Constitutional syndromes predisposing to acute leukaemia

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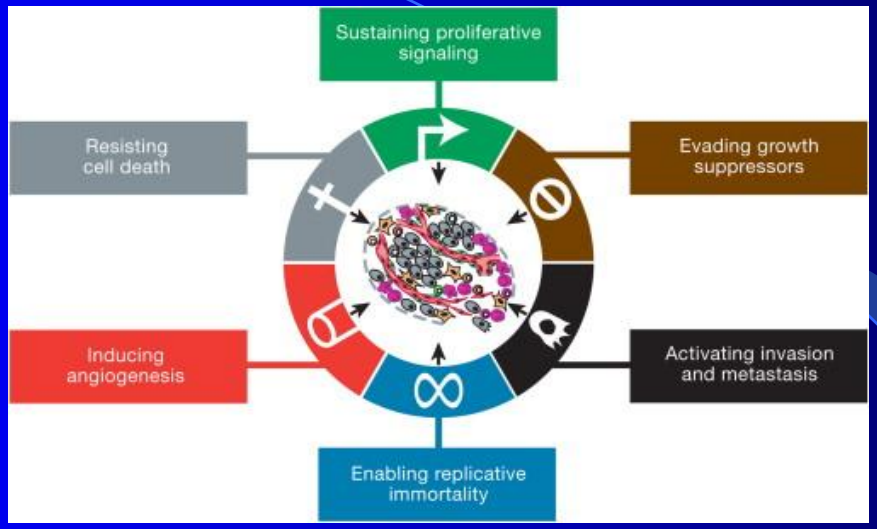
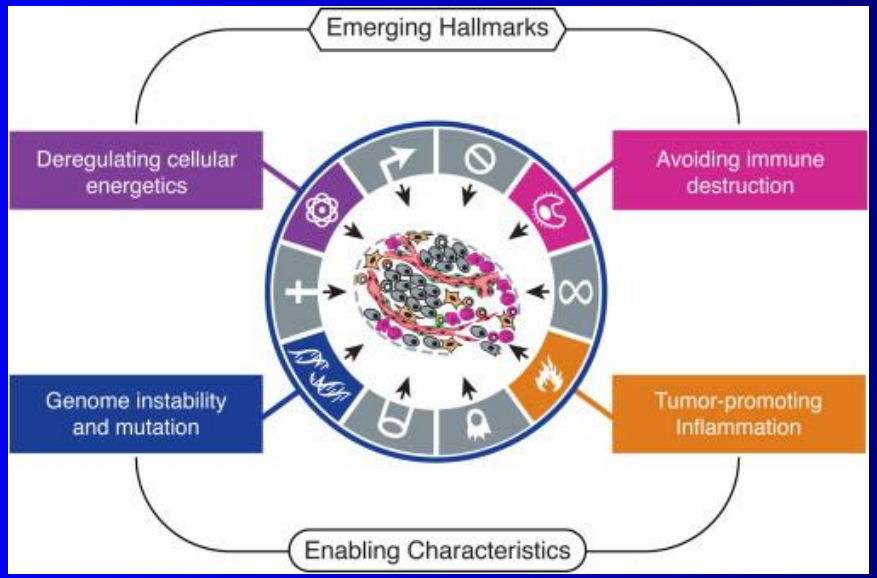
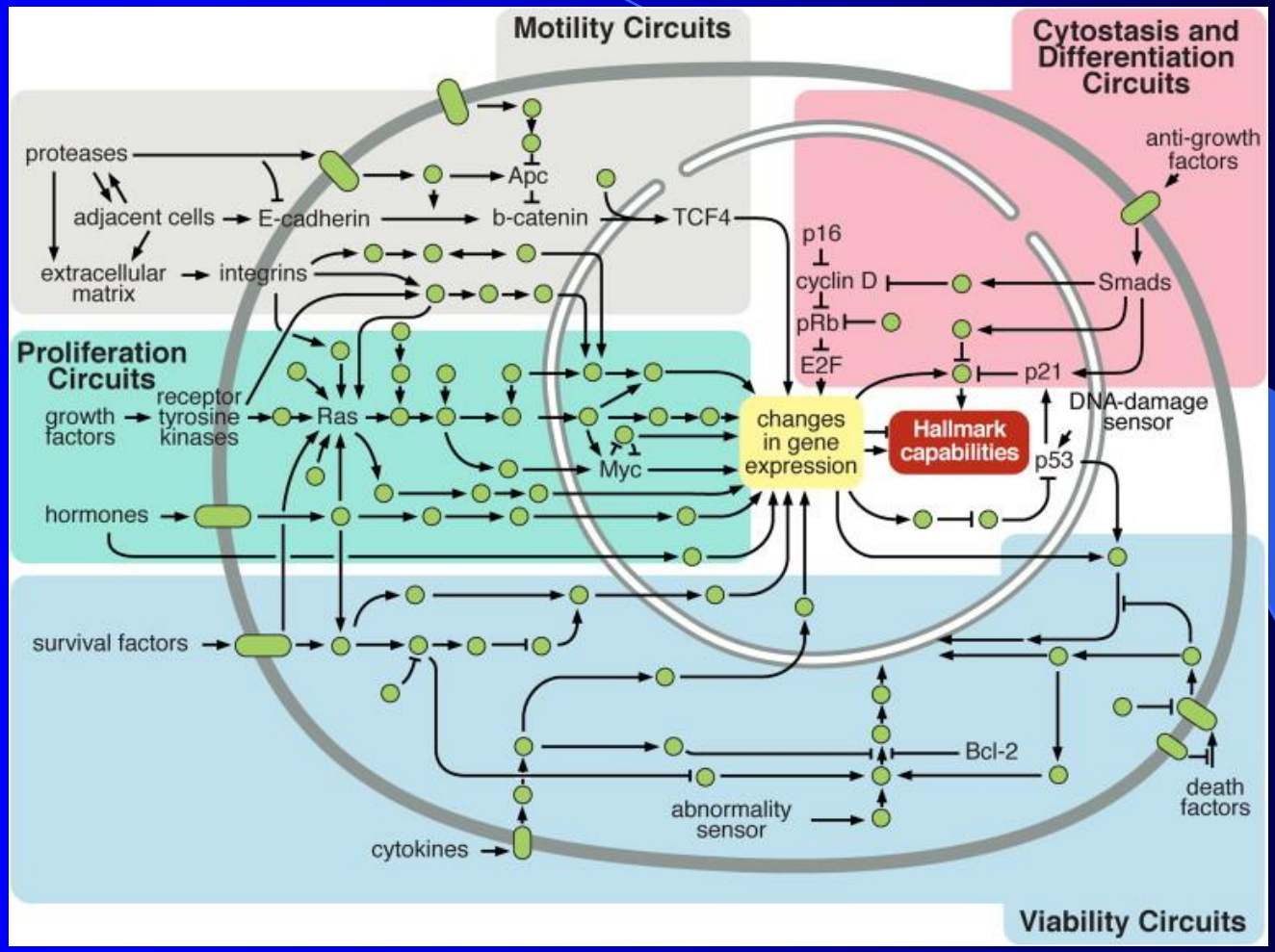
Pathways of tumorigenesis





Hanahan and Weinberg , Cell 2011

Pathways of tumorigenesis



Hanahan and Weinberg , Cell 2011

Leukaemogenesis

- Proliferation
- Evasion of apoptosis
- Differentiation arrest
- Oncogenes
- Tumour suppressor genes
- DNA repair genes

Genetic defects predisposing to leukaemia

Tumour suppressor genes

- Li-Fraumeni-*P53*
- Neurofibromatosis-*NF1*

DNA repair genes

- *Fanconi Anaemia*
- Ataxia –Teleangiectasia *-ATM*

Ribosomopathies

- *Blackfan-Diamond anaemia*
- *Shwachmann-Diamond s*
- *Dyskeratosis Congenita*

In utero mutations

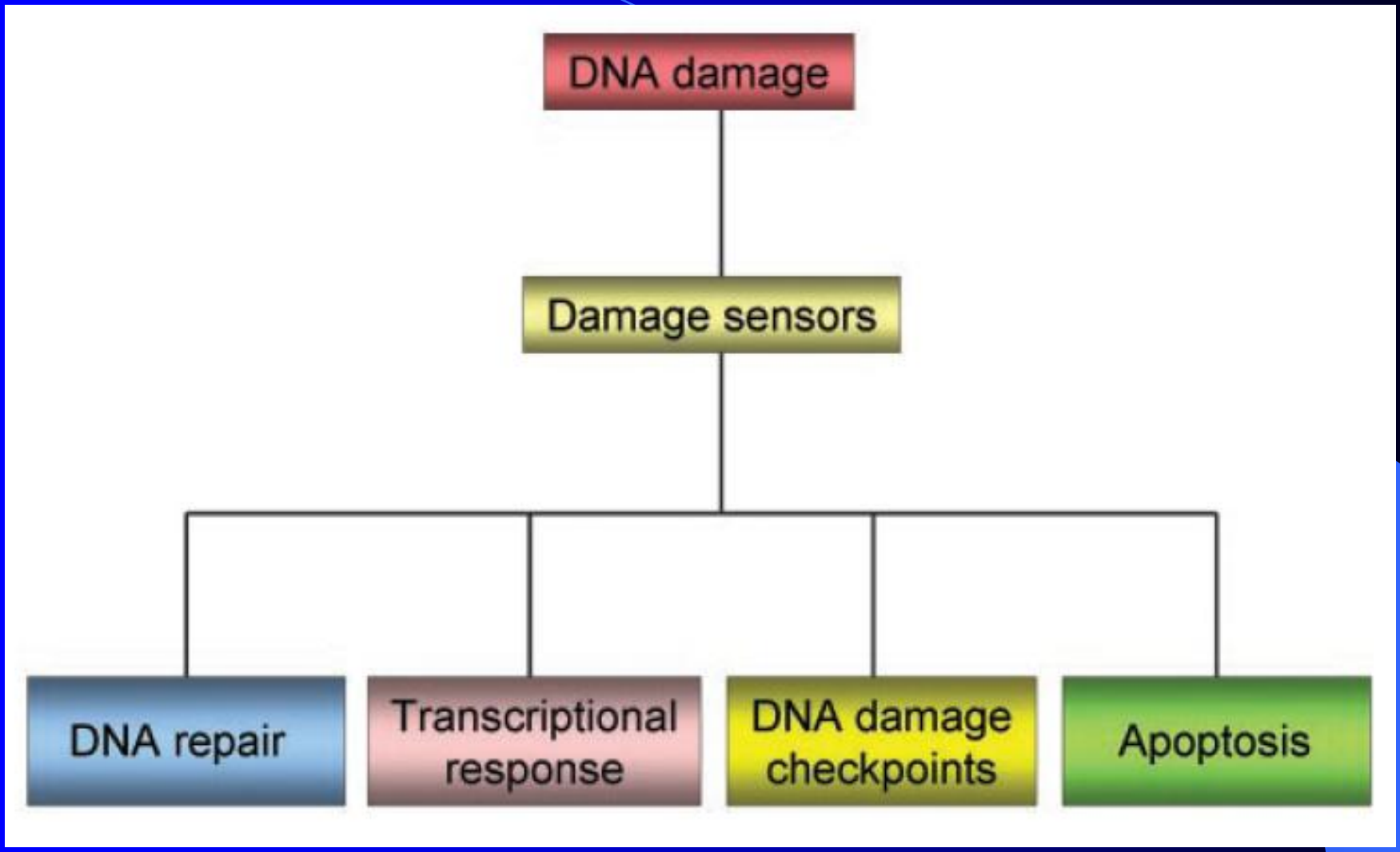
TEL-AML1

Aneuploidy

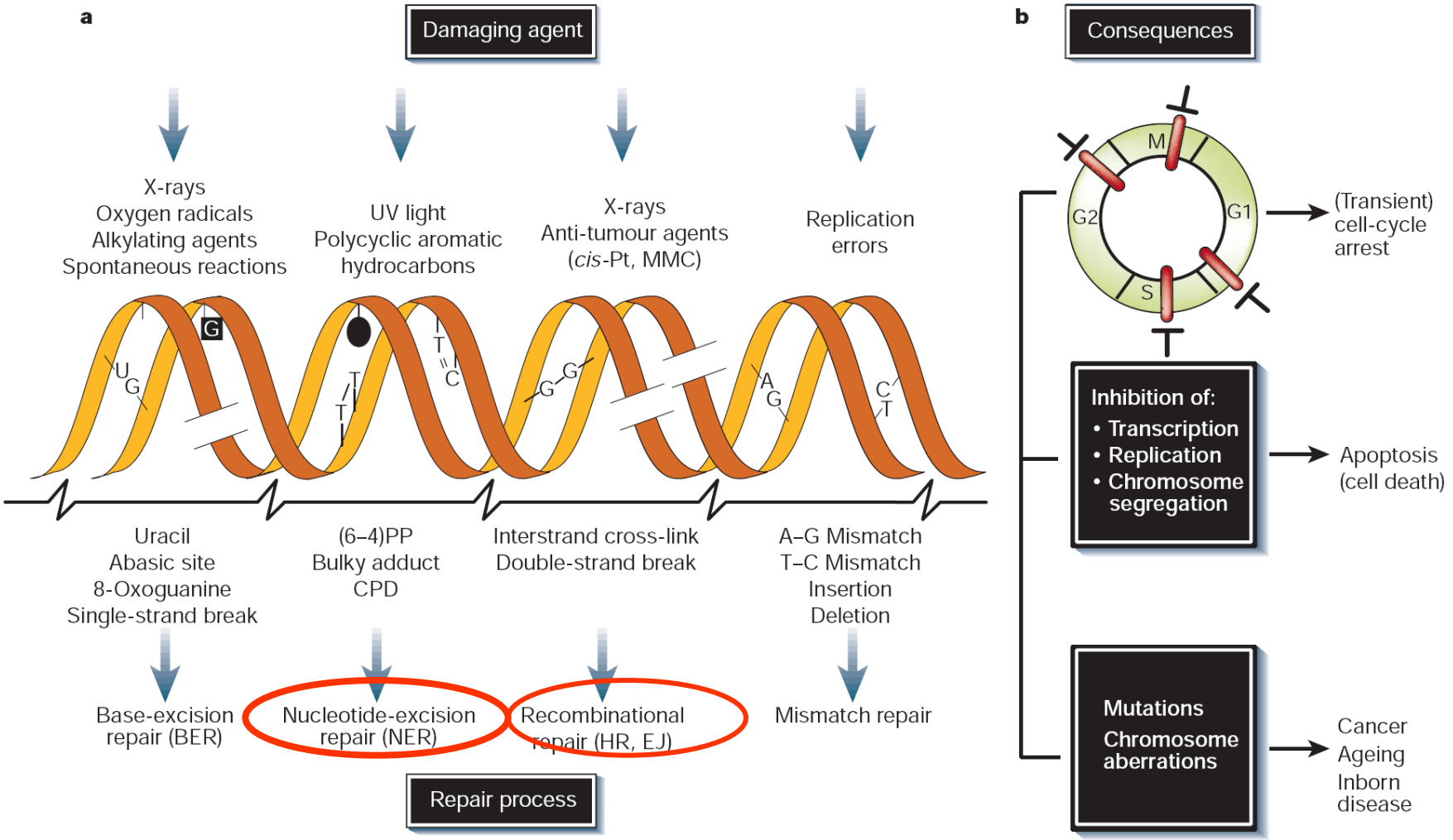
- Down syndrome

DNA repair genes and leukaemia

- Fanconi anaemia
- Others
  - Ataxia telangiectasia
  - Bloom syndrome
  - Nijmegen breakage syndrome
  - Ataxia-Telengiectasia

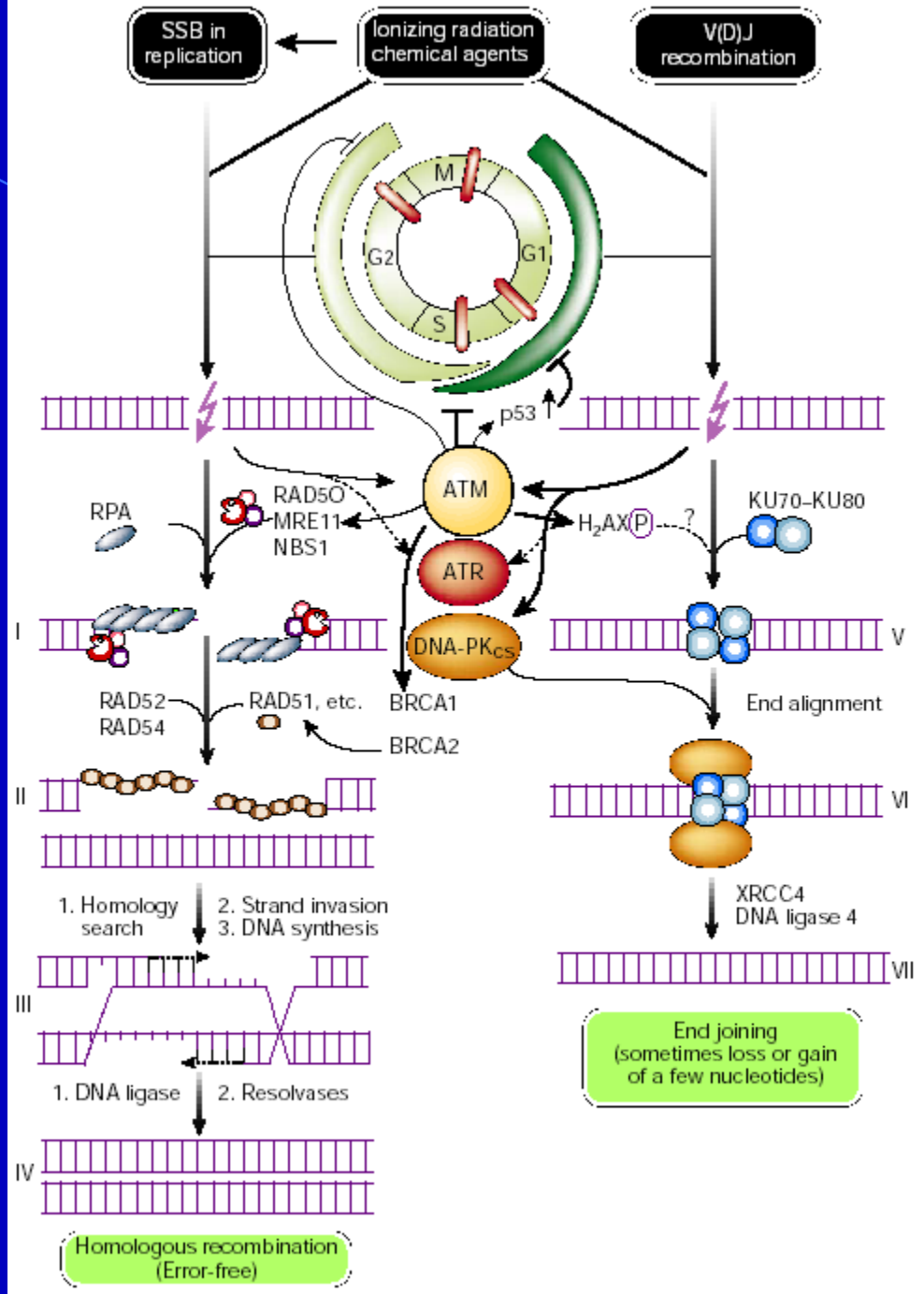

DNA damage
Damage sensors
DNA repair
Transcriptional response
DNA damage checkpoints
Apoptosis

DNA damage and DNA repair



Jan H. J. Hoeijmakers, Nature, 2001; 41: 366-374

Repair of dDNA strand breaks



Jan H. J. Hoeijmakers, Nature, 2001; 41: 366-374

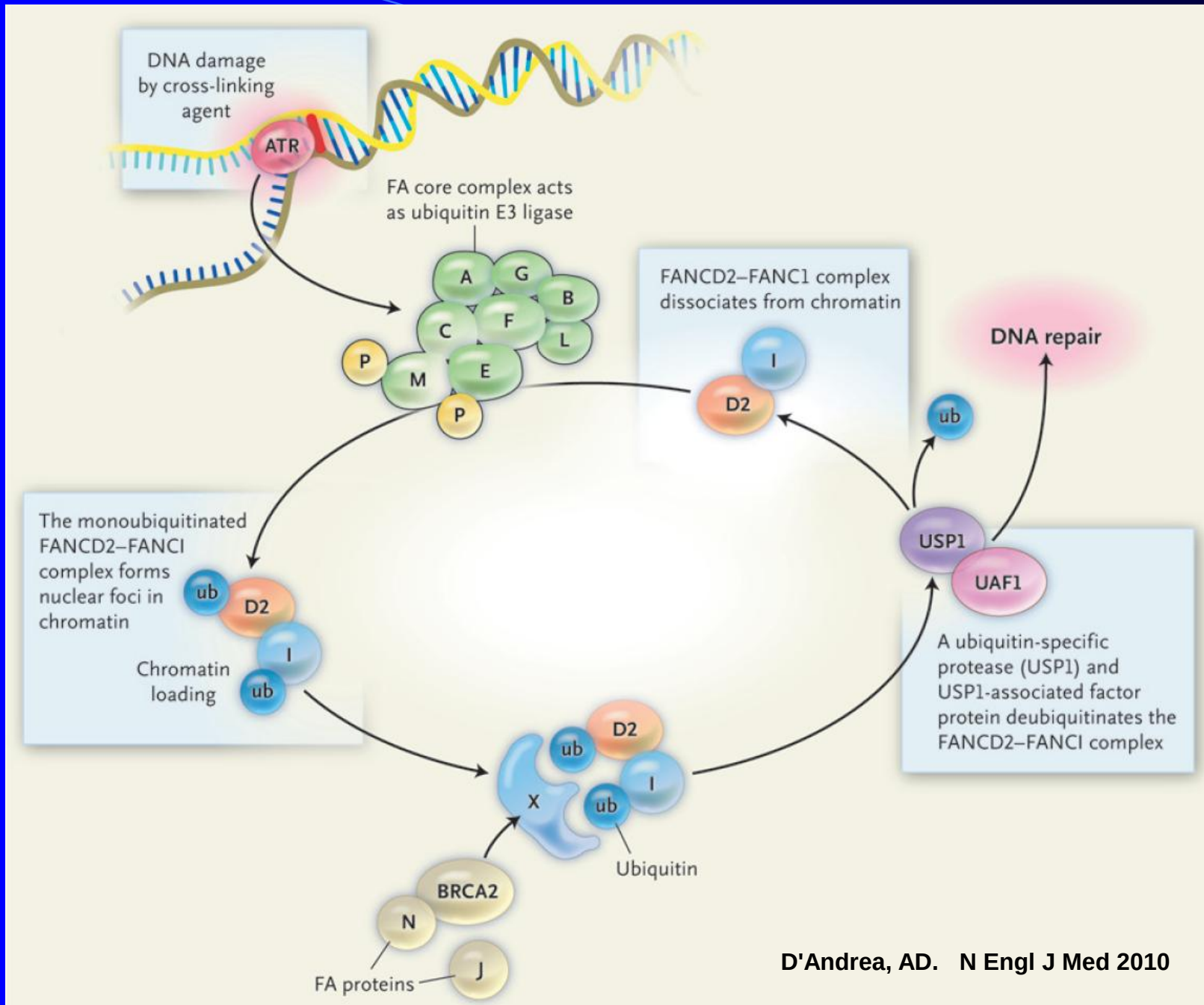
Fanconi anaemia

- autosomal recessive
- congenital malformations
- progressive bone marrow failure
- increased malignancy, including leukaemia and MDS

Table 1. Characteristics of the 13 Genes in Fanconi's Anemia.*

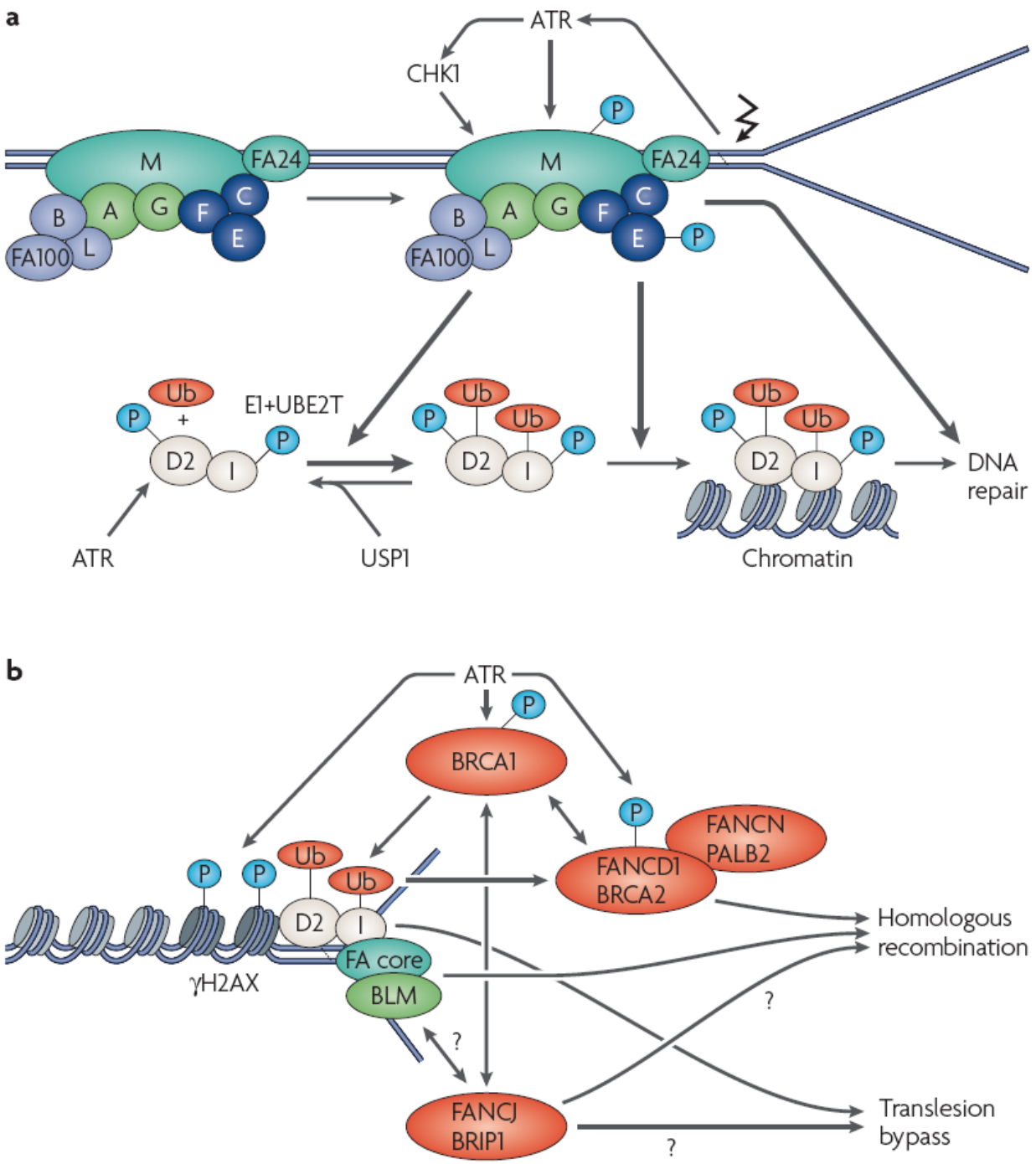
Gene	Prevalence	Position on Chromosome	Size of Protein Product (kD)	Activity
FANCA	66%	16q24.3	163	Core complex member; required for FANCD2–FANCI ubiquitination
FANCB	2%	Xp22.31	95	Core complex member; required for FANCD2–FANCI ubiquitination
FANCC	10%	9q22.3	63	Core complex member; required for FANCD2–FANCI ubiquitination
FANCD1	2%	13q12–13	380	HR mediator; FANCN interactor; functions downstream of ubiquitination
FANCD2	2%	3q25.3	155	Ubiquitinated after DNA damage
FANCE	2%	6p21–22	60	Core complex member; required for FANCD2–FANCI ubiquitination; binds directly to FANCD2
FANCF	2%	11p15	42	Core complex member; required for FANCD2–FANCI ubiquitination
FANCG	9%	9p13	68	Core complex member; required for FANCD2–FANCI ubiquitination
FANCI	<2%	15q25–26	140	Ubiquitinated after DNA damage
FANCJ	<2%	17q22–24	140	Helicase; BRCA1 interactor; functions downstream of ubiquitination
FANCL	0.2%	2p16.1	43	Core complex member; required for FANCD2–FANCI ubiquitination; ubiquitin-ligase activity
FANCM	0.2%	14q21.3	250	Helicase; localizes the core complex to DNA; required for FANCD2–FANCI ubiquitination
FANCN	<2%	16p12.1	140	FANCD1 and BRCA1 interactor; functions downstream of ubiquitination

D'Andrea, AD. N Engl J Med 2010



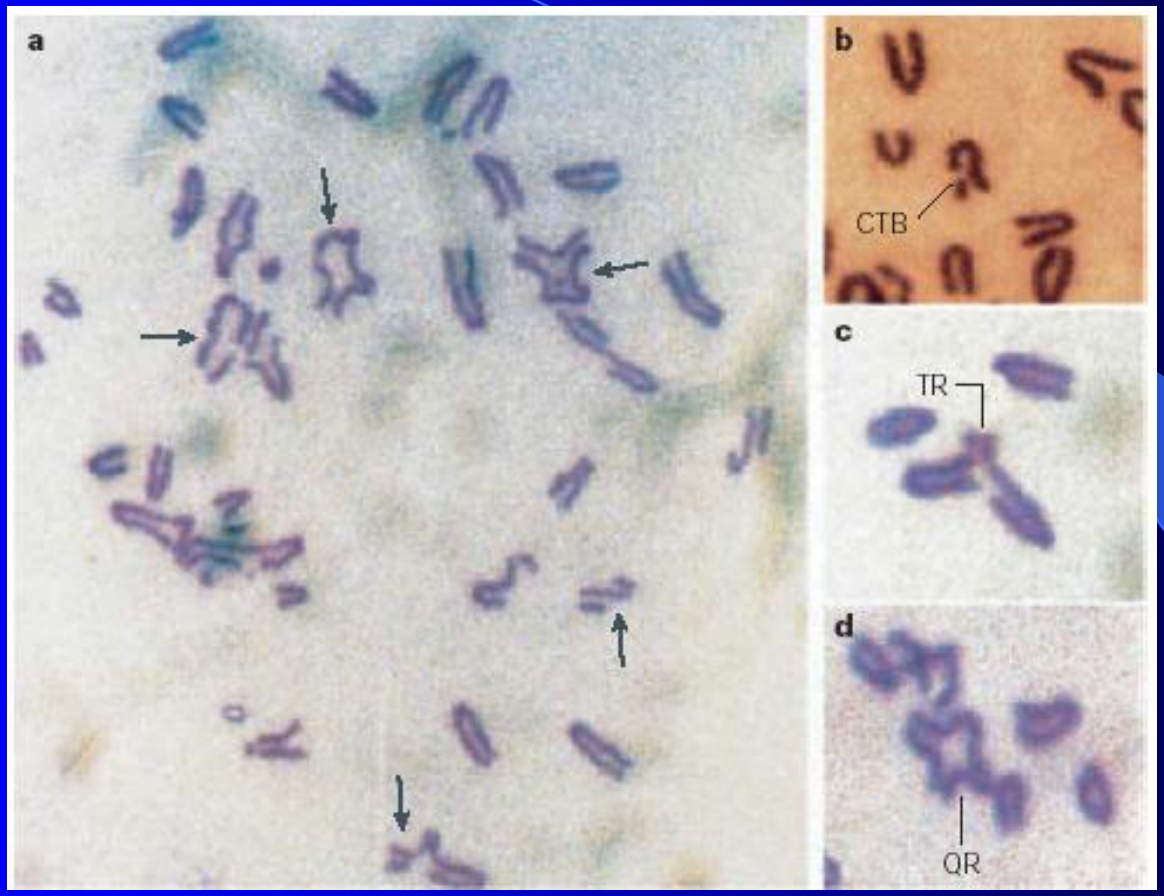
D'Andrea, AD. N Engl J Med 2010

FA genes and DNA repair



Wang W, Nat Rev Genet. 2007 (10):735-48

Fanconi anaemia



increased sensitivity to DNA damage by cross-linking agents eg diepoxybutane, MMC

Fanconi anaemia

- Haematological abnormalities
  - IFAR study 1994, 388 pts
  - Presentation abnormalities
  - 85% haem abnormalities, median age 7 yrs

Thrombocytopenia	38%
Pancytopenia	53%
MDS/AML	5%
Anaemia/neutropenia	2%

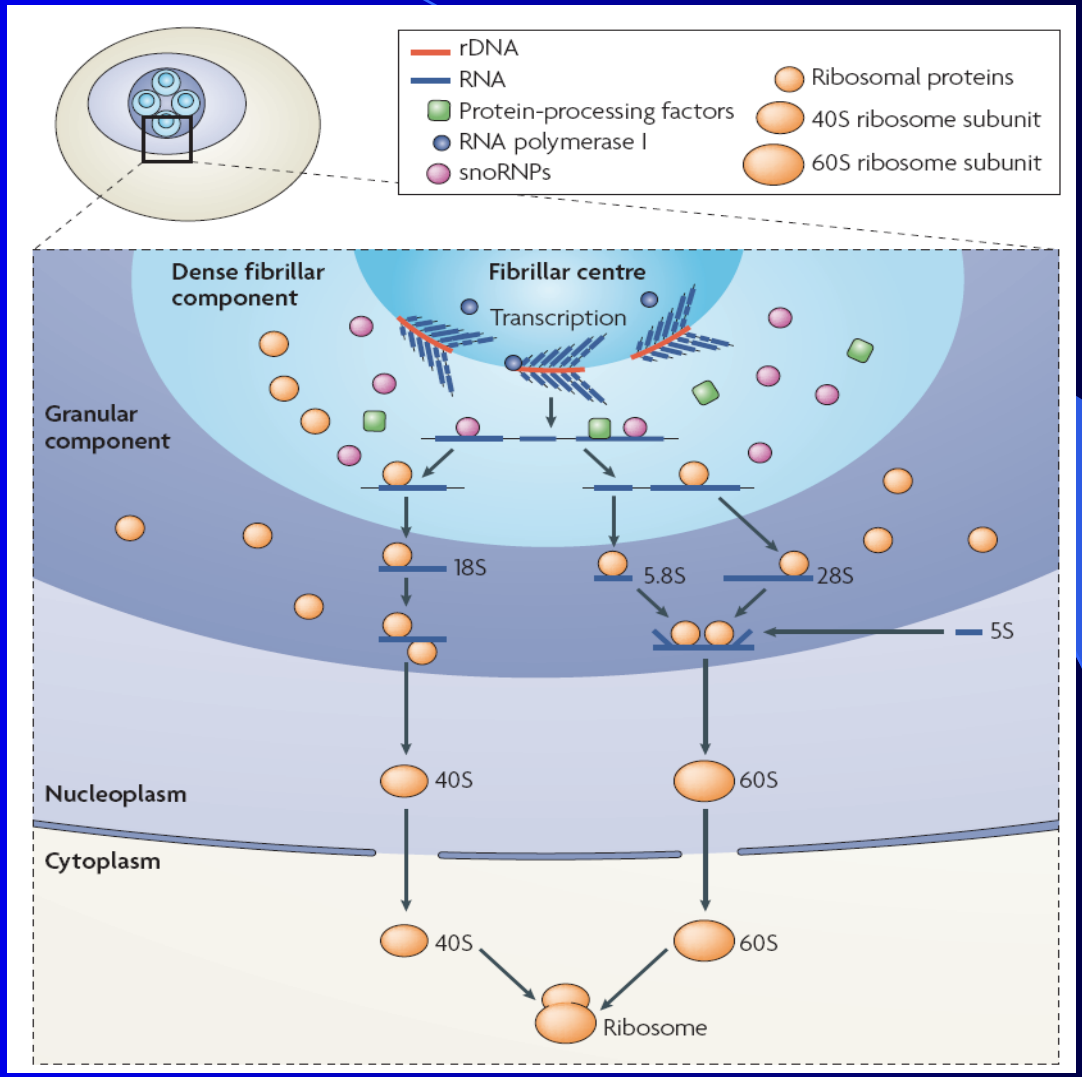
  - **Actuarial risk of MDS/AML by 40yrs: 52%**

- Epigenetic silencing of FA genes in sporadic cancers and leukaemias

Ribosome biogenesis and ribosomopathies

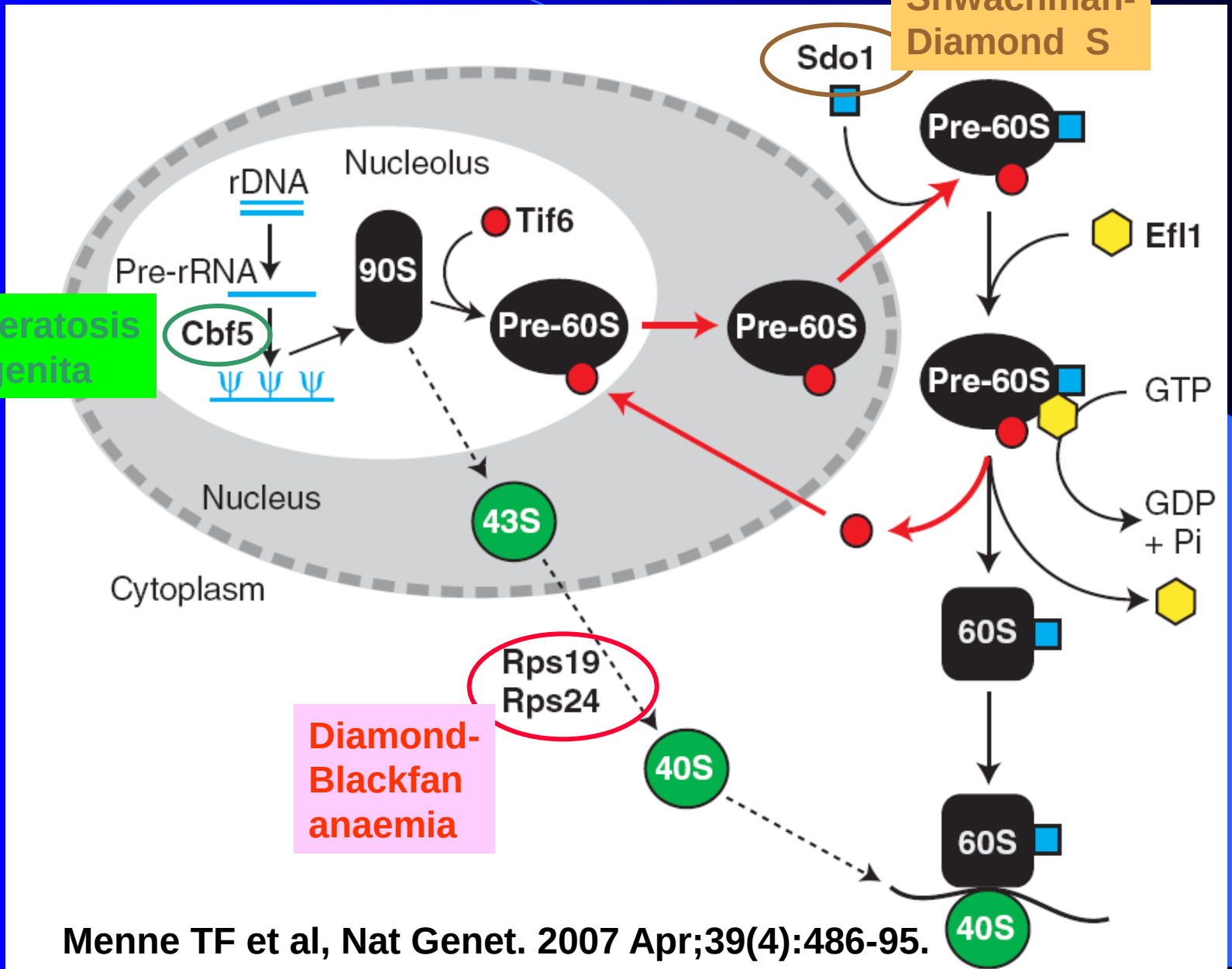
- **Ribosomes**: ribonucleoproteins
  - rRNA: splice products of same precursor RNA
  - Ribosomal proteins (80 genes)
  - Small and large subunits
- **Nucleolus**: the ribosome biogenesis factory

Ribosome biogenesis and ribosomopathies



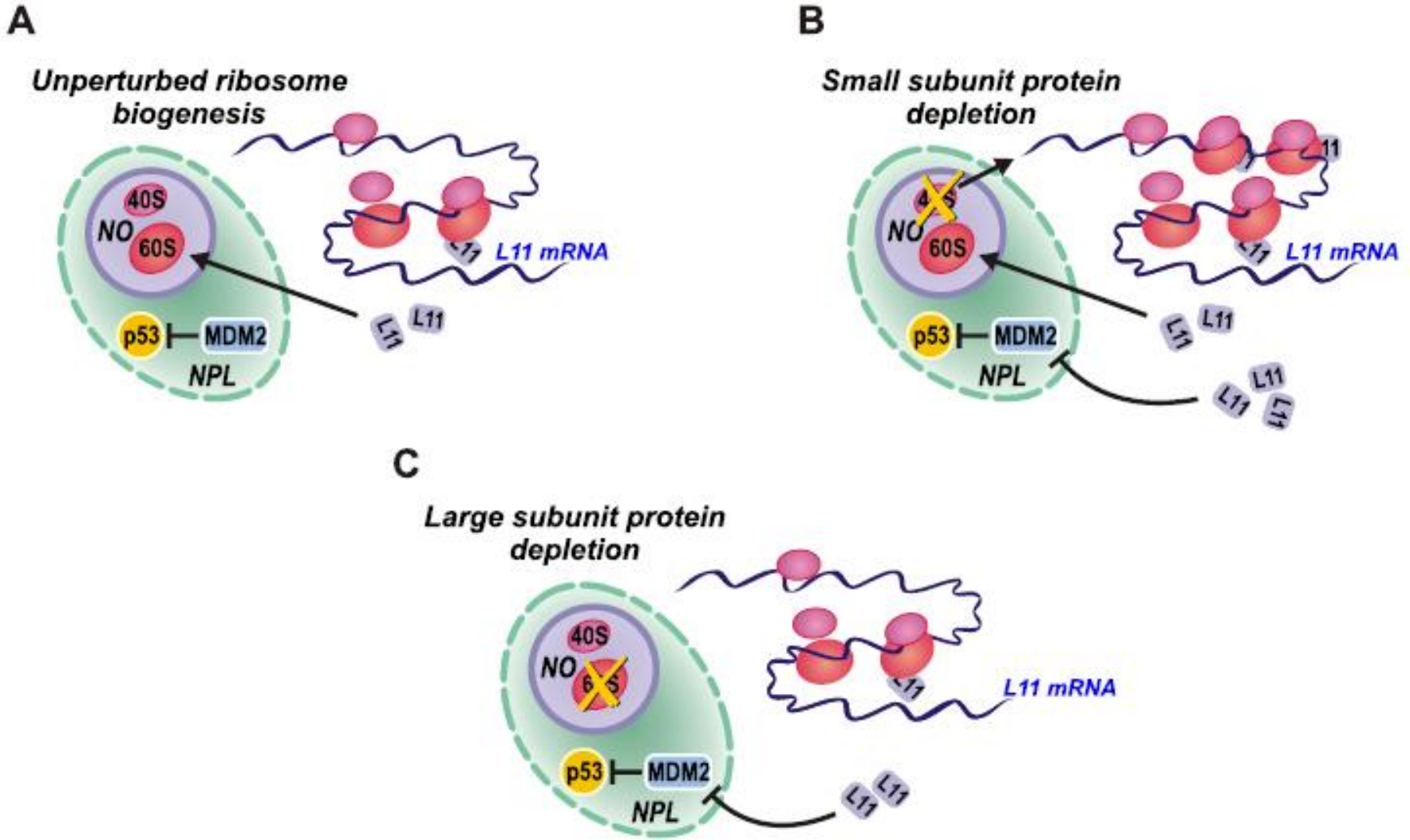
François-Michel Boisvert et al,
Nat Rev Mol Cell Biol. 2007 8(7):574-85

Ribosome biogenesis in the yeast



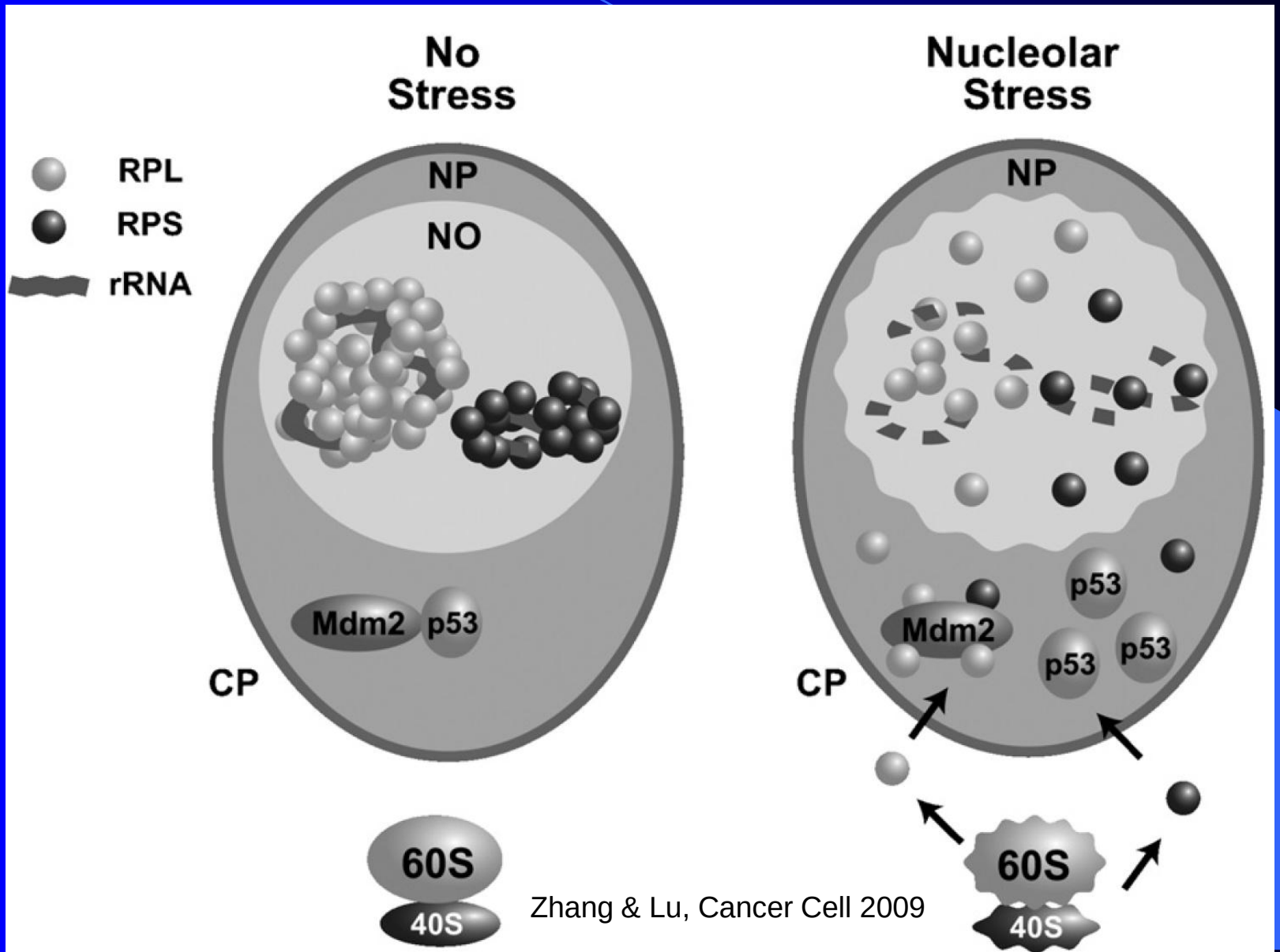
Menne TF et al, Nat Genet. 2007 Apr;39(4):486-95.

Ribosomal proteins, MDM2-p53 and Nucleolar Stress



Fumagalli and Thomas, Semin Hematol 2011

Ribosomal proteins, MDM2-p53 and Nucleolar Stress



Zhang & Lu, Cancer Cell 2009

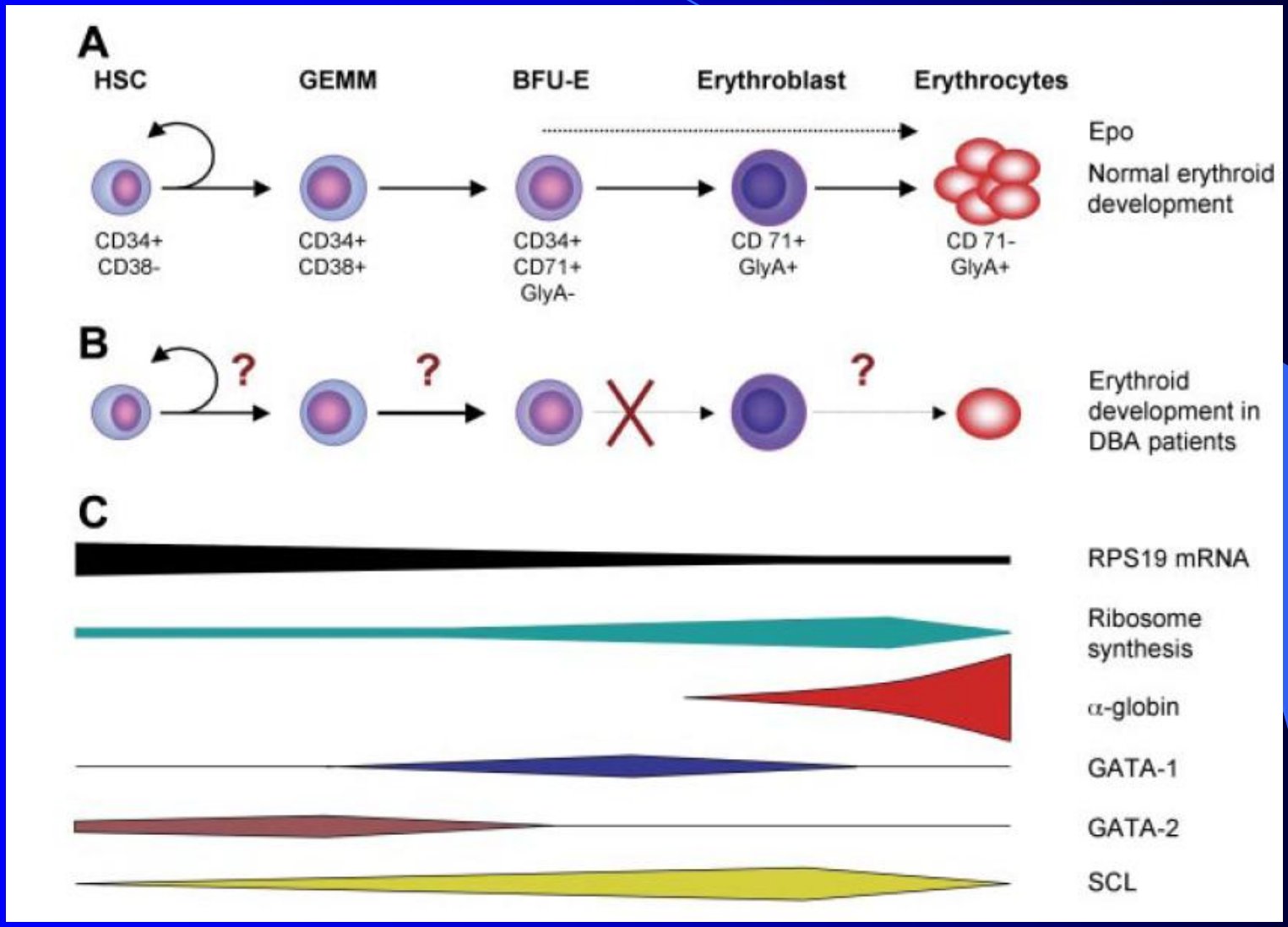
Diamond-Blackfan anaemia

- Early infancy
- Anaemia, macrocytosis, low retics
- Red cell aplasia with a paucity of erythroid precursors
- Red cell adenosine deaminase (ADA) activity elevated
- Associated congenital anomalies
- Hb may improve upon treatment with corticosteroids
- Spontaneous remission in a subset of patients
- Increased risk of AML and osteosarcomas
- Aplastic anemia in some patients

Molecular genetics of DBA

- Heterozygous mutations: AD
  -RPS19 (25%)
  -RPS24 (2%)
  -RPL35A
  -RPS17 (<2%)
  -RPL5 & 11
- Haploinsufficiency
- Many cases arise spontaneously
- Yeast RPS19 is required for maturation of the 18S rRNA
- Defective ribosome biogenesis is toxic to cells

Erythropoiesis and Cellular defect in DBA

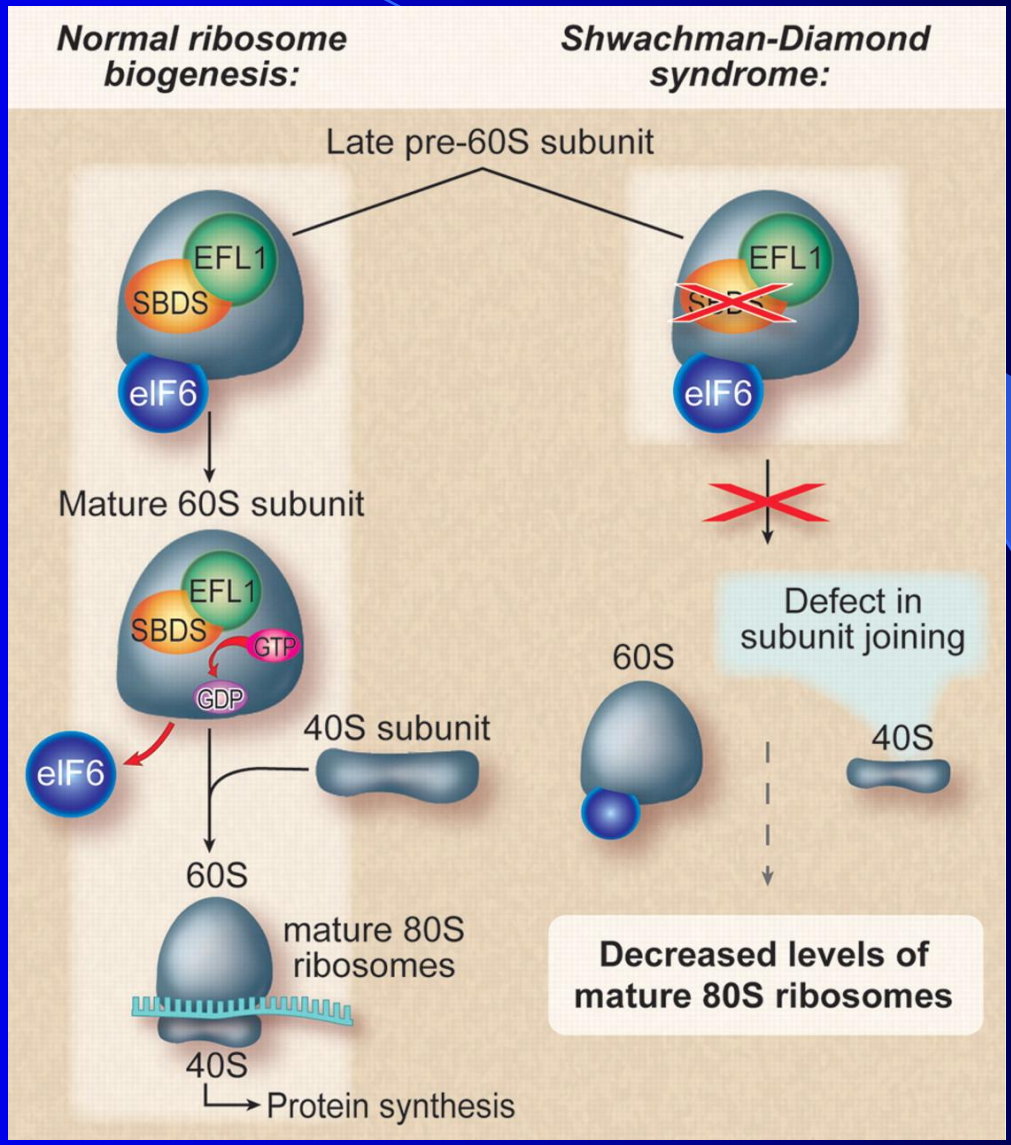


Johan Flygare and Stefan Karlsson, Blood, 2007 109: 3152-3154

Shwachman-Diamond syndrome

- **Mutations in SBDS gene; autosomal dominant**
- **Bone marrow failure**
  -Neutropenia most common
  -Cytopenias may be intermittent
- **Exocrine Pancreatic insufficiency**
  -Early infancy
  -Steatorrhea and failure to thrive
  -Function may improves with age
- metaphyseal dysostosis
- **Increased risk of developing aplastic anaemia and MDS/AML**

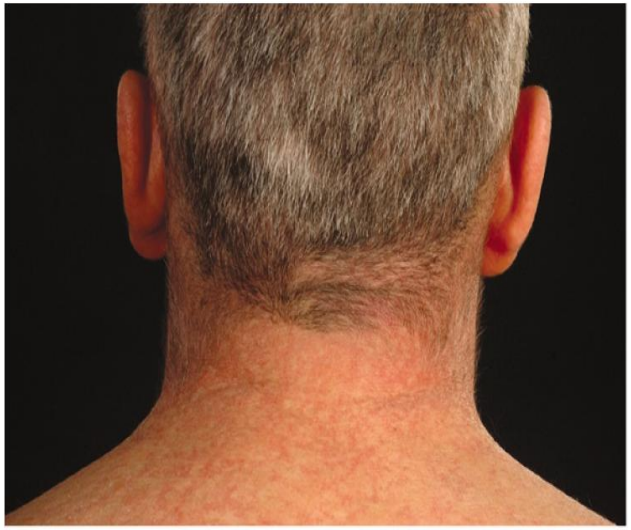
Proposed mechanism for the cellular consequences of mutations in Shwachman-Bodian-Diamond syndrome

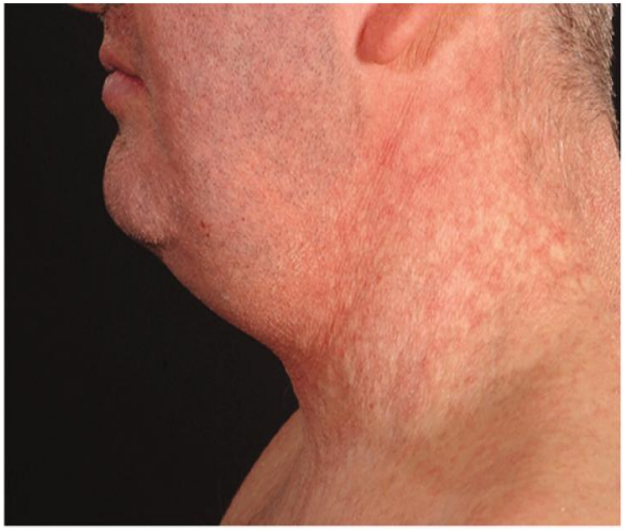


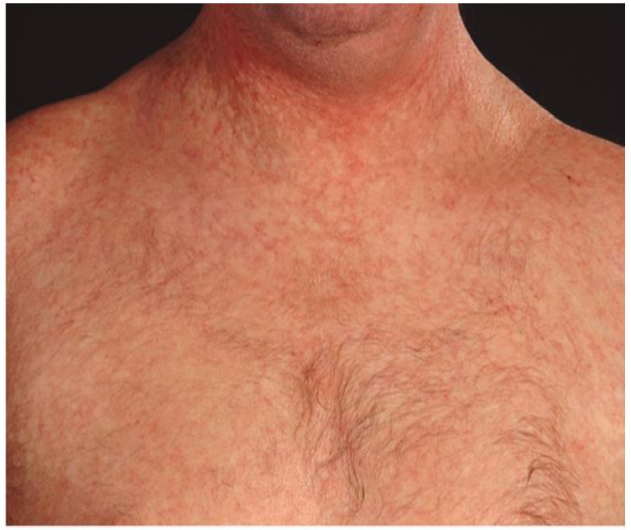
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Narla A , Ebert B L Blood 2011;118:4300-4301

Dyskeratosis congenita







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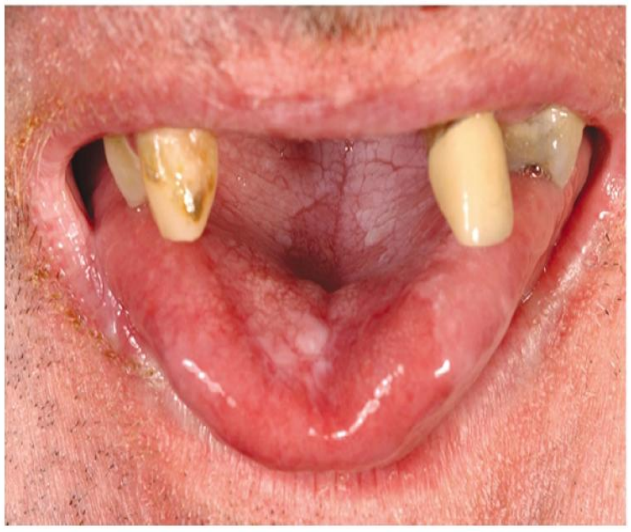

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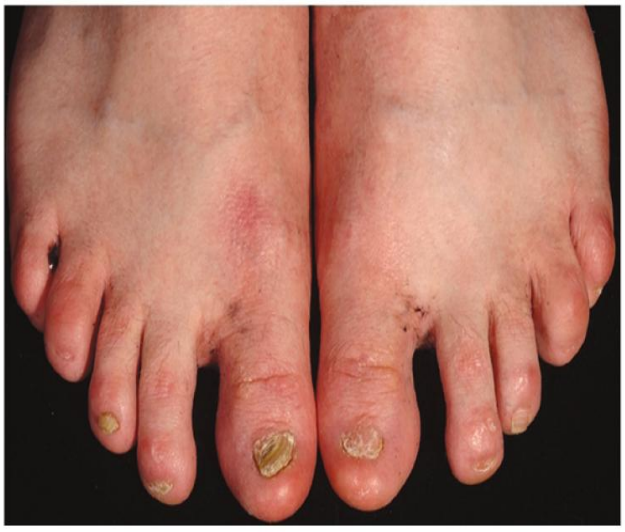

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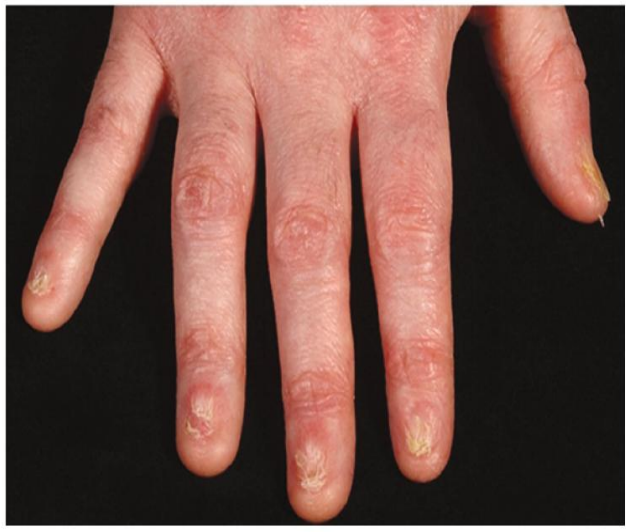


Table 1. Summary of clinical features associated with dyskeratosis congenita

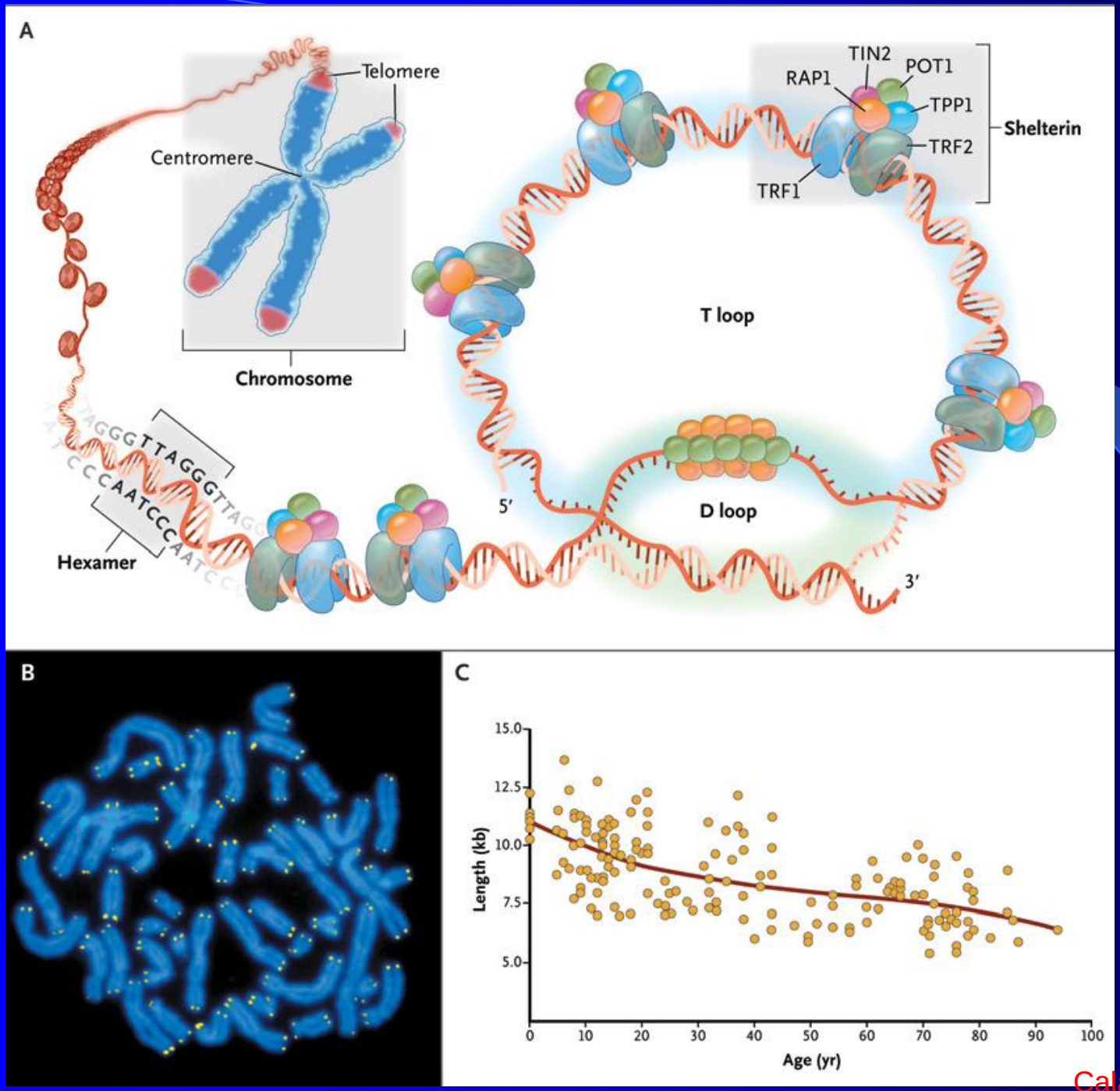
Key clinical features	Percentage of patients affected
Main mucocutaneous triad	
Skin pigmentation	89%
Nail dystrophy	88%
Mucosal leukoplakia	78%
Additional clinical features[a]	
Bone marrow failure	85.5%
Pulmonary disease	20.3%
Premature loss of teeth	16.9%
Premature hair loss/greying	16.1%
Cancer	9.8%

[a] There are also many other somatic abnormalities in any given patient.

Marrone A and Dokal I. Expert Rev Mol Med. 2004 Dec 20;6(26):1-23.

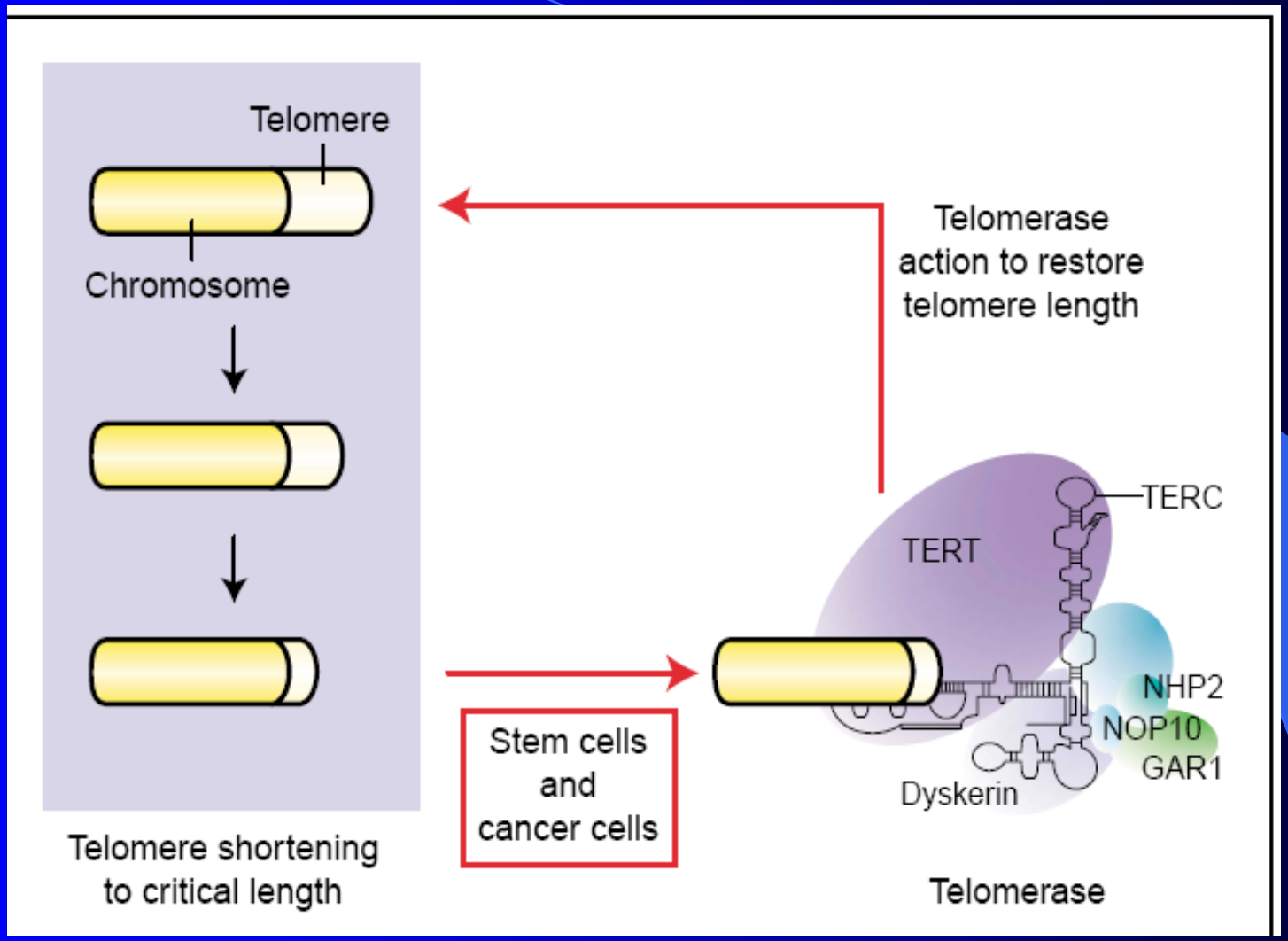
Telomeres

- Stabilize the chromosome ends to prevent their shortening during replication,
- protect chromosome ends from DNA damage-induced breaks
- Inhibit end-to-end fusions
- 6-basepair repeated sequences (TTAGGG)
- Shorten with each cell division; maintained by the telomerase enzyme



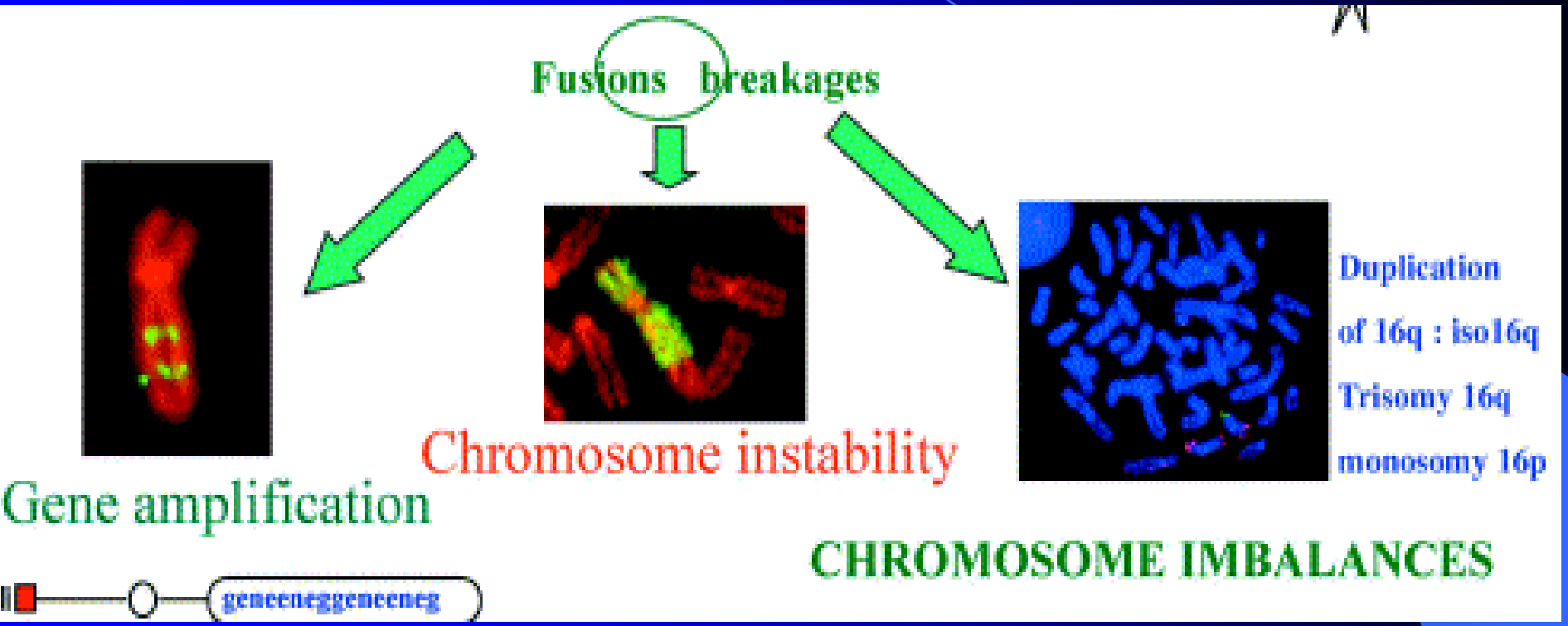
Calado and Young NEJM 2009

Telomere maintenance



Marrone A and Dokal I. Expert Rev Mol Med. 2004 Dec 20;6(26):1-23.

Telomere maintenance failure

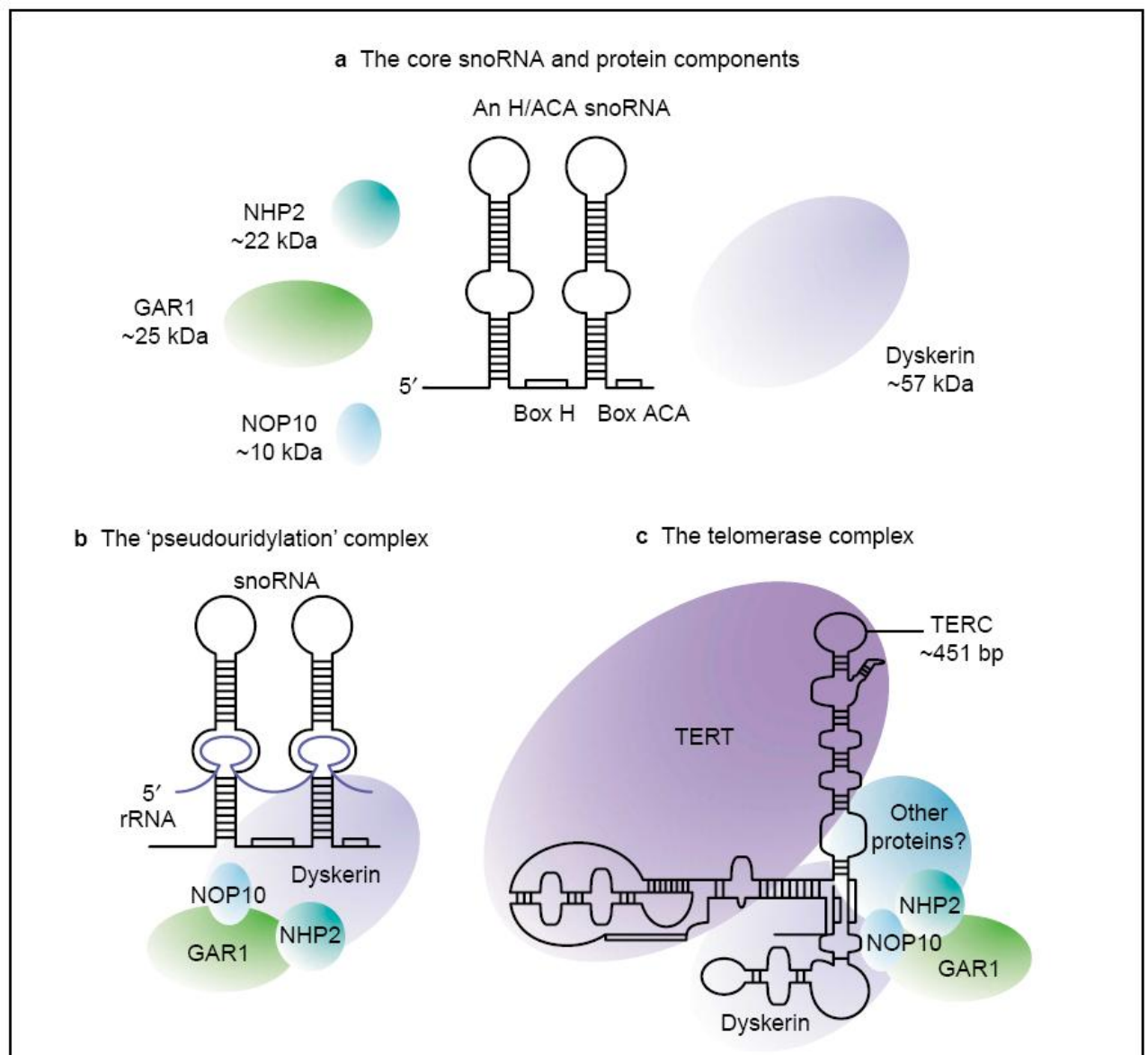


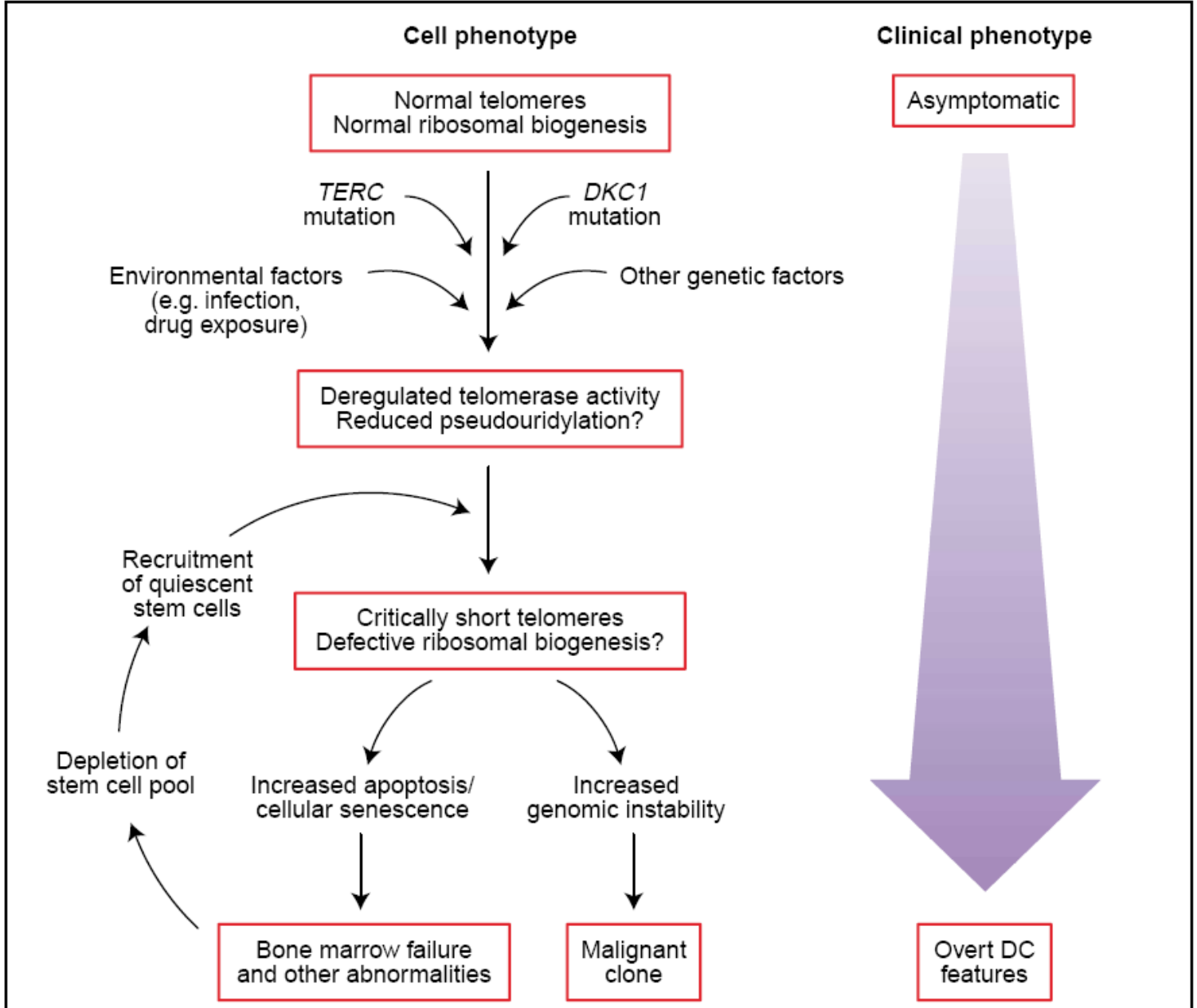
Summary of dyskeratosis congenita subtypes

DC subtype	frequency	phenotype	Chromos location	RNA/protein product
X-linked DC	35%	DC, HH	Xq28	Dyskerin
AD-DC	5%	DC, AA, MDS	3q26	TERC
AR-DC	<5%	DC, HH	5p15	TERT
Uncharacterised	60%	DC, HH	Unknown	Unknown

AA, aplastic anaemia; AD, autosomal dominant; AR, autosomal recessive; DC, dyskeratosis congenita;
HH, **Hoyeraal–Hreidarsson syndrome**; MDS, myelodysplastic syndrome; TERC, RNA component of telomerase.

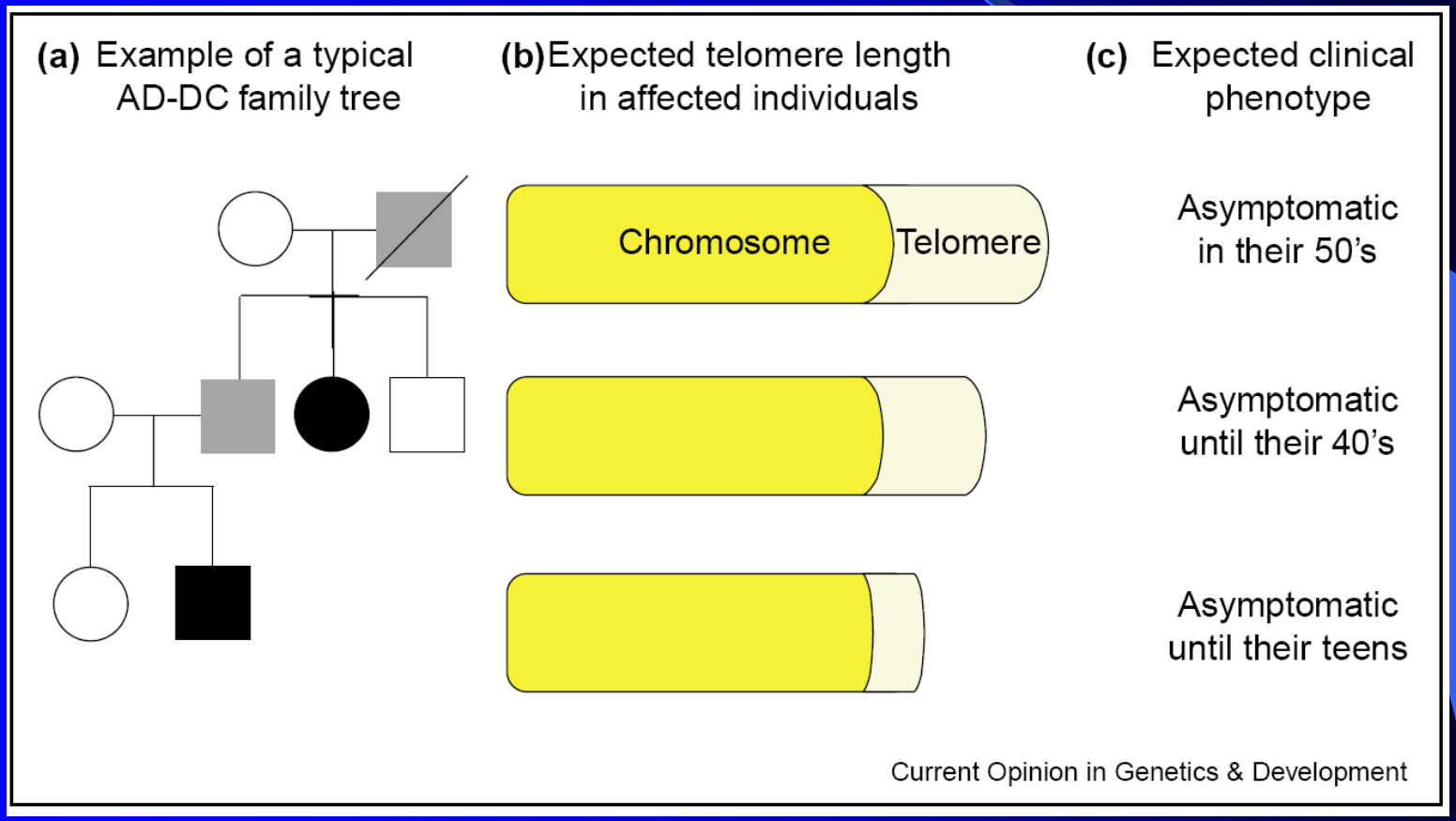
DC: telomere maintenance and ribosome biogenesis





Proposed pathogenesis model for dyskeratosis congenita

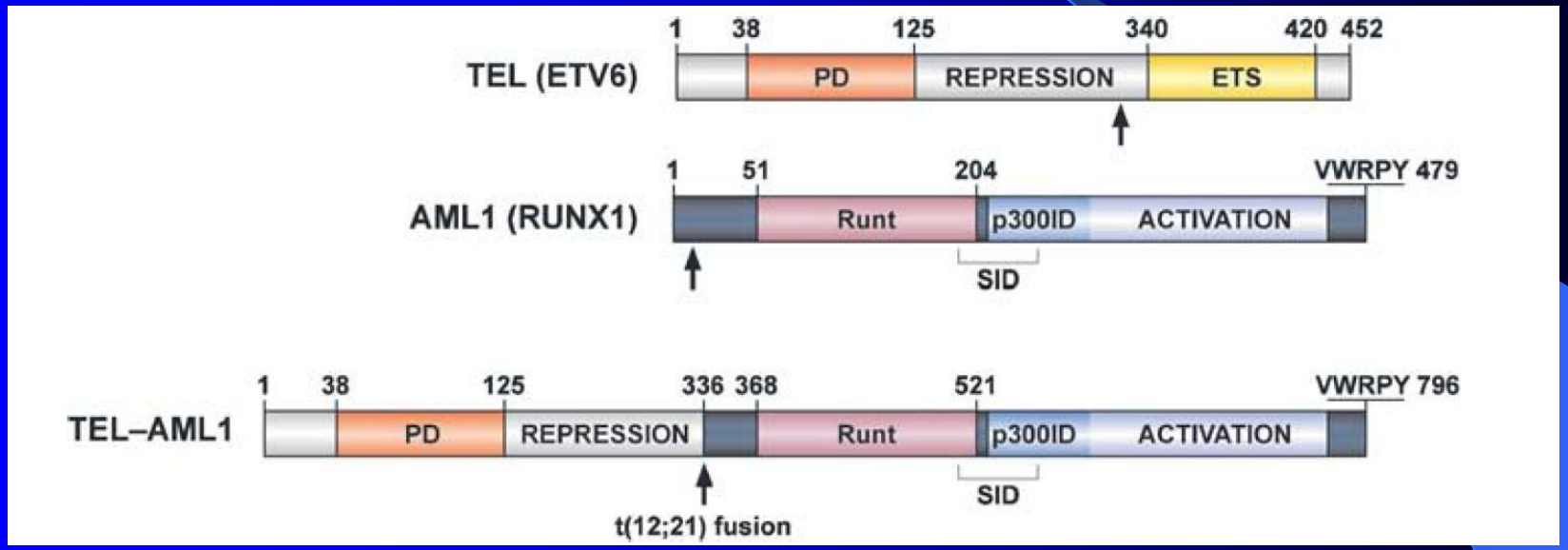
DC and Telomere maintenance: Anticipation



Fetal origin of childhood leukaemia

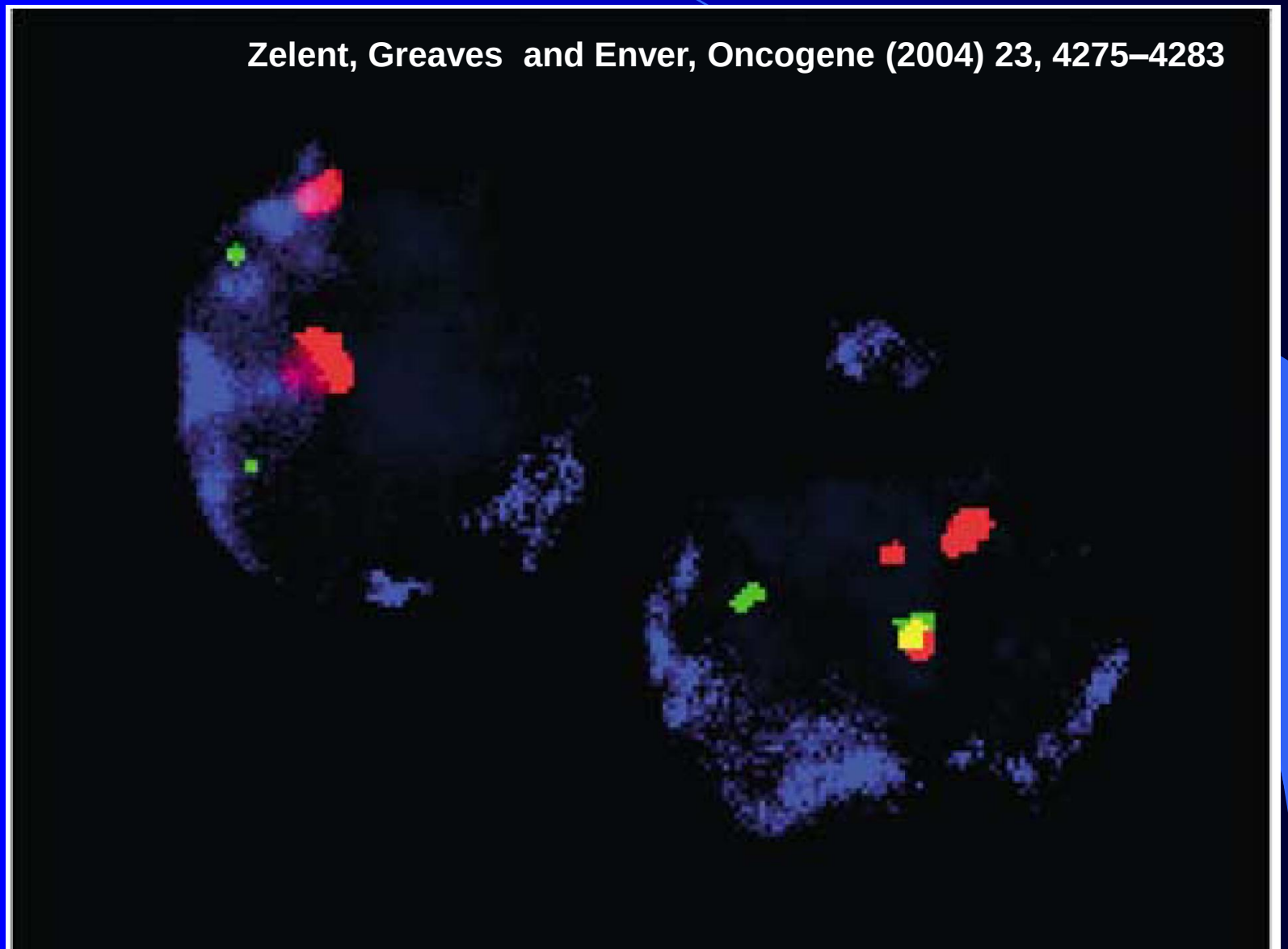
- chromosome translocations and covert leukaemic clones generated during normal fetal development
- subsequent events may be required to generate leukaemia
- t(12;21) childhood B ALL; TEL-AML (RUNX1) fusion
  -arises in utero in 1% of infants
  -only 1% develop leukaemia

Genetics of TEL-AML1

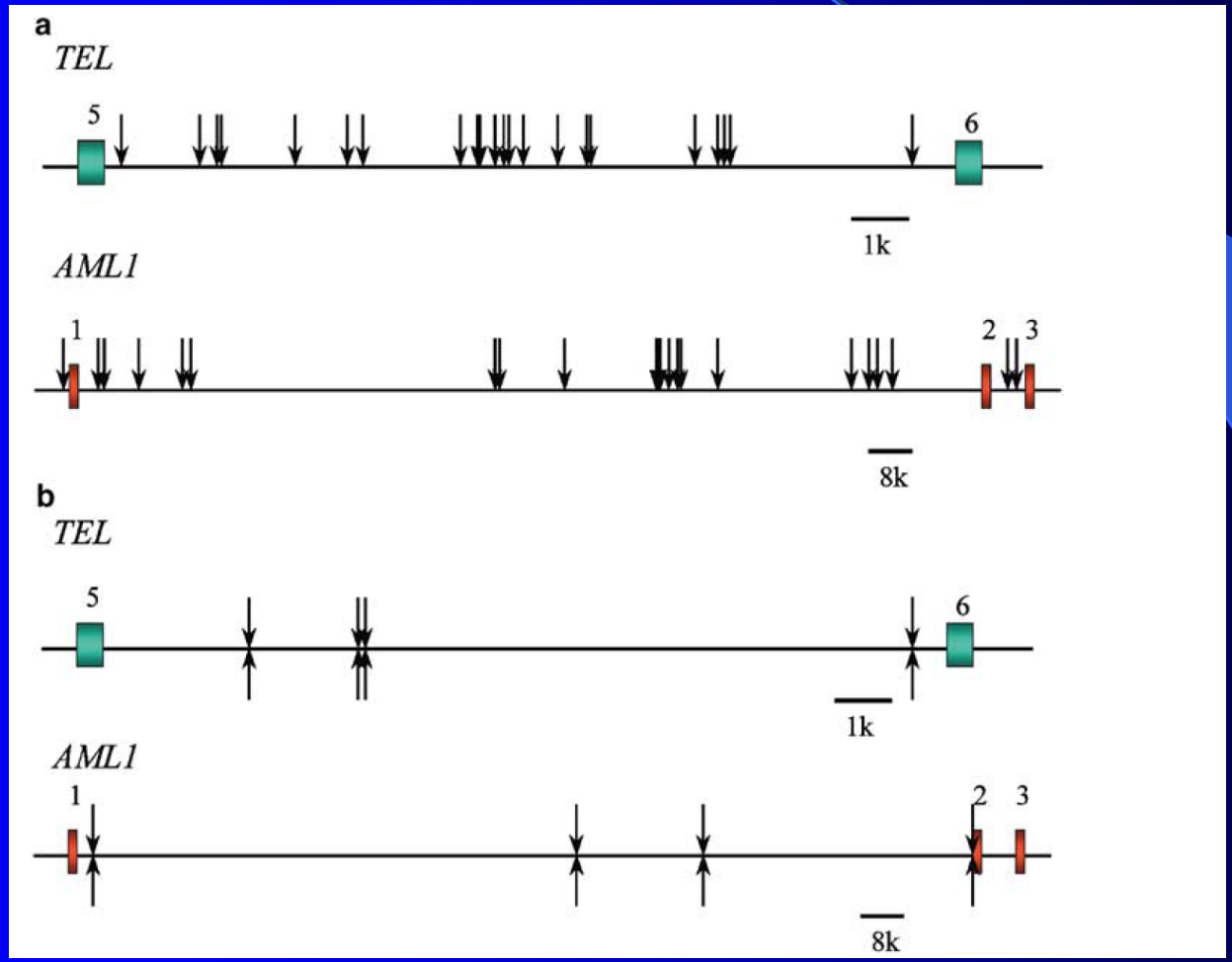


Zelent, Greaves and Enver, Oncogene (2004) 23, 4275–4283

TEL-AML1 fusion detected by FISH

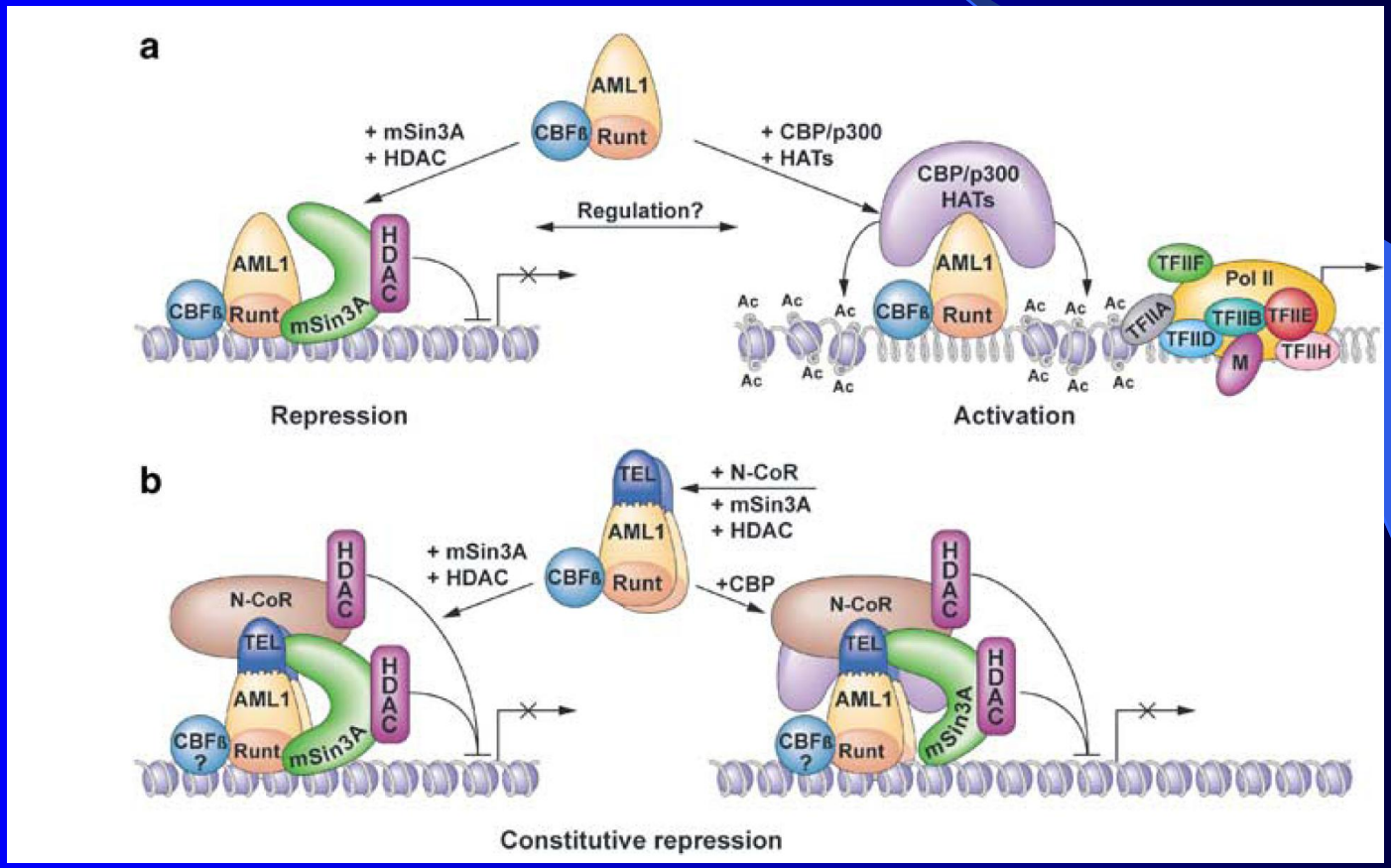


Fetal origin of childhood ALL: Same breakpoints in monozygotic twin siblings



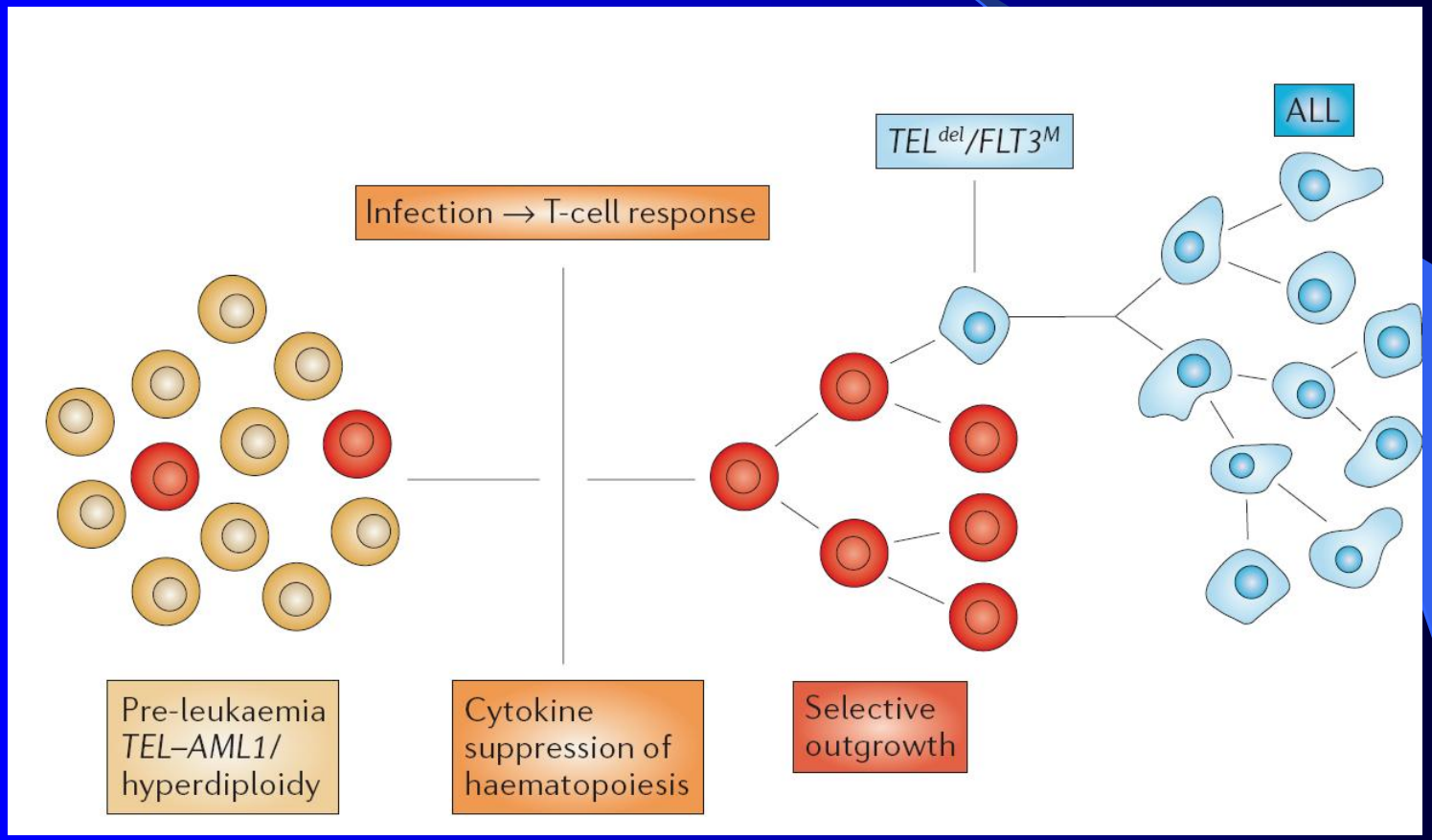
Zelent, Greaves and Enver, Oncogene (2004) 23, 4275–4283

Molecular pathogenesis of TEL-AML1 leukaemia



Zelent, Greaves and Enver, Oncogene (2004) 23, 4275–4283

In utero TEL-AML1 only the first step to leukaemia



Greaves M, Nat Rev Cancer. 2006 Mar;6(3):193-203