Aplastic anemia

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Definitions

Aplastic anemia is a clinical state in which peripheral blood pancytopenia results from reduced or absent production of blood cells in bone marrow, in the absence of abnormal infiltration.

Table 1
Classification of aplastic anemia according to severity

Severity	Criteria
Severe	Bone marrow cellularity <25%[a] AND at least two of the following: Peripheral blood neutrophil count $<0.5 \times 10^9$/L Peripheral blood platelet count $<20 \times 10^9$/L Peripheral blood reticulocyte count $<20 \times 10^9$/L
Very severe	Same criteria as severe, but peripheral blood neutrophil count $<0.2 \times 10^9$/L
Nonsevere	Decreased bone marrow cellularity AND Peripheral blood cytopenias do not fulfill the criteria for severe or very severe aplastic anemia

Classification

Inherited

- Occur during childhood
- Associated to congenital abnormalities

Acquired

- Exposure to toxics,drugs, viruses, radiations
- Idiopathic (immune process)

Classification

Inherited

Acquired

- Acquired AA also in childhood (immune, long evolution)

- Inherited AA without congenital anomalies are underdiagnosed in adulthood
  - Improved prognosis, survivors become adult

I. Inherited bone marrow failure

- 25% of BM failure in pediatric.
- Also present and underdiagnosed in adult medicine:
  - Associated congenital anomalies are not constant
  - Symptoms occurs during the 2nd or 3rd decade (DKC)
  - Long term follow-up, cancer predisposition needs to be managed life-long
  - Do not respond to immunosuppressive therapy
  - Specific conditioning regimen (low intensity) are required if HSCT

I. Inherited bone marrow failure

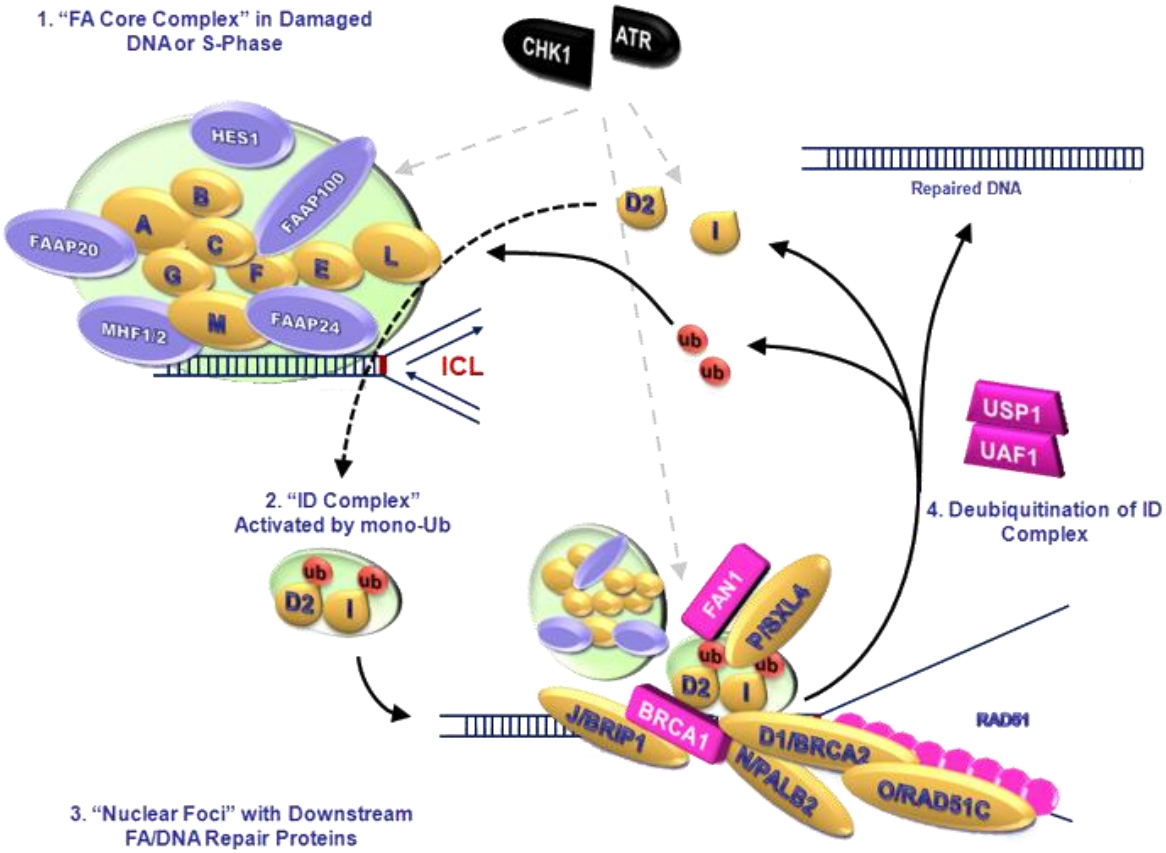
- **Fanconi's anemia**
- **Blackfan Diamond anemia**
- **Dyskeratosis congenita**
- Swachman-Diamond syndrome
- Amegakaryocytic thrombocytopenia
- Reticular dysgenesis
- Familial aplastic anemias
- Non hematologic syndrome (Down, Dubowitz, Seckel, …)

I.A. Fanconi's anemia

- Autosomal and X-linked disorder characterized by:
  - Progressive BM failure
  - Congenital anomalies
  - Predisposition for malignancies
- Rare (1/100,000 live births) but represents the most common inherited BMF syndrome
- Aberrations in the FA pathway (> 13 genes) involved in the response to DNA damage

I.A. Fanconi's anemia: the FA pathway

Group	Gene	Chr. location
	Core complex	
A	FANCA	16q24.3
B	FANCB	Xp22.31
C	FANCC	9q22.3
E	FANCE	6p21-22
F	FANCF	11p15
G	FANCG	9p13
L	FANCL/PHF9	2p16.1
M	FANCM	14q21.3
	ID complex	
D2	FANCD2	3p25.3
I	FANCI	15q25-26
	« Downstream effectors »	
D1	FAND1/BCRA2	13q12.13
J	FANCJ/BRIP1/BACH1	17q22-24
N	FANCN/PALB2	16p12



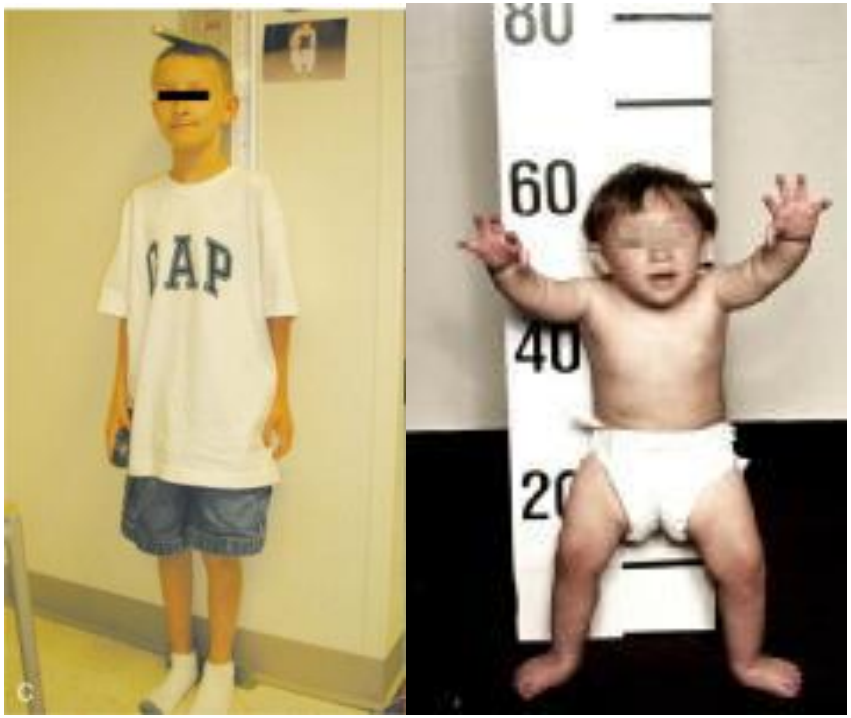
From Atlasgeneticsoncology.org

Rôle in the DNA damage sensing and repair (+ others…)

I.A. Fanconi's anemia: clinical manifestations

- Heterogeneous clinical presentation (variable penetrance and expressivity)
- **Congenital abnormalities: (2/3 patients)**
  - Orthopedic:
    - ✓ thumb absent or hypoplastic or supernumerary
    - ✓ radius absent or hypoplastic (with abnormal thumbs)
    - ✓ facial dysmorphy, café-au-lait spots,…
  - Genito-urinary: ectopic kidney, horseshoe,…
  - Cardiac malformations
  - Slow development, other CNS malformation

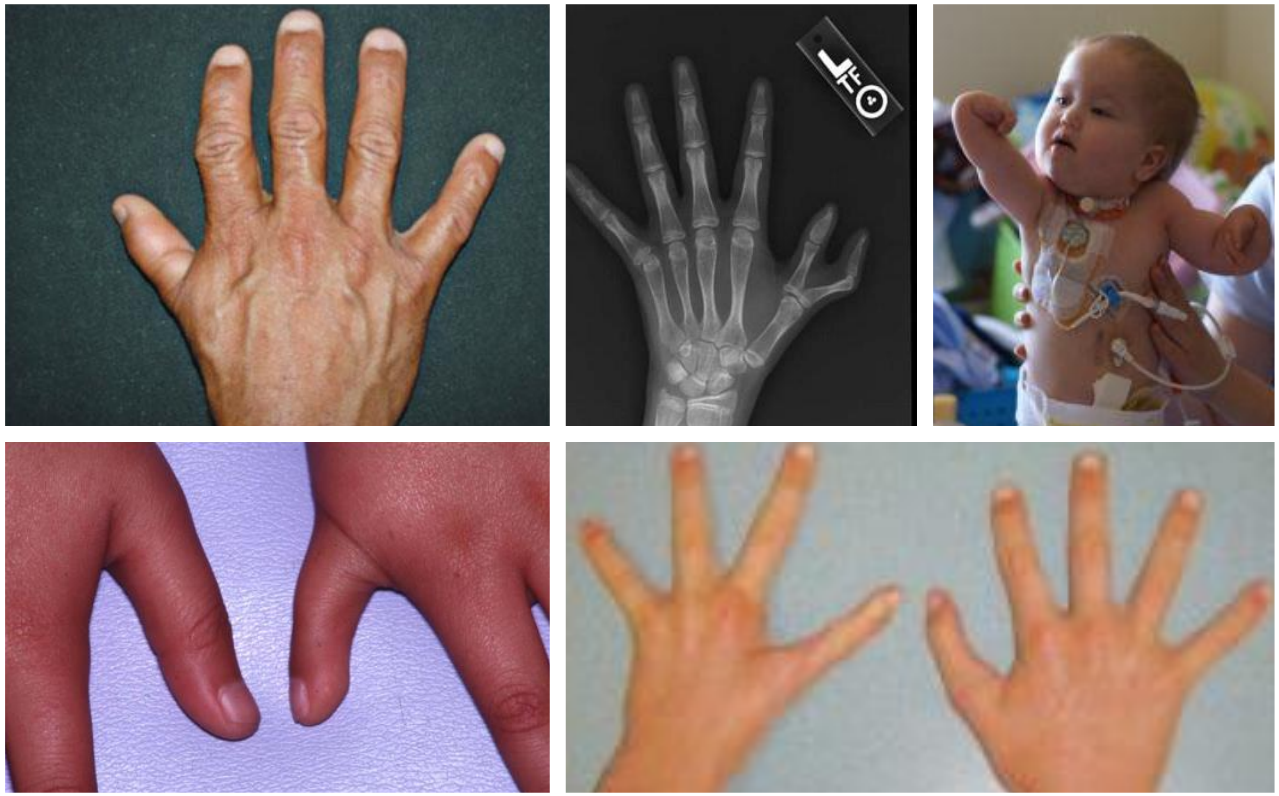
I.A. Fanconi's anemia: clinical manifestations



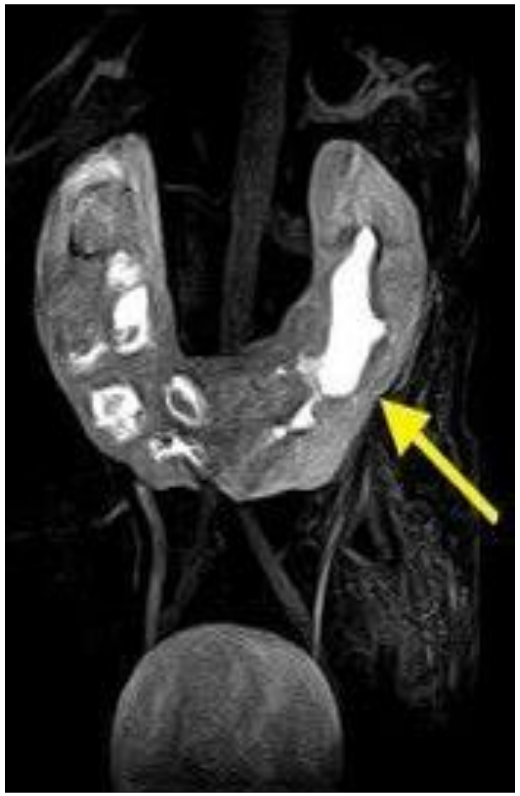
short stature, underweight

facial dysmorphy

I.A. Fanconi's anemia: clinical manifestations



Abnomalities of thumbs +/- absence of radius



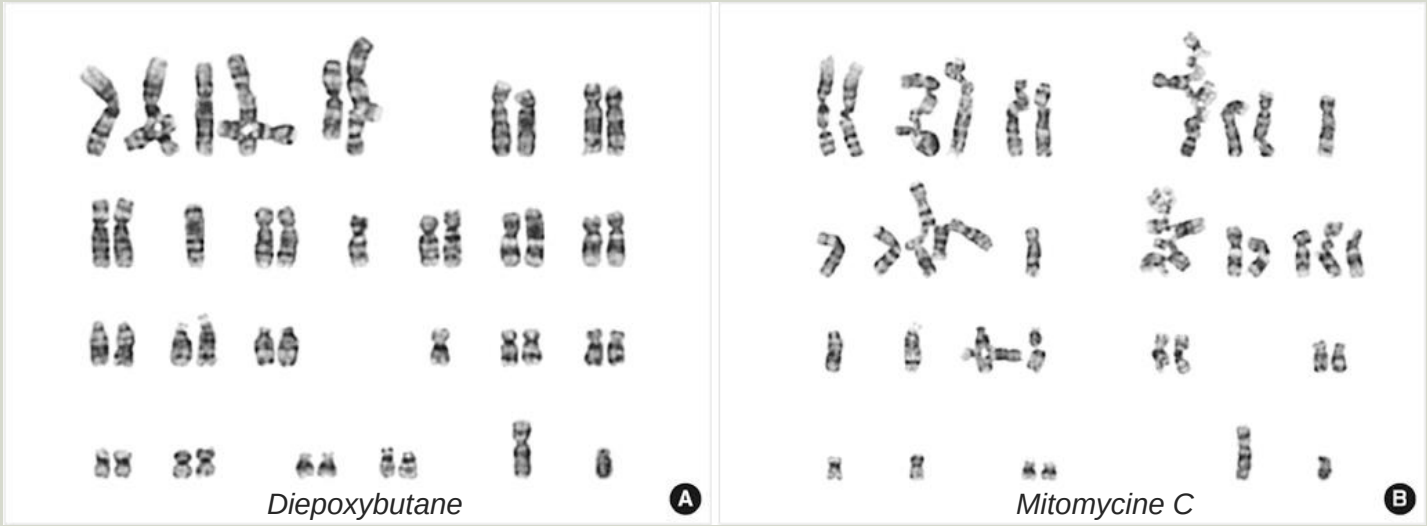
Kidney malformation « horseshoe kidney »

I.A. Fanconi's anemia: clinical manifestations

- **Hematologic abnormalities:**
  - Progressive BM failure
  - Typically initiated by thrombocytopenia
  - Macrocytosis, high level of Hb F and high expression of Ag "I" on RBC
  - Detected at median age of 7 years
  - Progression in 3-4 years in 50%
  - 9% diagnosed after 16years (progressive BMF, malignancy)
- **DNA repair problem: increased risk of MDS, leukemia and solid tumors (x1000) (30% at 40 years)**

I.A. Fanconi's anemia: diagnosis

- Careful clinical examination (thumbs, skin, …)
- Thrombocytopenia, anemia, reticulocytopenia (↗ HbF)
- Chromosome breakage test
- BM aspiration and biopsy (exclusion of MDS, AML)
- Genetics, molecular biology



I.A. Fanconi's anemia: management

- **Supportive care** (transfusion)
- **Androgens ?** transient improvement but masculinization, liver toxicity
- **HSCT** (even with unrelated donor if severe)
  - Low intensity conditioning regimen (fludarabin ,ATG)
- **Long term follow-up** (HSCT late effets, cancers !)

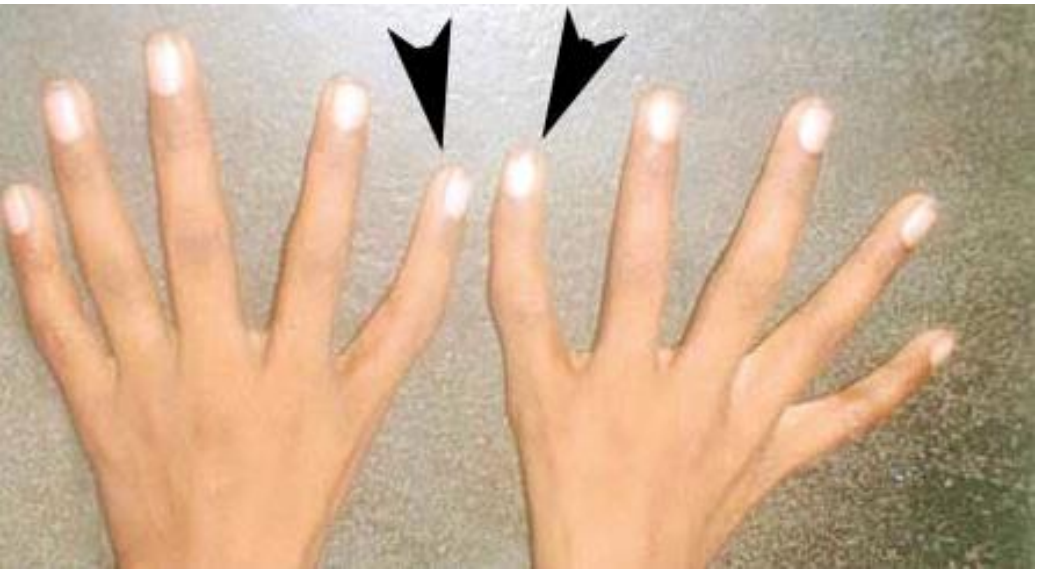
I.B. Diamond-Blackfan anemia

- **Autosomal dominant disorder** with:
  - Typically: isolated macrocytic anemia with reticulocytopenia, during the 1st year of life (90%)(but described in adulthood)
  - Neutropenia and thrombocytopenia may occur later
  - Elevated Hb F and elevation of erythrocyte ADA
- **Predisposition to malignancy** (AML, osteosarcoma)

I.B. Diamond-Blackfan anemia: clinical manifestations

- **Congenital abnormalities** (in about 50%):
  - Short stature (despite corticoids, iron overload)
  - Midline craniofacial defect
  - Upper limb
    - ✓ thumb absent or hypoplastic or bifid or triphalangeal
    - ✓ Flat thenar eminence, syndactyly
    - ✓ Absence of radial artery
  - Genito-renal abnormalities
  - Cardiac malformations

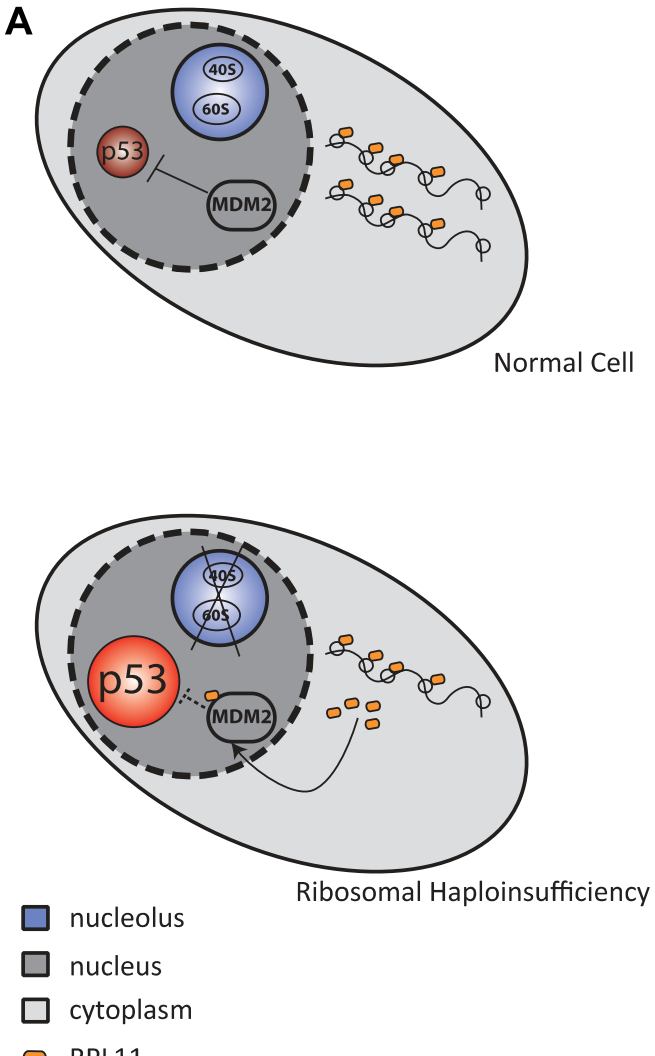
I.B. Diamond-Blackfan anemia: clinical manifestations



I.B. Diamond-Blackfan anemia: molecular aspects

- Familial (50%) and sporadic cases
- Autosomal dominant inheritance
- Mutations of ribosomal protein genes found in 60% of DBA
  - *RPS19* 25%
  - *RPS24* 3%
  - *RPS17* in a family
  - *RPL35a* 2%
  - *RPL5* 10%
  - *RPL11* 6,5%

I.B. Diamond-Blackfan anemia: molecular aspects



Mutations result in a decreased formation of mature ribosome. This leads to a relative up-regulation of RPL11, which interacts to MDM2 and causes p53 activation. This induces apoptosis and cell-cycle arrest.

High demand for ribosome synthesis during red cell productions (8-12 weeks)

Narla, 2010

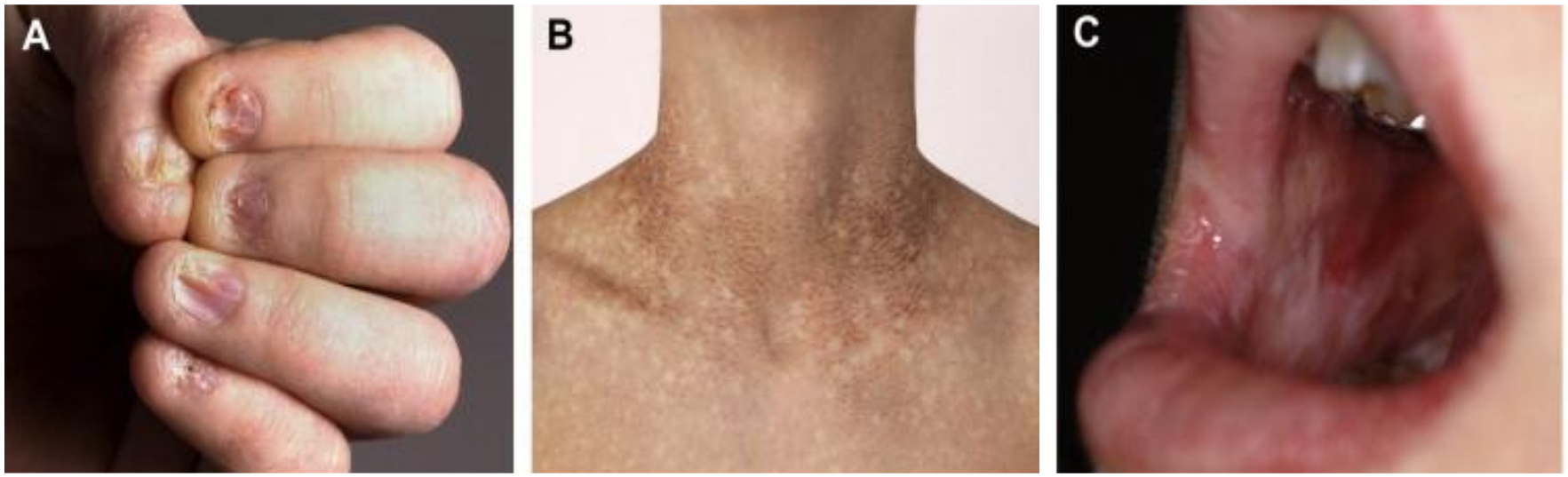
I.B. Diamond-Blackfan anemia: management

- Corticoids
  - 80% respond but 40% have a long term response
  - improvement within a month
- RBC transfusion (! Iron overload)
- HSCT: front-line therapy if unaffected related donor (survival 75% if related vs 19% if unrelated)
- Cancer surveillance

I.C. Dyskeratosis congenita

- Progressive bone marrow failure and typical cutaneous manifestations
- High risk of developing leukemia, solid tumors and lung fibrosis
- “Telomerase” deficiency

I.C. Dyskeratosis congenita: clinical manifestations



A: nail dystrophy

B: Reticular skin pigmentation

C: Leukoplakia

occuring during the first decade

Savage, Alter , 2009

I.C. Dyskeratosis congenita: clinical manifestations

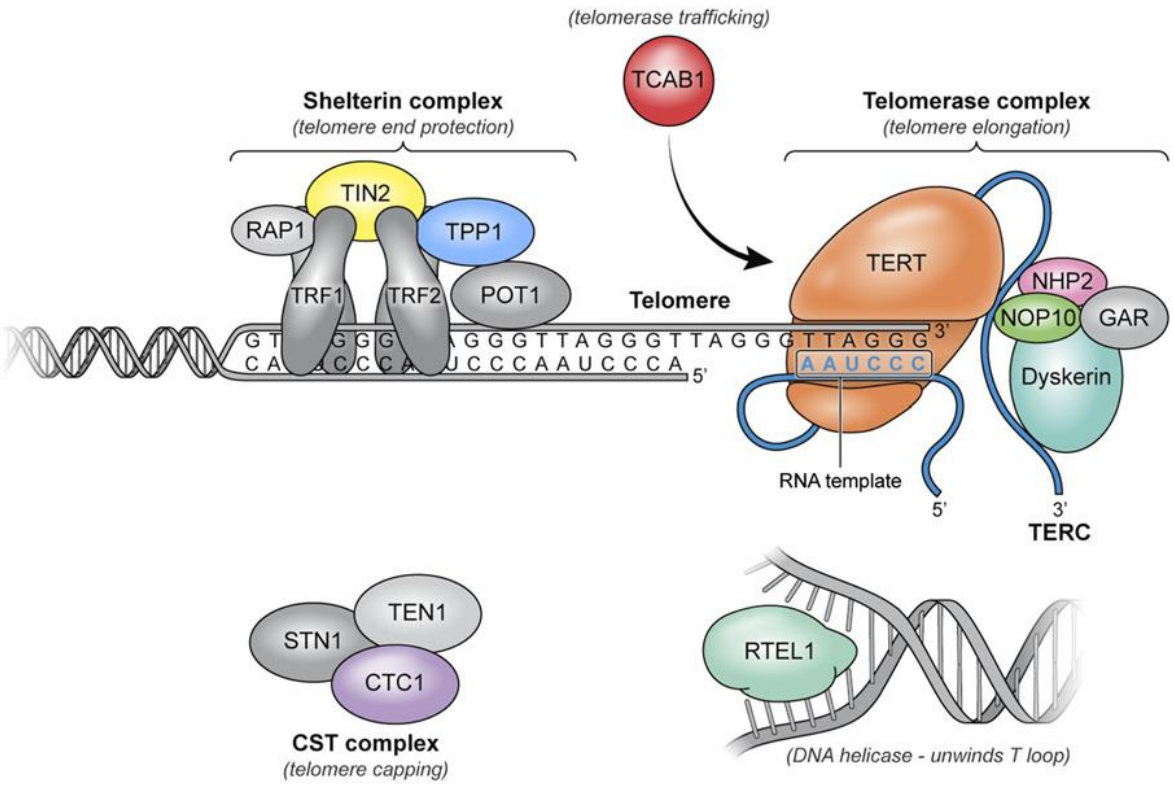
- Progressive bone marrow failure as presenting sign around 10 years of age (80-90%)
- Lung fibrosis (20%)
- Increased risk of cancer (leukemia, lymphoma, MDS, epithelial cancers)
- Gastrointestinal: enteropathy, liver fibrosis
- Neurologic: developmental delay, cerebella hypoplasia
- Osteonecrosis, osteoporosis
- Endocrine: hypogonadism
- Ophtalmologic: exsudative retinopathy, lacrymal stenosis

I.C. Dyskeratosis congenita: molecular aspects

- Autosomal dominant, recessive and X-linked inheritance as well as sporadic cases
- Mutations in 10 genes identified in 50% of DKC patients. These genes are involved in telomere synthesis.
- **Diagnosis**: short length telomere (flow-fish), mutation in 50%

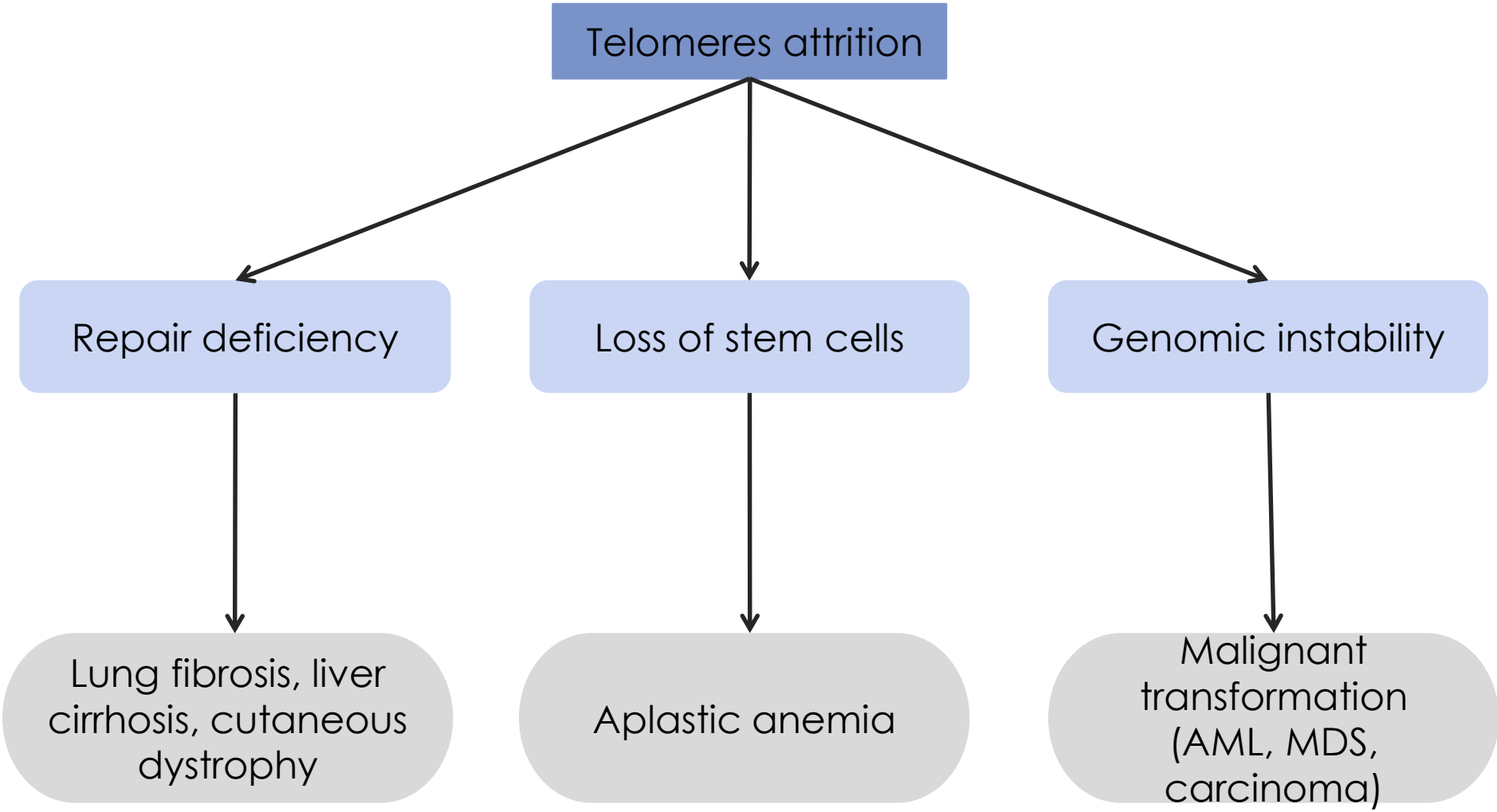
I.C. Dyskeratosis congenita: molecular aspects

Gene	Location	Frequency
DKC1	Xq28	17-36%
TERC	3q21-q28 (AD)	6-10%
TERT	5p15.33 (AD,AR)	1-7%
TINF2	14q12 (AD)	11-24% (+retinopathy)
NOLA3 (NOP10)	15q14-q15 (AR)	<1%
NOLA2 (NHP2)	5q35.3 (AR)	<1%
TPP1		
WRAP53 (TCAB1)	AR	<1%
RTEL1		+Cerebellar hypoplasia
CTC1	AD	+microangiopathy



Townley, Young, 2014

I.C. Dyskeratosis congenita: molecular aspects



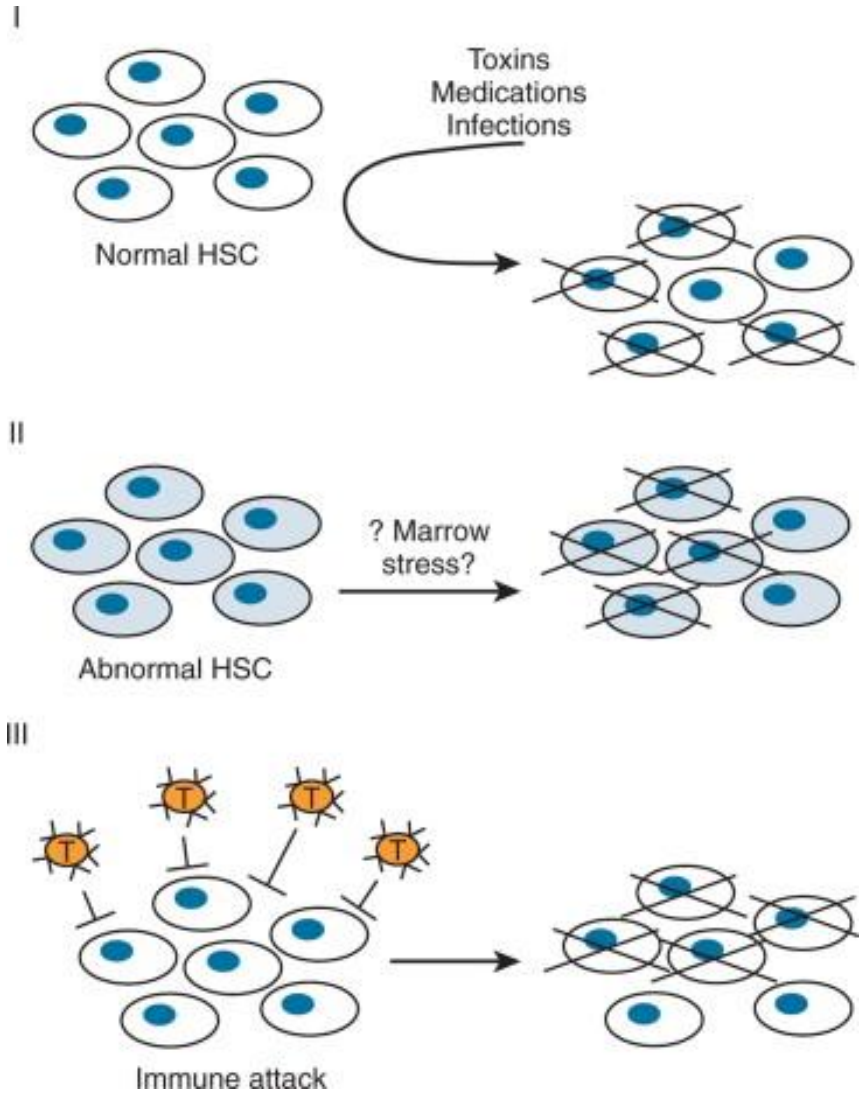
I.C. Dyskeratosis congenita: management

- Supportive (transfusion) and detection of AML, MDS
- HSCT but treatment toxicity ! (reduced conditioning regimens)
- Cancer surveillance

II. Acquired aplastic anemia

- **Secondary**
  - Radiation
  - Drugs and chemical
  - Viruses
  - Immune diseases
  - Thymoma
  - GVHD in ID
  - PNH
  - Myelodysplasia
- **Idiopathic**

II. Acquired aplastic anemia: pathogenesis



Stem cells are damaged by exogeneous agent

Abnormal stem-cells undergo premature attrition (increased by external factors)

Immune-mediated attack of stem cells

Nathan, Oski, 2009

II. Acquired aplastic anemia: management

- **Supportive**
  - Transfusion
  - Growth factors
  - Infection prevention
- **Immunotherapy vs HSCT ?**

II. Acquired aplastic anemia: management

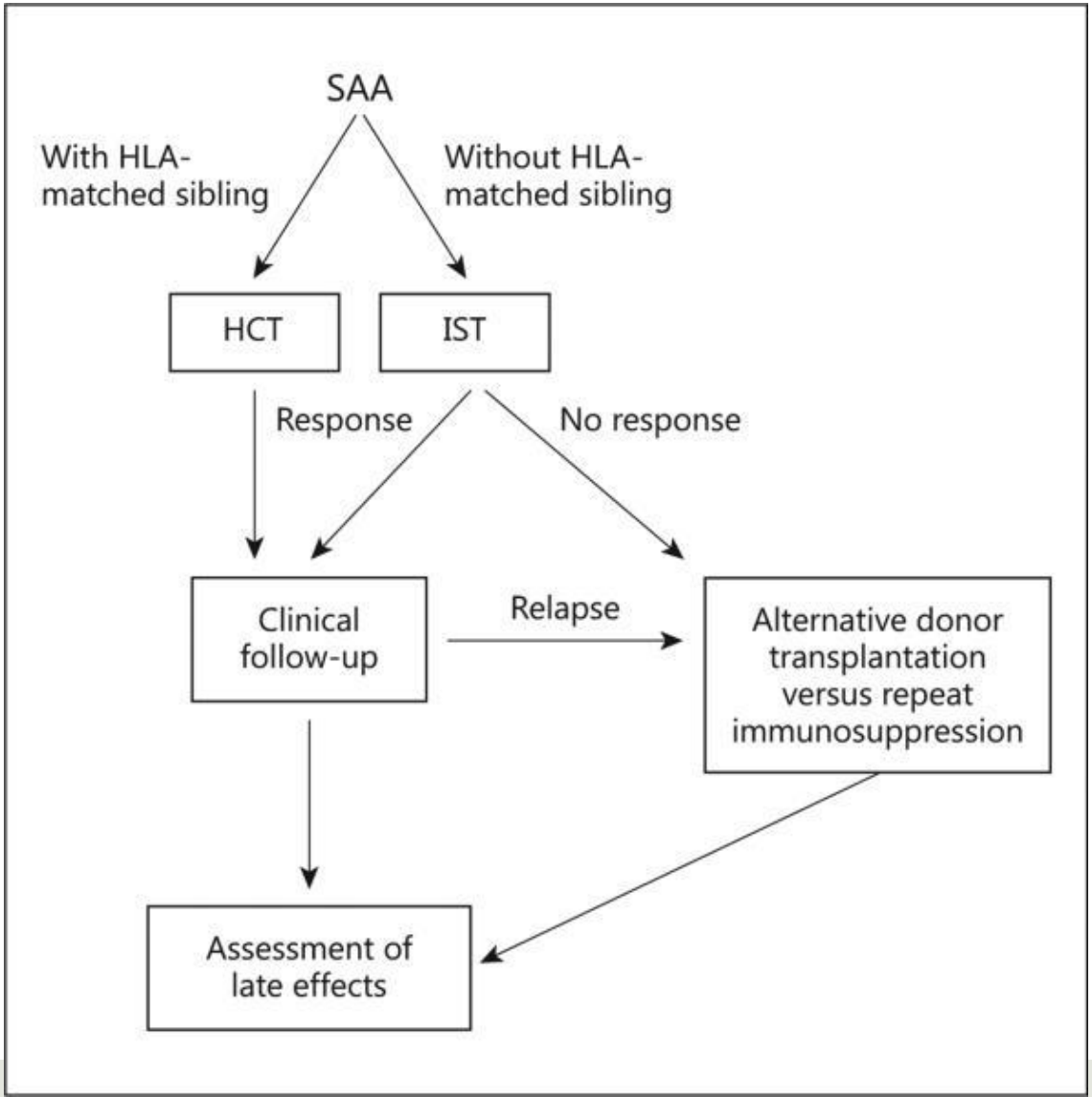
- **HSCT**
  - First-line if HLA-matched sibling donor in young patients (< 30y)
  - EBMT (1500 pts, 1991-2002): better prognosis if :
    - ✓ matched sibling donor
    - ✓ < 16y
    - ✓ Early HSCT (less than 83 days) survival 75-95% !
  - Reduces the risk of relapse and MDS
  - In young patients BM better than PBPC

II. Acquired aplastic anemia: management

- **Immunotherapy**
  - ATG, CSA, Corticoids
  - Response in 80% of young patients but 40% relapse
  - Follow- up for relapse, MDS

…for your attention !

II. Acquired aplastic anemia: management



Aplastic anemia in adolescents and young adults (DeZern and Guinan, 2014)