plat	Oxy, GFs	BMT
DBA	Rbc	Pred, CSA, MCP	BMT
KN	-	G-CSF	BMT

Supportive Care

- Antibiotics
- Transfusions
- Tranexamic acid
- Growth factors
- Preparation for dental and surgical procedures
- Some restrictions on physical activities, drugs etc. depending on the condition

Summary

- A significant number of the patients with severe aplastic anemia might have inherited diseases (40?)
- A significant number of the children with MDS might have an inherited marrow failure syndrome (40%?)
- There are many disorders of inherited marrow failure syndrome with significant similarities
- Careful follow-up is important to detect complication at an early stage
- Treatment include transfusions, bone marrow stimulants or bone marrow transplantation.

Acknowledgement

- **The patients in our Marrow Failure and Myelodysplasia Program (MFMP)**
- **The MFMP team (Ms. Pat Canning, Dr. Isaac Odame, Diana Cottingham, Carla Seabrook)**
- **BMT and leukemia/lymphoma Sections, HSC**
- **CIMFR co-investigators**
- **Research Laboratory (Chris Allen, Sally-Lin Adams, Hanming Wang, Trainees)**
- **Support Groups (FA Canada, SDS Canada, Neutropenia Association Inc., Barth Association, AAMAC)**