Bone marrow failure syndromes – not only for pediatric hematologists

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20/11/2024

Crossover between pediatrics and adult medicine

- One decade ago…

  "The inherited bone marrow failure syndromes are a diverse group of genetic diseases associated with inadequate production of one or more blood cell lineages…the management of these disorders was once the exclusive domain of pediatric sub-specialists but increasingly physicians who care for adults are being called upon to diagnose or treat these conditions."

REVIEW ARTICLE

Inherited bone marrow failure syndromes in adolescents and young adults

David B. Wilson[1], Daniel C. Link[2], Philip J. Mason[3] & Monica Bessler[3,4]

Annals of Medicine, 2014; 46: 353–363

Crossover between pediatrics and adult medicine

Now what have we learned…

Studies on MDS with germline predisposition have provided unique insights into the pathogenesis of hematologic malignancies and mechanisms of somatic genetic rescue *vs.* disease progression. Increasing recognition in adult patients will inform medical management and may provide potential opportunities for the prevention or interception of malignancy.

Lessons From Pediatric MDS: Approaches to Germline Predisposition to Hematologic Malignancies

*Serine Avagyan and Akiko Shimamura**

Dana-Farber/Boston Children's Hospital Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, United States

Frontiers in Oncology March 2022

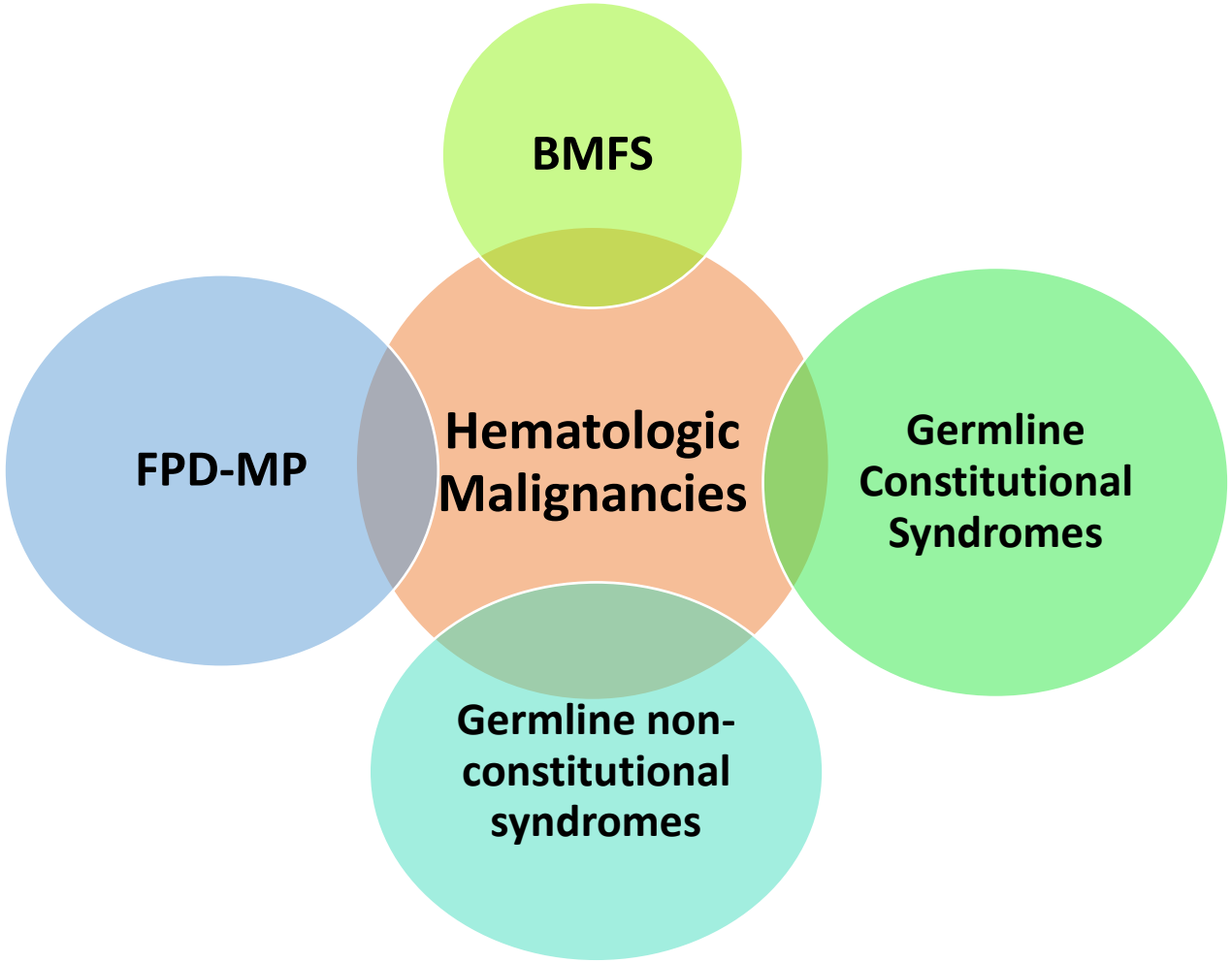
The International Consensus Classification (ICC) of hematologic neoplasms with germline predisposition, pediatric myelodysplastic syndrome, and juvenile myelomonocytic leukemia

Martina Rudelius[1] · Olga K. Weinberg[2] · Charlotte M. Niemeyer[3,4] · Akiko Shimamura[5] · Katherine R. Calvo[6]

Virchows Archiv (2023) 482:113–130

Germline predisposition should be considered in patients with a history of multiple cancers, first- or second-degree relative(s) with hematologic neoplasms or solid tumors, immunodeficiency, thrombocytopenia or bleeding disorder preceding myeloid malignancy, or physical stigmata associated with predisposition syndromes. While many germline mutations are associated with neoplasia that develops at a young age, malignancy can occur at any age, and even in the elderly population for some genes including *DDX41* or *TERT*. Germline mutations are often associated with family history of malignancy; however, variable penetrance and expressivity can cloud recognition of the familial nature of disease.

How do these diseases meet?



BMFS=bone marrow failure syndromes

FPD-MP=familial platelet disorders with malignancy predisposition

What are we talking about? - Classification

Bone Marrow Failure Syndromes

Multilineage Bone Marrow Failure

- Fanconi Anemia (FA)
- Dyskeratosis Congenita (DC)

Single Hematopoietic Lineage

- Diamond-Blackfan Anemia (DBA)
- Severe Congenital Neutropenia (SCN)
- Shwachman-Diamond syndrome (SDS)
- Congenital Amegakaryocytic Thrombocytopenia (CAMT)
- Thrombocytopenia and Absent Radii (TAR)

Familial platelet disorder with associated hematologic malignancy

- Runx1
- ANKD26
- ETV6

Germline constitutional disorder with predisposition to hematologic malignancy

- GATA2 haploinsufficiency
- SAMD9
- SAMD9-L

Inherited Bone Marrow Failures

Congenital anomalies

Bone marrow failure -insidious development of aplasia

If involves RBC- reticulopenia

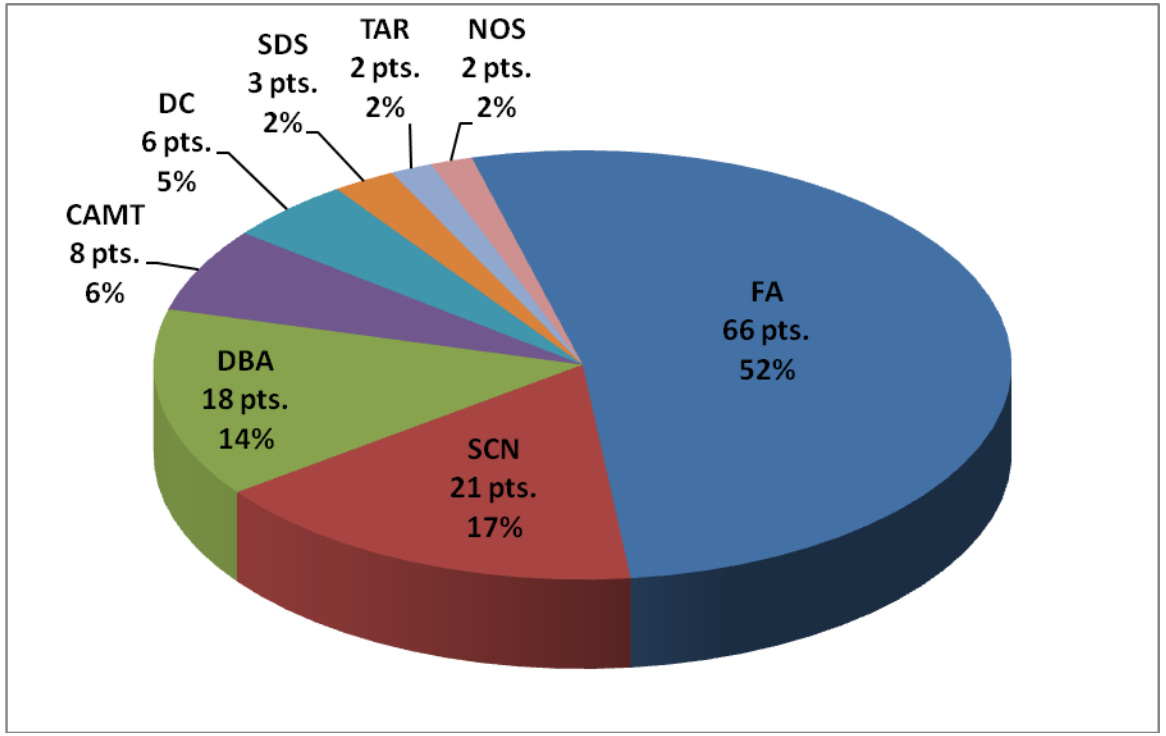
Stress erythropoiesis

Macrocytosis (MCV >90fl), HbF ↑,

i-antigen ↑ (immature RBC)

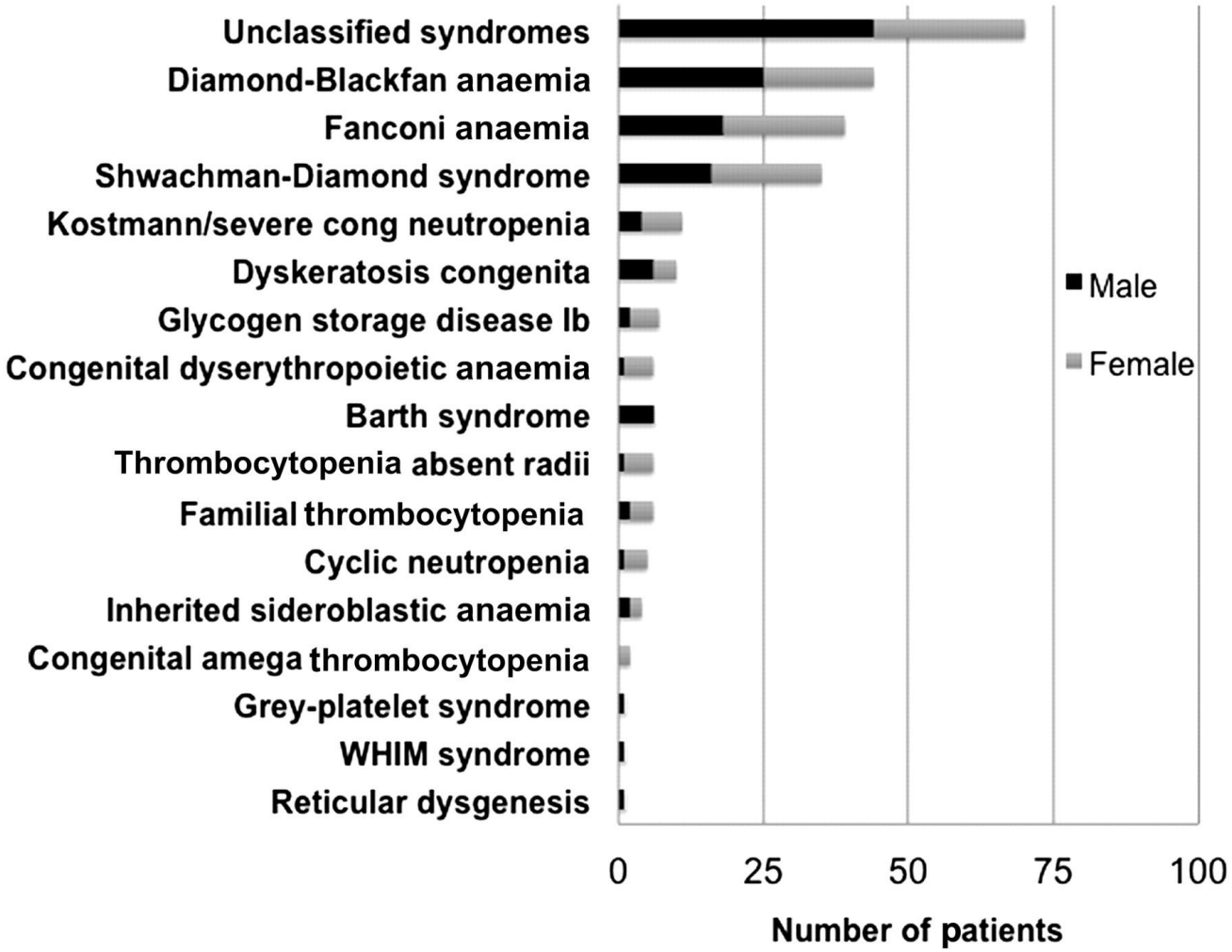
Tendency to malignancies

Israeli Inherited Bone Marrow Failure Registry (n=126)



Tamary et al, Haematologica. 2010

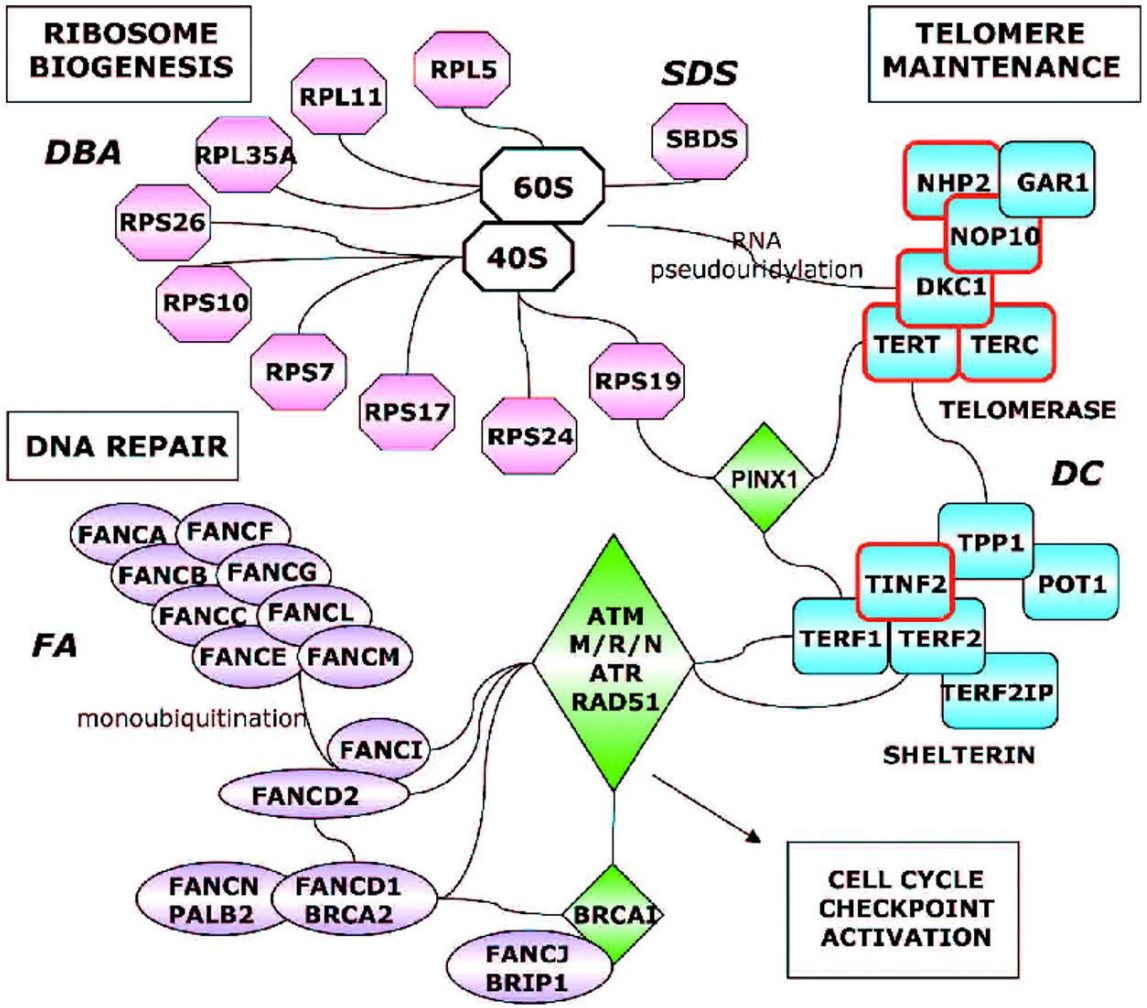
Distribution of primary inherited bone marrow failure syndromes in this study.



E Tsangaris et al. J Med Genet 2011;48:618-628

Genetic analysis of inherited bone marrow failure syndromes from one prospective, comprehensive and population-based cohort and identification of novel mutations

Interconnected pathways that cause bone marrow failure.



Inderjeet Dokal, and Tom Vulliamy Haematologica 2010;95:1236-1240

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Characteristics of the inherited bone marrow failure syndromes.

	FA	DC	SDS	DBA	CAMT	SCN
Inheritance pattern	AR, XLR AD	XLR, AR	AR	AD AR	AR	AD
Somatic abnormalities	Yes	Yes	Yes	Yes	Rare	Rare
Bone marrow failure	AA (>90%)	AA (~80%)	AA (~20%)	RCA[a]	Meg[b]	Neut[c]
Short telomeres	Yes	Yes	Yes	No	?	?
Cancer	Yes	Yes	Yes	Yes	Yes	Yes
Chromosome instability	Yes	Yes	Yes	?	?	?
Genes identified	13	6	1	9	1	3

FA: Fanconi anemia; DC: dyskeratosis congenita; SDS: Shwachman-Diamond syndrome; DBA: Diamond-Blackfan anemia; CAMT: congenital amegakaryocytic thrombocytopenia; SCN: severe congenital neutropenia; AD: autosomal dominant; AR: autosomal recessive; XLR: X-linked recessive; RCA[a]: Red cell aplasia although some patients can develop global bone marrow failure. Meg[b]: low megakaryocyte count which can progress to global bone marrow failure. Neut[c]: usually low neutrophils count.

Inderjeet Dokal, and Tom Vulliamy Haematologica 2010;95:1236-1240

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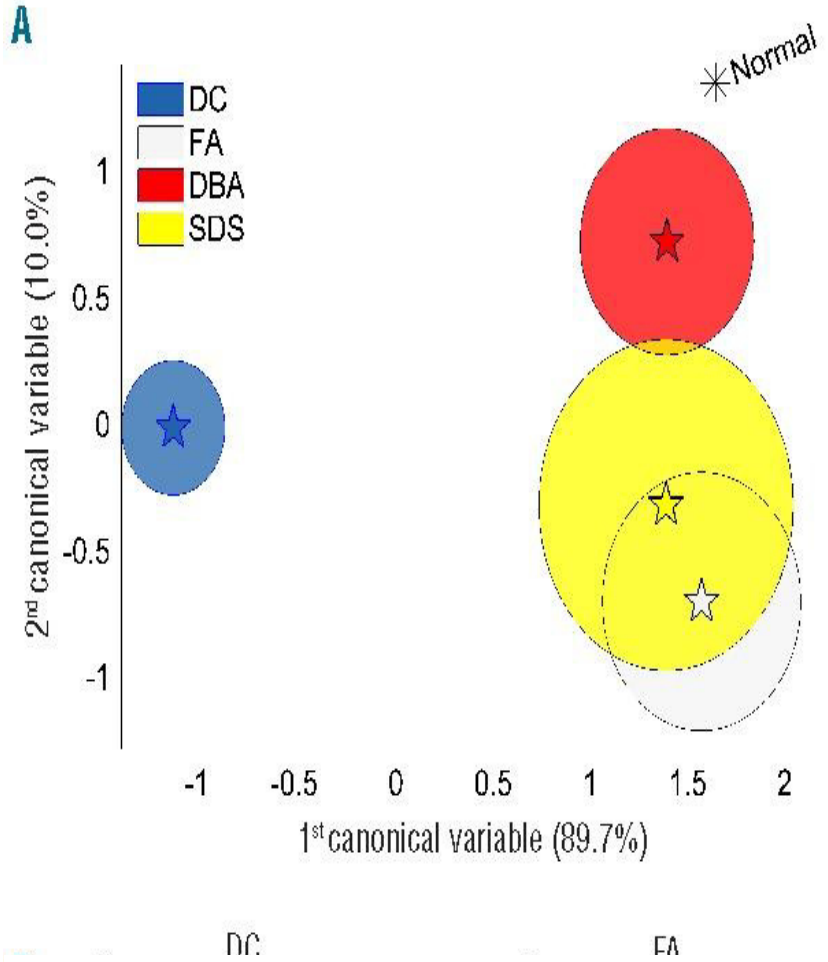
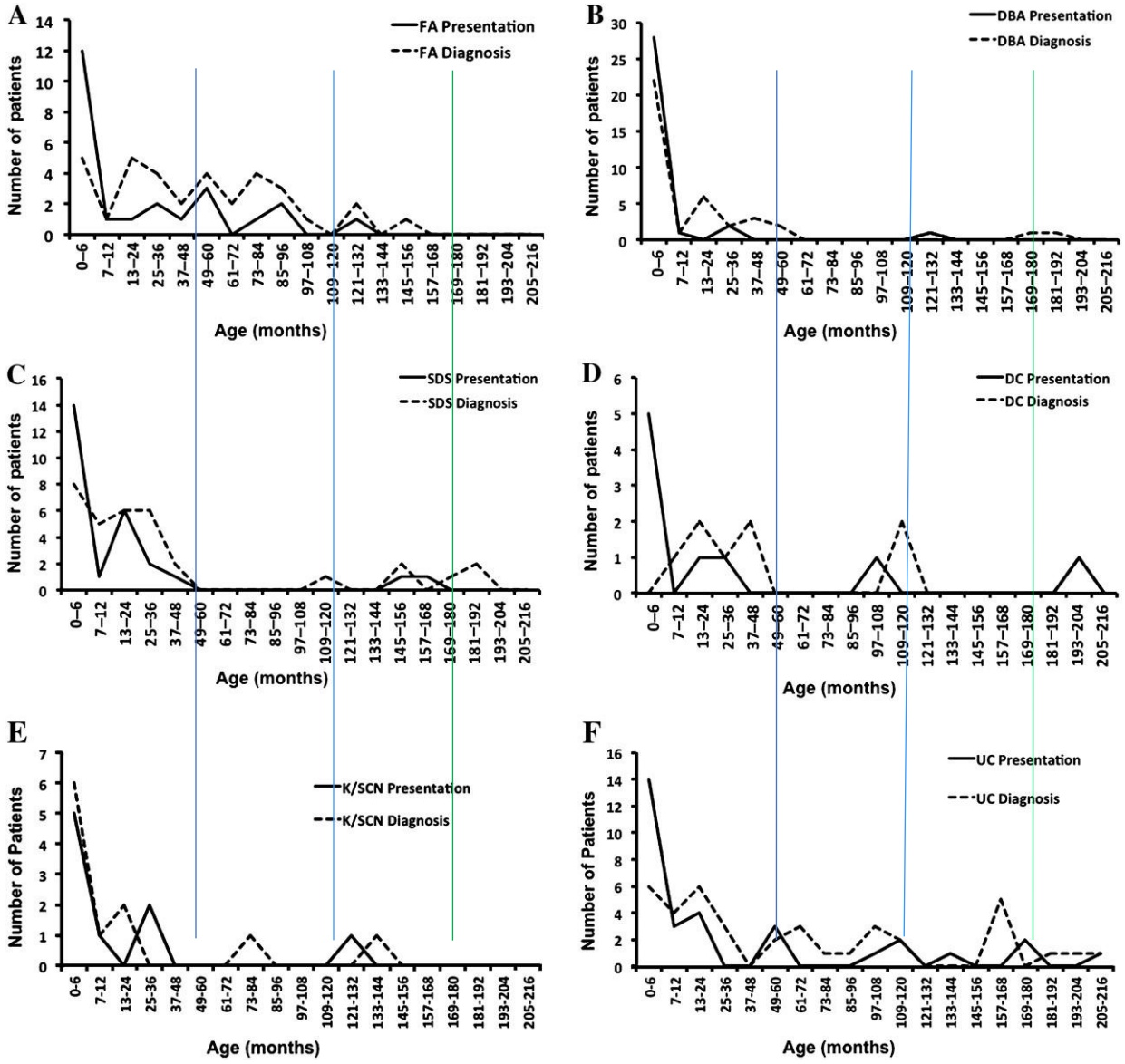
Telomere lengths of IBMF patients

- 100 patients with DC, 34 with DBA, 30 with FA, and 14 with SDS
- measure peripheral blood leukocyte subsets by flow-FISH in all of the IBMFS
- Overall, unlike in dyskeratosis congenita, telomere lengths in patients with non-dyskeratosis congenita inherited bone marrow failure syndromes were usually in the normal range, albeit shorter than in unaffected individuals



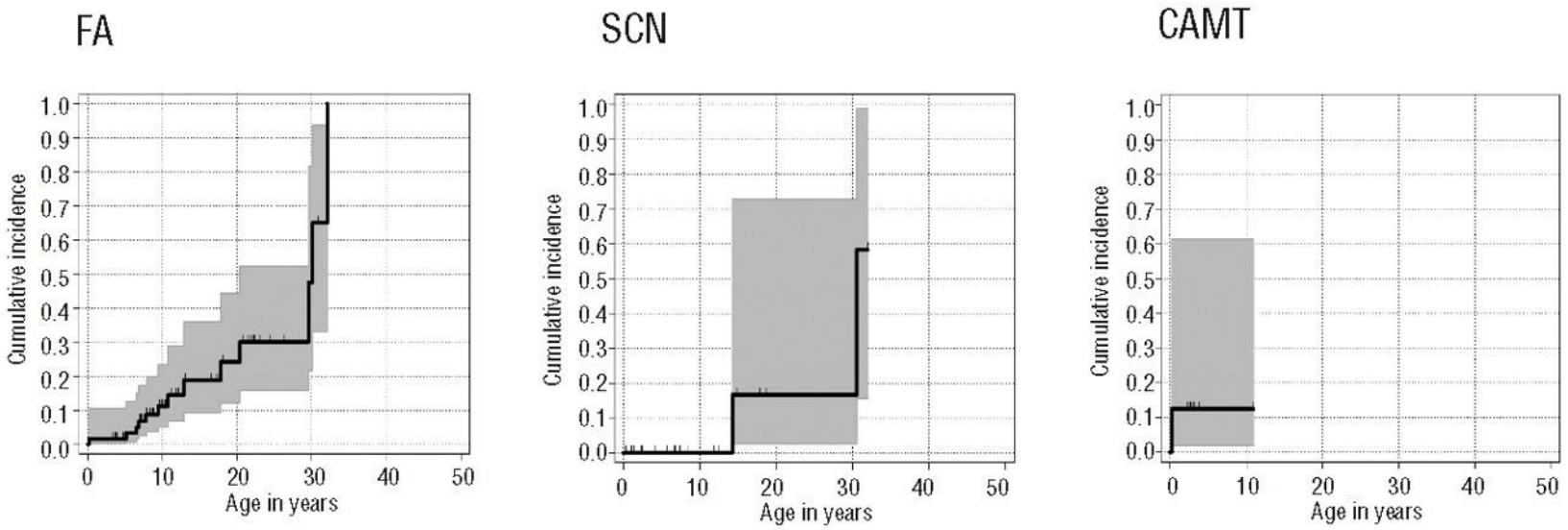
Alter et al, Haematologica. 2015

Age at presentation and diagnosis of the common inherited bone marrow failure syndromes.



Adapted from: E Tsangaris et al. J Med Genet 2011;48:618-628

Cumulative incidence by age of development of malignancy in IS-IBMFR patients.



Hannah Tamary et al. Haematologica 2010;95:1300-1307

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Short Report

Comparative analysis of Shwachman-Diamond syndrome to other inherited bone marrow failure syndromes and genotype–phenotype correlation

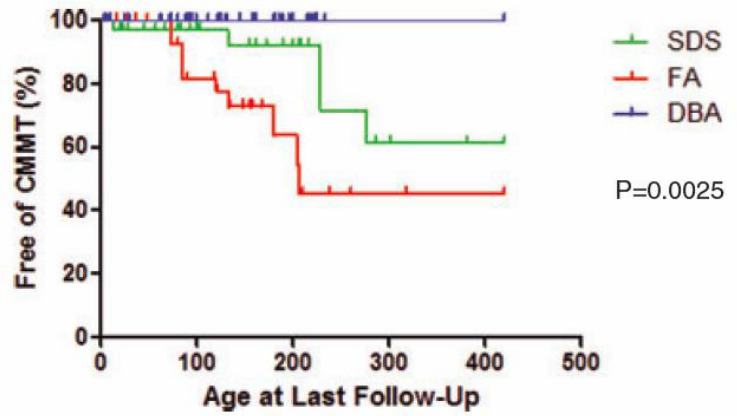
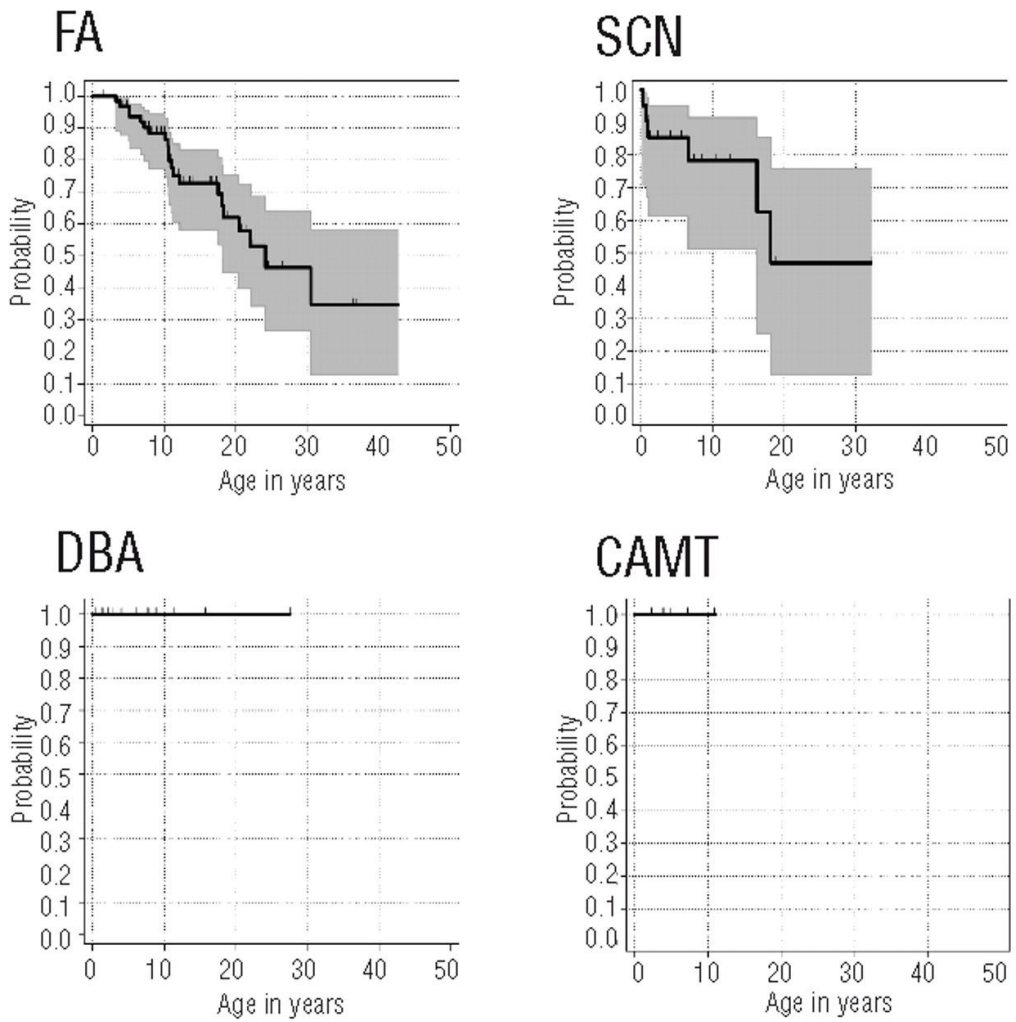


Fig. 2. Estimated risk of clonal marrow cytogenetic abnormalities, myelodysplastic syndrome and leukemia in patients with Shwachman–Diamond syndrome, Fanconi anemia, and Diamond Blackfan anemia in our study (CMMT, clonal and malignant myeloid transformation).

a median age of 20 years, 18% of the SDS patients developed clonal and malignant myeloid transformation compared to 41%, 13%, 10% and 0% in FA, DC, K/SCN and DBA patients, respectively

SBDS patients without mutations had significantly more severe hematological disease and milder pancreatic disease.

Cumulative survival of IS-IBMFR patients calculated using the Kaplan-Meier method.



Hannah Tamary et al. Haematologica 2010;95:1300-1307

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Fanconi Anemia

Fanconi Anemia (FA)

- **Autosomal recessive condition – described in 1927 by Gudio Fanconi**
- **Familial aplastic anemia in 3 brothers with short stature, skin pigmentation and hypogonadism**
- **Prevalence 1-5:1,000,000 live birth**

Diverse congenital anomalies

Progressive bone marrow failure

Propensity towards malignancy

Fanconi Anemia-Case History

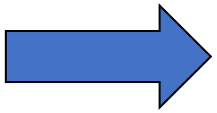
- AD, 10-year-old boy
- Referred for evaluation of thrombocytopenia
- Past history-born 37w, BW 1.750Kg, known to have single kidney
- Family healthy, Moroccan and Yemenite extraction.
- Sibling now 19 yrs, no thumb, height = 145 cm, endocrine follow up

Fanconi Anemia-Case History

- Weight and height below 3rd percentile
- Hyperpigmentation area - Lt thigh
- CBC: Hb 11.5gr%, MCV 95fl, WBC-4450/mm^3, ANC 1600/mm^3, PLT 80,000/mm^3
- HbF 5.9%

Fanconi Anemia-Case History

- BM - Normal cellularity, normal number of megakaryocytes
- DEB test positive, also in 19-year-old sibling

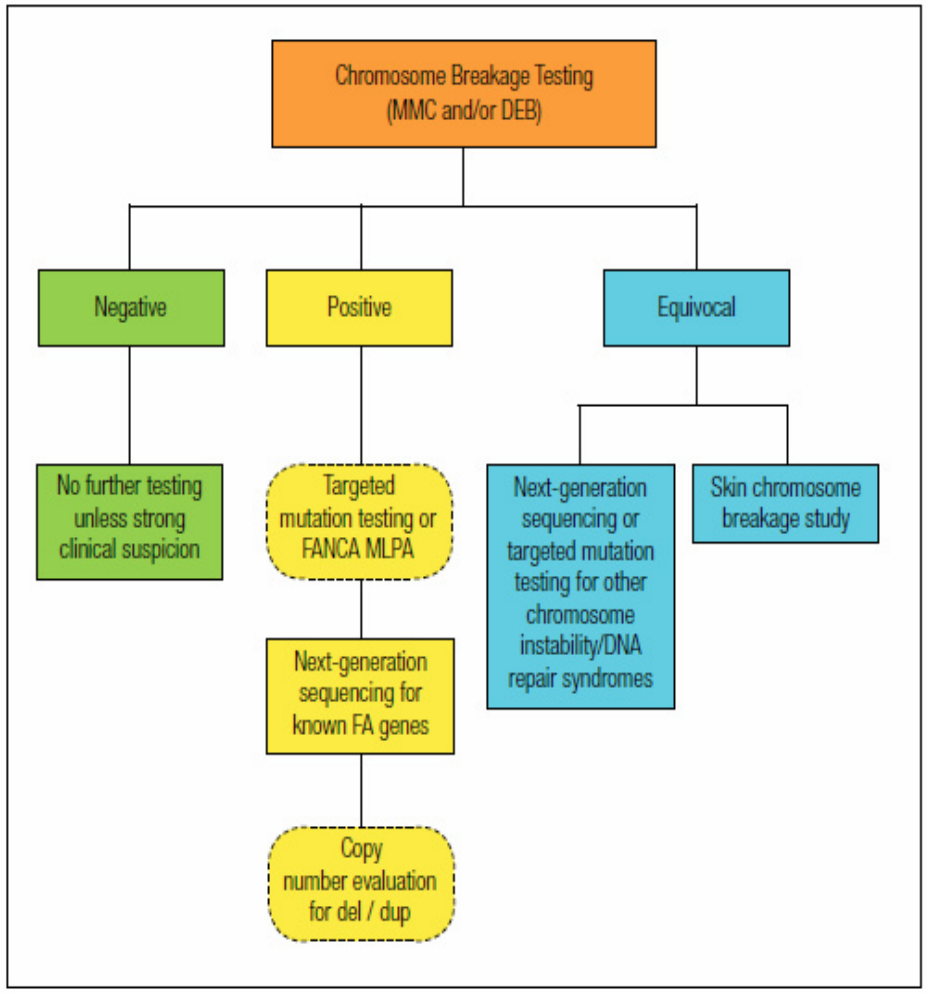


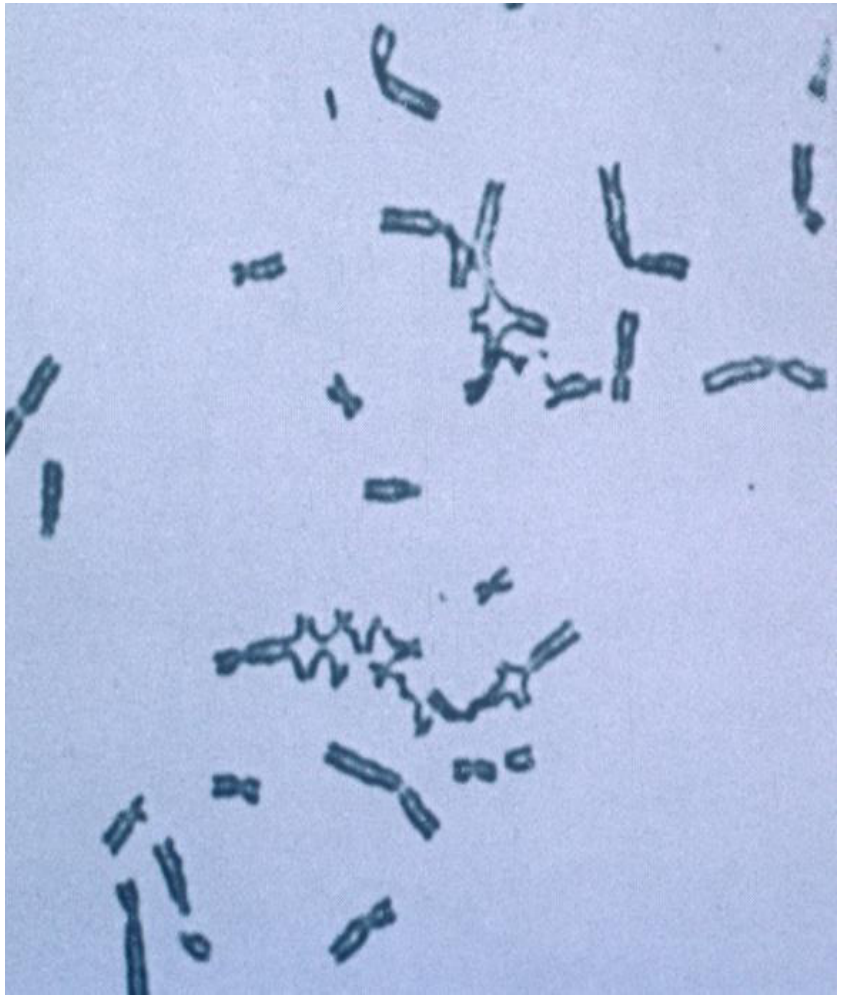
compound heterozygotes for 2 *FANCA* mutations

Chromosomal Fragility Tests-

diepoxybutane (DEB)/mitomycin C (MMC)

Figure 1. Flow chart for FA-related laboratory tests.





The equivocal results

Approximately 10-20% of patients with FA have a form of mosaicism in which the fibroblast cultures show increased breakage, while the lymphocytes do not. The percentage of normal cells in the blood of these patients may range from less than 50% to 100%.

Table 1. Disorders that may share clinical features with FA and manifest with chromosome instability.

Disorder	Putative Genes Involved
Ataxia-telangiectasia	*ATM*
Ataxia-telangiectasia-like disorder	*MRE11*
Bloom syndrome	*BLM*
DNA ligase 4 syndrome	*LIG4*
Dubowitz syndrome	
Dyskeratosis congenita	*DKC1, TERT, TERC, WRAP53, NOP10, NHP2, TINF2, RTEL1, CTC1*
Nijmegen breakage syndrome	*NBN*
Nijmegen breakage syndrome-like disorder	*RAD50*
Roberts syndrome	*ESCO2*
Rothmund-Thomson syndrome	*RECQL4*
Seckel syndrome 1	*ATR*
Severe combined immunodeficiency	*NHEJ1*
Warsaw breakage syndrome	*DDX11*

This does not represent correction in the bone marrow (difficult to assess) or necessarily decreased risk for leukemia!

FA- Congenital Abnormalities (1)

- Growth retardation
- Skin abnormalities (hyperpigmentation and/or cafe au lait spots)
- Anomalies of upper extremities (thumbs or forearms)
- Anomalies of kidney
- Gastrointestinal anomalies
- Males- undeveloped gonads and defective spermatogenesis

25% no obvious congenital anomalies

FA -Hematological Complications

- Progressive pancytopenia during first decade of life
- "Fetal like" erythropoiesis: macrocytosis, increased HbF & i antigen
- Thrombocytopenia

25-40% no cytopenias

FA leukemia and solid tumors

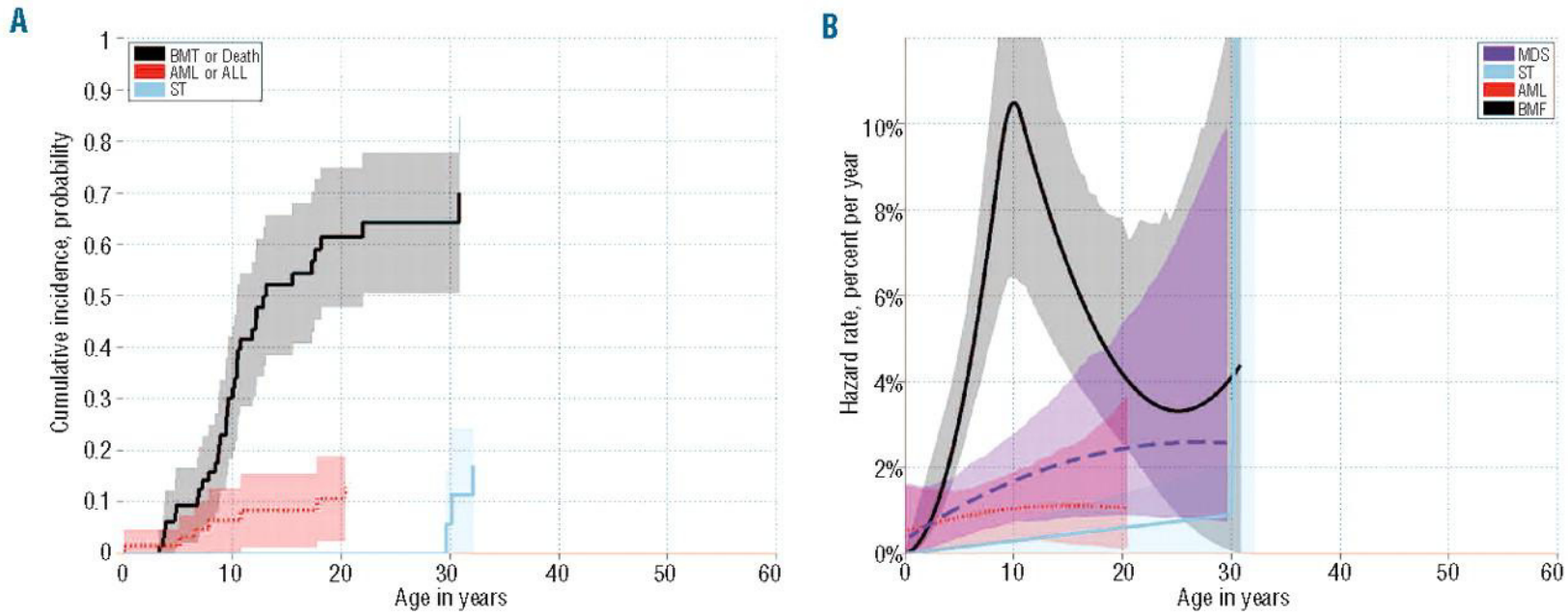
- The probability of developing a solid tumor was calculated to be 75% by age of 45 years
- The probability of developing leukemia ➔ 30% by age of 30 years
- The probability of developing any malignancy = 85% by age of 45, median age was 15

Haematologica. 2018 Jan; 103(1): 30–39.

FA and Cancer

- Organ system: skin, GI, gynecological, head and neck- squamous cell Ca
- Maximize surgical techniques
- Modification of chemotherapy to use agents that do not damage DNA, biologic agents
- Regular cancer surveillance!! – MFS, ENT, Gastro, OB/GYN,

Cumulative incidence by age of adverse events and adverse event rates in IS-IBMFR with Fanconi anemia.



Hannah Tamary et al. Haematologica 2010;95:1300-1307

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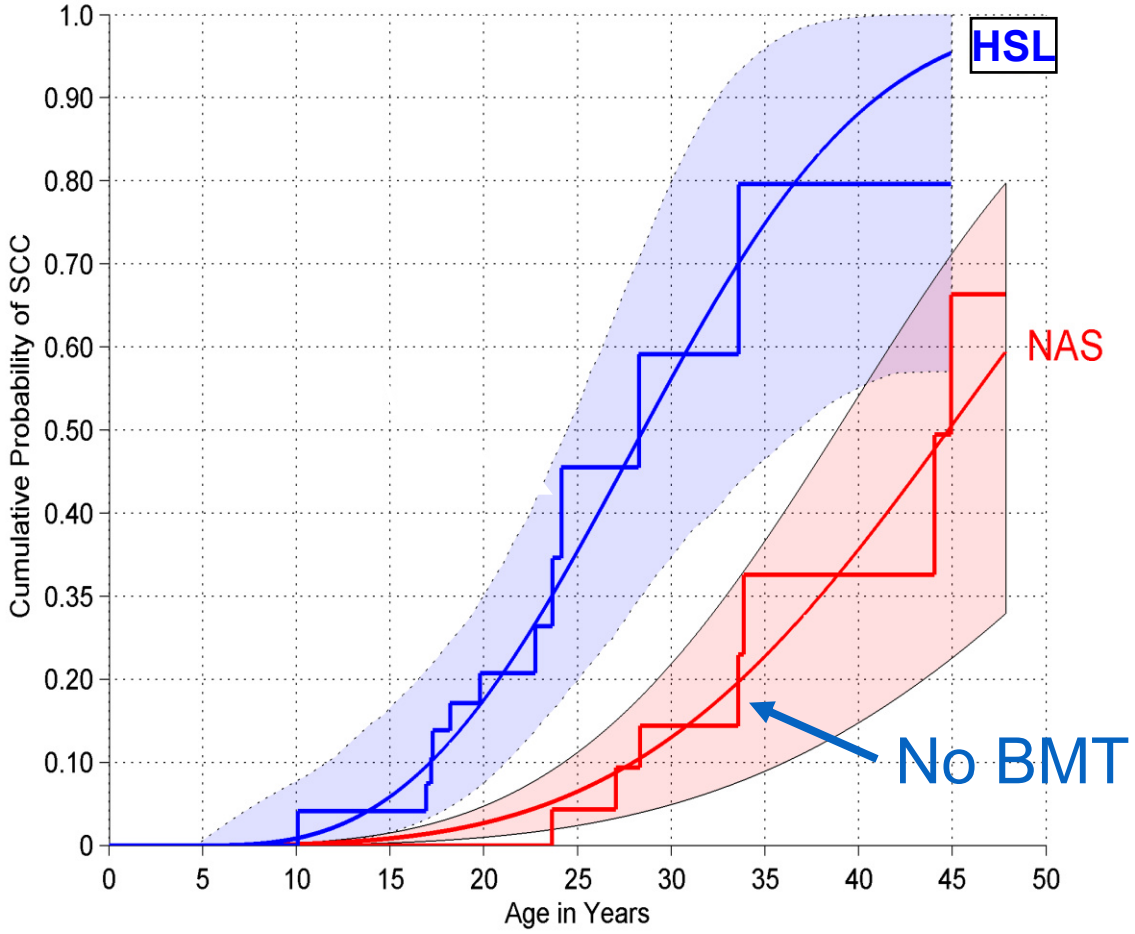
Treatment of FA - BMT

- Reduced conditioning treatment due to underlying DNA repair defect
- Stem cell transplant with an HLA compatible donor- 85% survival
- Increased risk of head and neck squamous cell cancer in patients with FA who received transplants (x4 risk of solid tumor and appears earlier)

Hazards of Head and Neck Squamous Cell Carcinoma: BMT vs no-BMT



HSL - Hôpital St Louis.
NAS - North American Survey

- The age-specific hazards was x 4.4 in BMT group.
- SSC in BMT group in a younger age (median 18 vs 33)

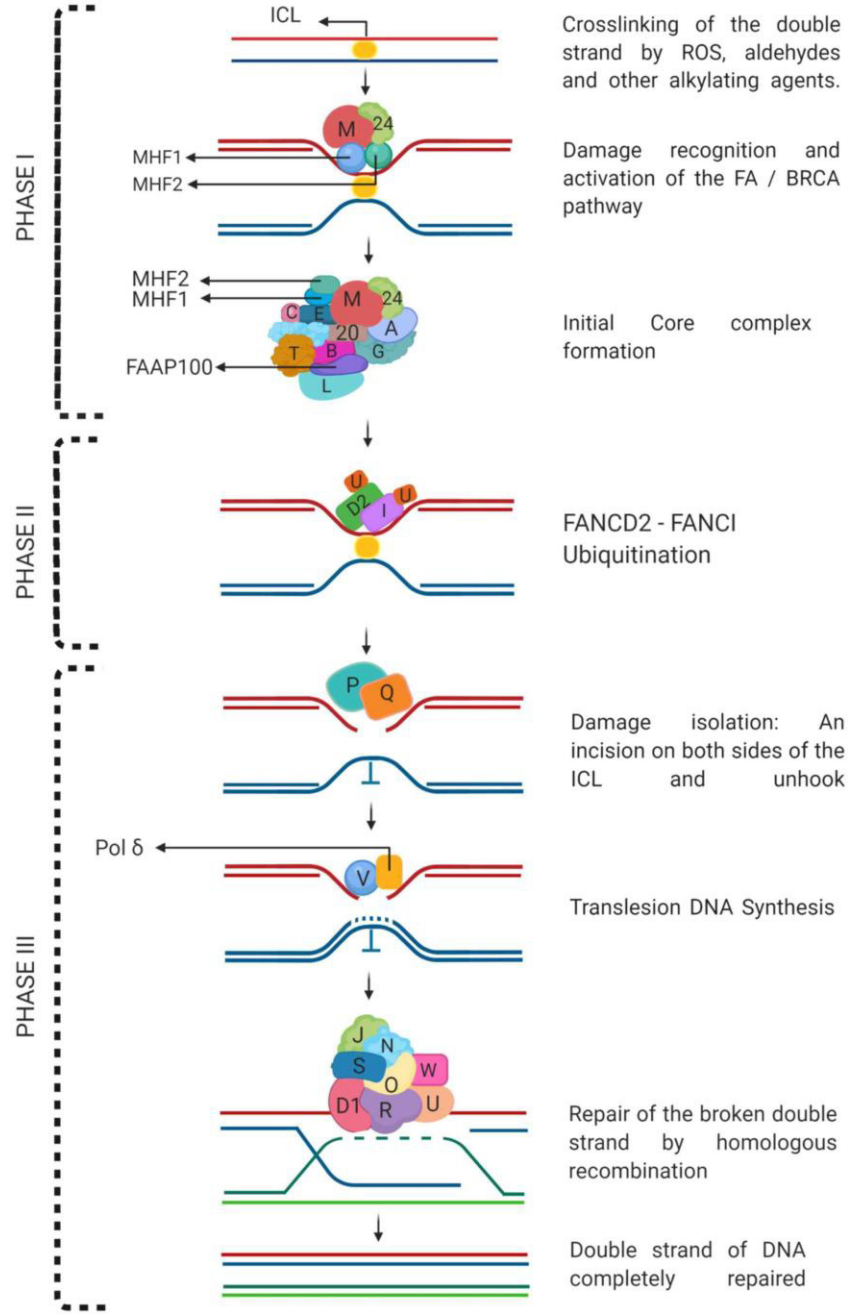
Rosenberg, Socie, Gluckman, Alter, Blood 195:97, 2005

Molecular Basis of FA

Fanconi Anemia Genes

- Fusion studies and linkage analysis identified at least 22 different DNA repair genes related to the clinical phenotype

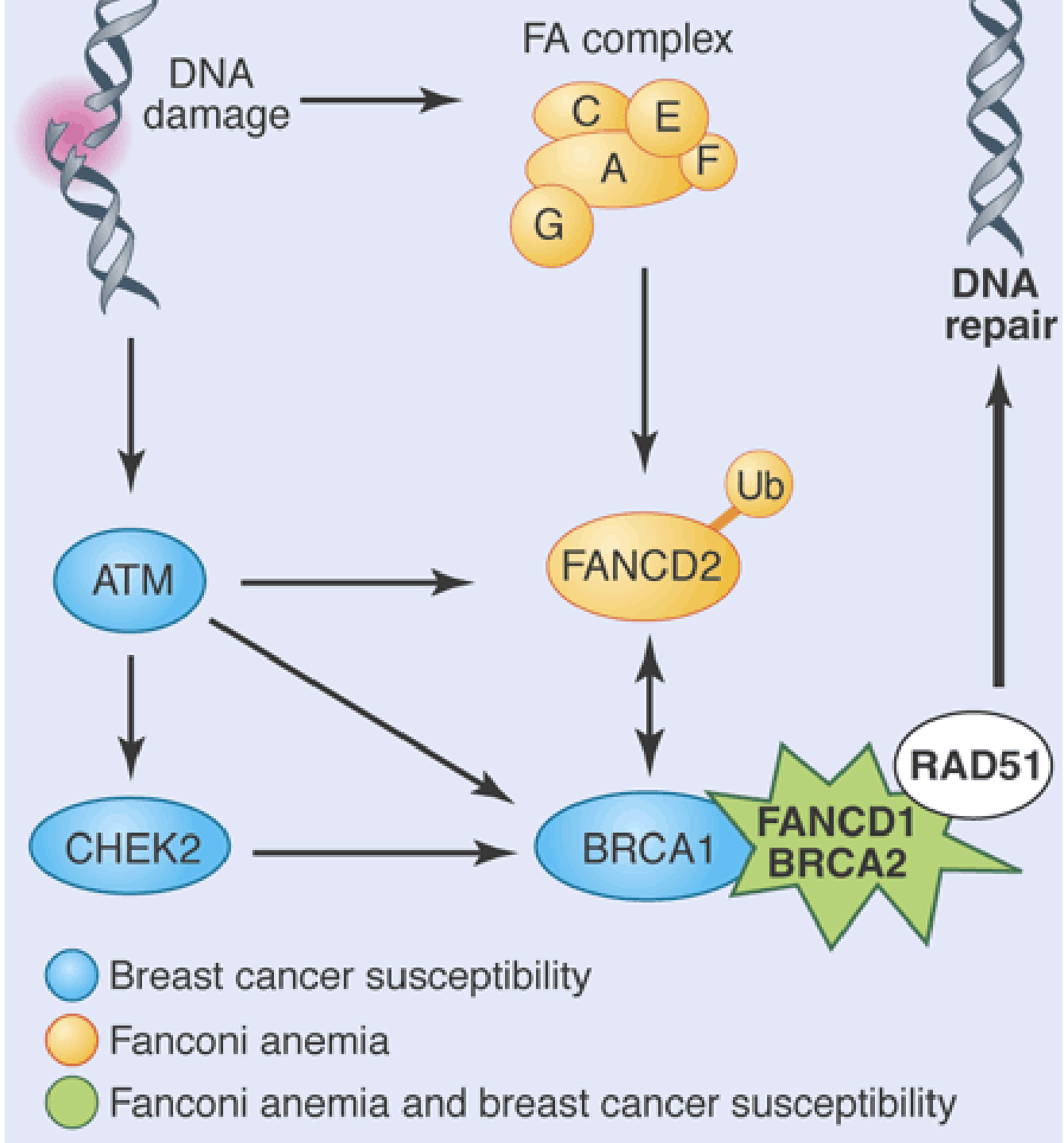
- Autosomal recessive with exception of FANC-B (X-linked)



BIOMEDICAL REPORTS 15: 74, 2021

FA genes and Cancer

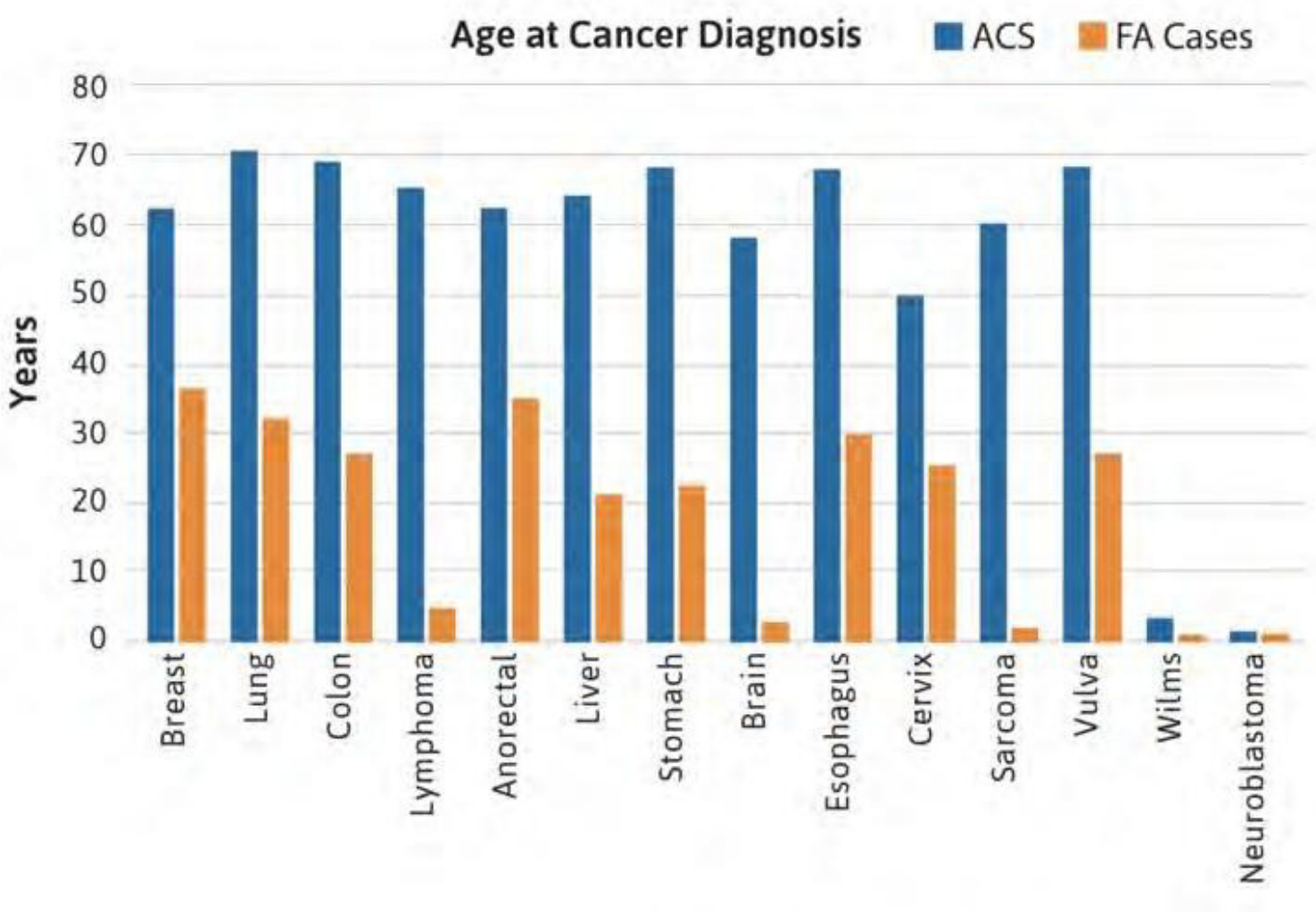
- Inactivation of FA/BRCA pathway results in chromosomal instability activation of new oncongens and the inactivation of tumor suppressor genes thus enhancing the malignant phenotype



DNA repair Proteins

Science 297:534, 2002

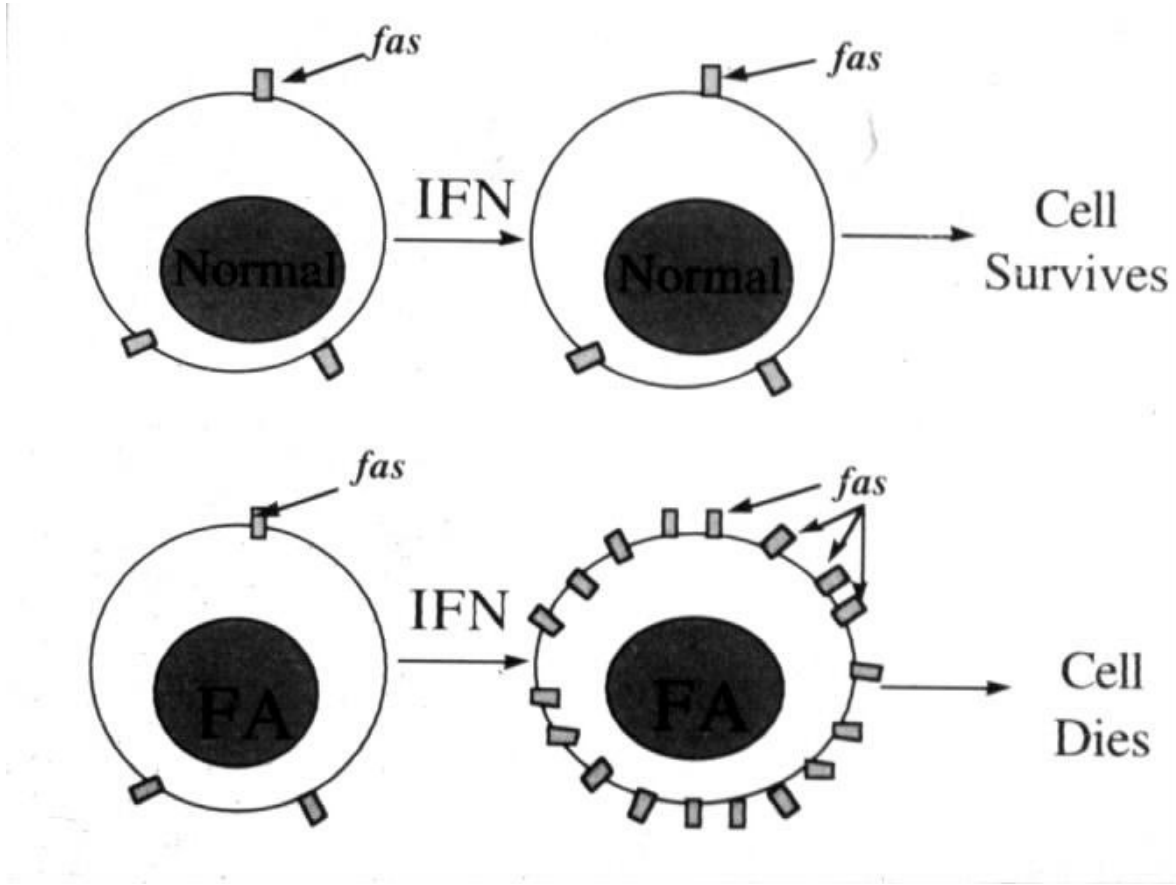
FA and Cancer



Fanconi Anemia Clinical Care Guidelinces 2020

FA and Bone Marrow Failure

- Hypersensitivity to γ-interferon
- Mediated by *fas* induced apoptosis
- *FANCC*-knockout mice



FA-MDS and Leukemia

- Somatic mutated stem cells clones have competitive advantage on the background of disadvantage population of stem cells

FA genotype-phenotype correlations

- **Some genotypes are more severely affected**
- **FANCC IVS4+4A>T Ashkenazi Jews founder mutation**
- ***FANCD1/BRCA2* high rates of severe birth defects and early childhood onset brain tu, Wilm's tu and AML**

FANC-C Gene-Mutational Analysis

- Small number of characteristic mutations
- IVS4+4 A to T >80% Ashkenazi-Jewish with FA, carrier frequency 1.1%

FANCA Mutation in Jewish Patients

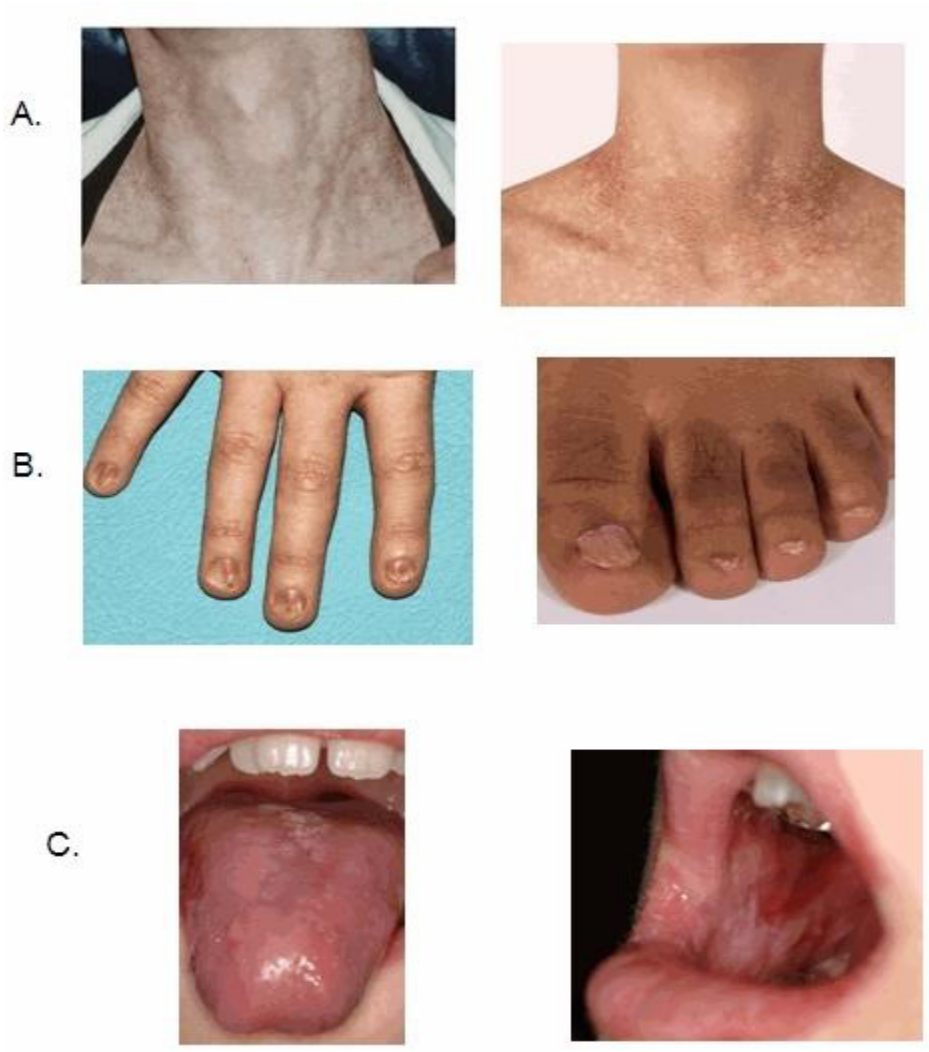
Mutation	No of alleles	Origin
2754C>G	4	Indian
2172-2173+G	14	Moroccan
4257delT	3	Moroccan
890-893del	3	Tunisian

Tamary et al. Br J Haematol 111:338, 2000

Dyskeratosis Congenita

100-year-old disease

- 1st described by Zinsser in 1910 – 2 brothers
- Later also reported by Eneman and Cole thus the name: Zinsser-Engman-Cole Syndrome
- Initial focus was mainly on the dermatological manifestations - classical triad
    1. Dysplastic nails
    2. Lacey reticular pigmentations on neck or upper chest
    3. Oral leukoplakia



More “recent” developments

- Originally Dyskeratosis Congenita (DC) was considered to be a disease of defective ribosomal RNA processing

  Tellervey & Kiss, *Curr Opin Cell Biol* 1997

  Luzzato & Karadimitris, *Nat Genetics* 1998

- In 1998-1999 the connection between shortened telomeres, a genetic defect and DC was first described

  Heinss et al, *Nat Genetics* 1998

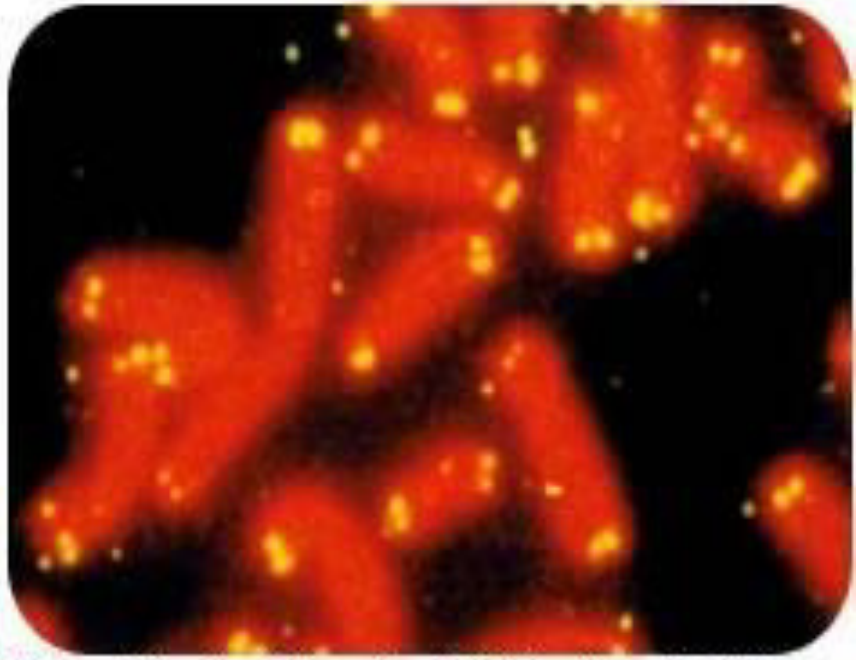
  Mitchell et al, *Nature* 1999

- Today there are studies demonstrating the major influence of short telomeres on disease presentation however dysfunctional dyskerin also is connected to ribosomal abnormalities which probably contribute to the bone marrow failure and cancer susceptibility

Kirwan & Dokal, *Clin Genet* 2008

Telomeres

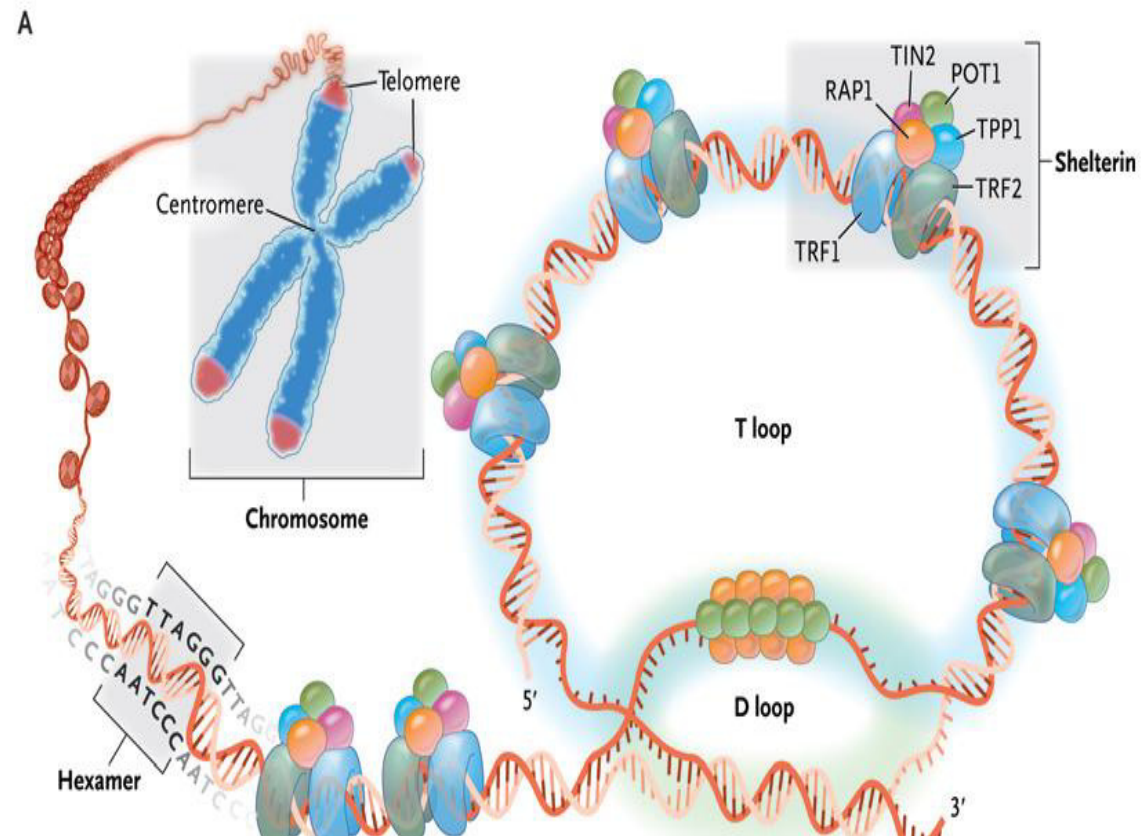
“Telomeres have been compared with the plastic tips on shoelaces because they prevent chromosome ends from fraying and sticking to each other”



Robert Moyzis, University of California, Irvine, CA;
U.S. Department of Energy Human Genome Program

Telomeres

- Protect chromosomal ends from degradation in cell proliferation
- Length of the duplex telomeric repeats = 1000s of base pairs at birth – e.g. 10 kb pairs in leukocytes
- Each telomere terminates with 100-200 nucleotide single strand 3’ G-rich overhang
- Tandem repeats of TTAGGG coated by capping proteins – ”shelterin”



NEJM Calado & Young, 2009

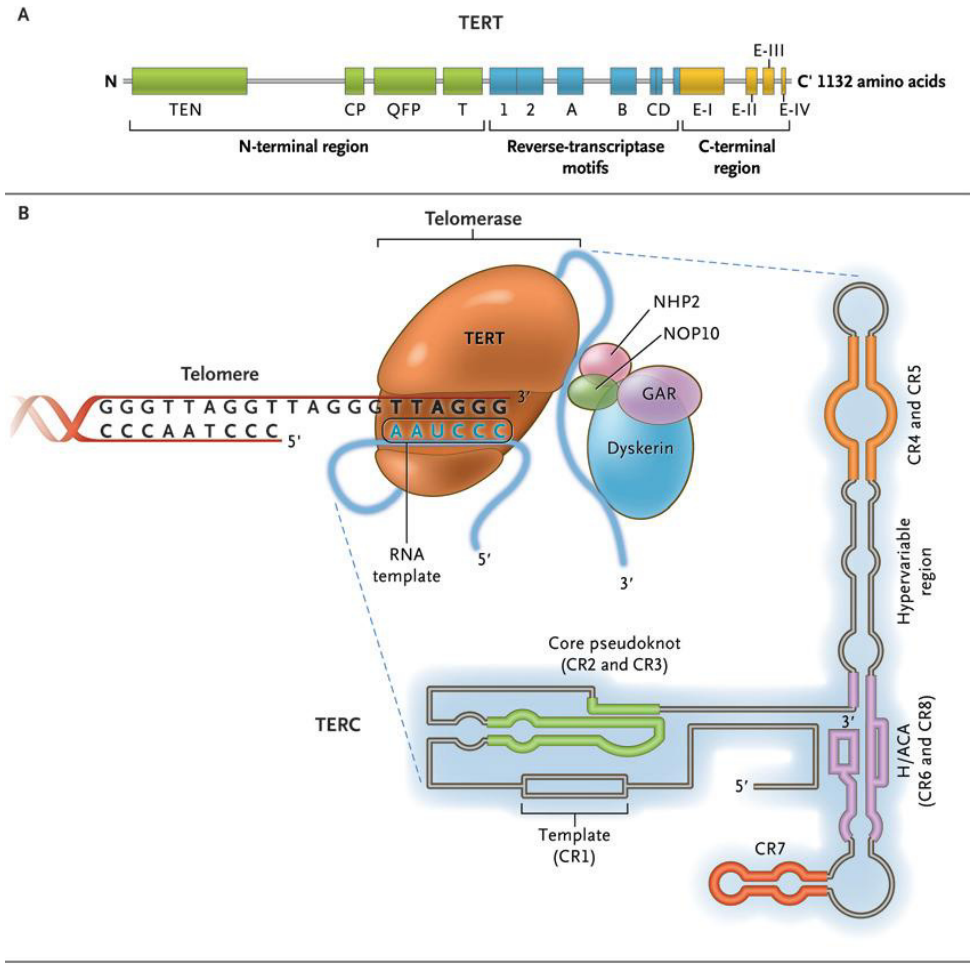
Telomere protection

- Without restoration mechanism – lose 50bp of telomeric repeats/generation
- When telomeres are too short, they signal for proliferation arrest, senescence and apoptosis
- Uncontrolled proliferation (eg p53) causes telomere degradation, end-to-end fusion of chromosomes and instability

Telomerase – catalyzing DNA synthesis to maintain telomere length

Telomerase

- **TERT** – catalytic protein subunit, reverse transcriptase
- **TERC** – RNA templated
- *In vitro* – TERT+TERC are enough for telomerase activity!
- *In vivo* need additional factors for assembly, trafficking and recruitment of telomerase to telomeres

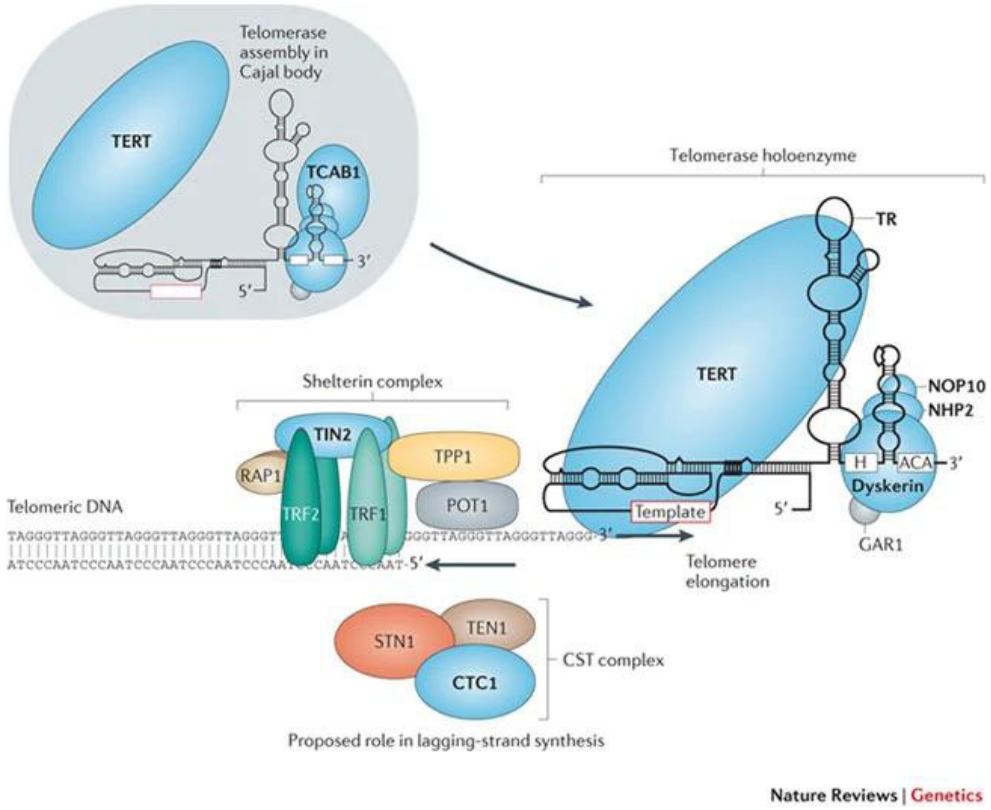


Calado & Young, *NEJM* 2009,
Gramatges & Bertuch *Transl Res* 2013

Telomerase

- Interacts with dyskerin complex which includes dyskerin, NOP10, NHP2 & GAR1
- Dyskerin facilitates assembly and TERC stability
- NOP10+NHP2 essential for telomerase biogenesis
- TCAB1 binds TERC and recruits telomerase to Cajal body

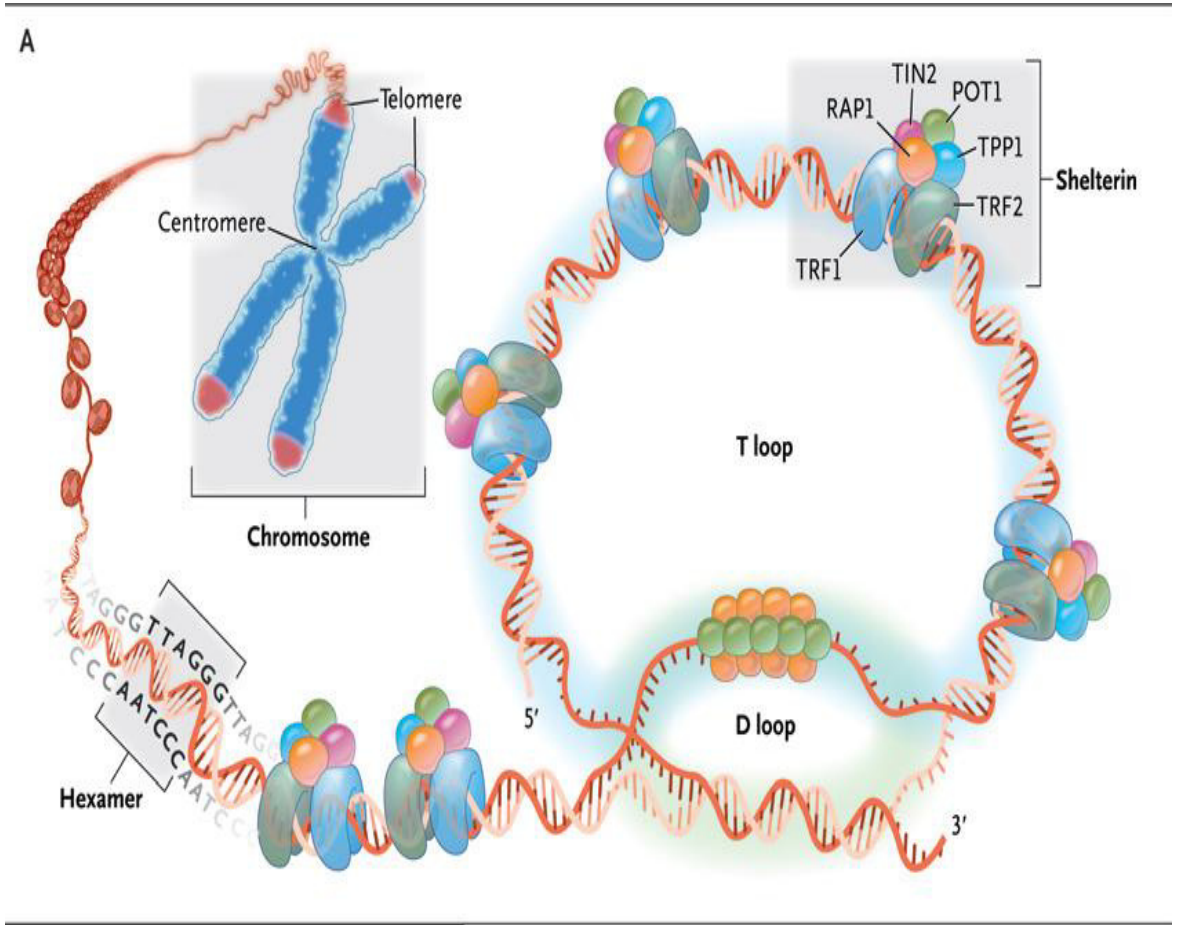
(Cajal bodies- nuclear bodies enriched in proteins and RNAs involved in mRNA processing)



Calado & Young, *NEJM* 2009,
Gramatges & Bertuch *Transl Res* 2013
Armanios & Blackburn *Nature Reviews Genetics* 2012

Shelterin

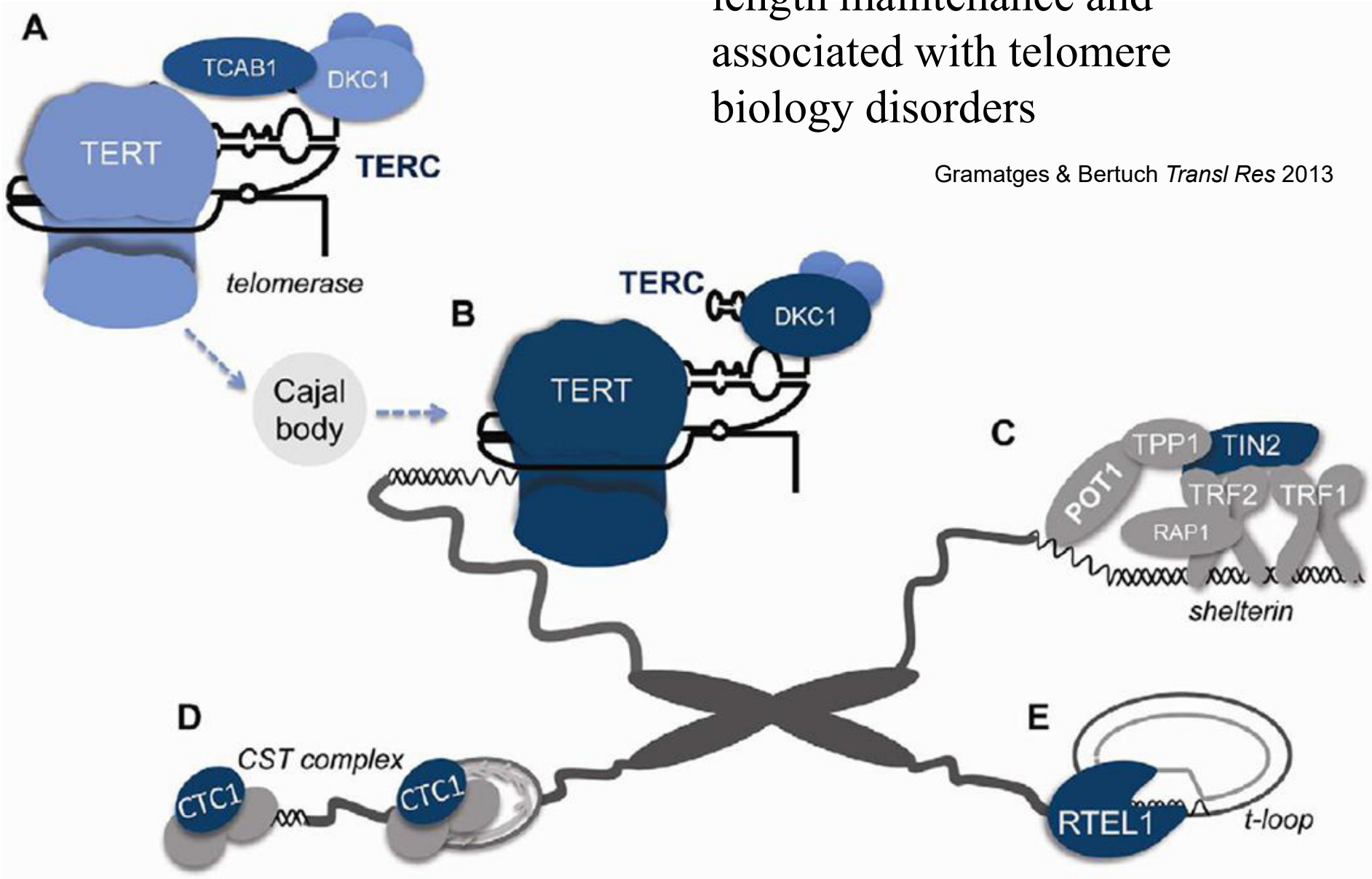
- **Shelterin** proteins protect telomeres from being mistaken for ds breaks and undergoing degradation, responsible for telomere maintenance
- TPP1 recruits telomerase to telomeres

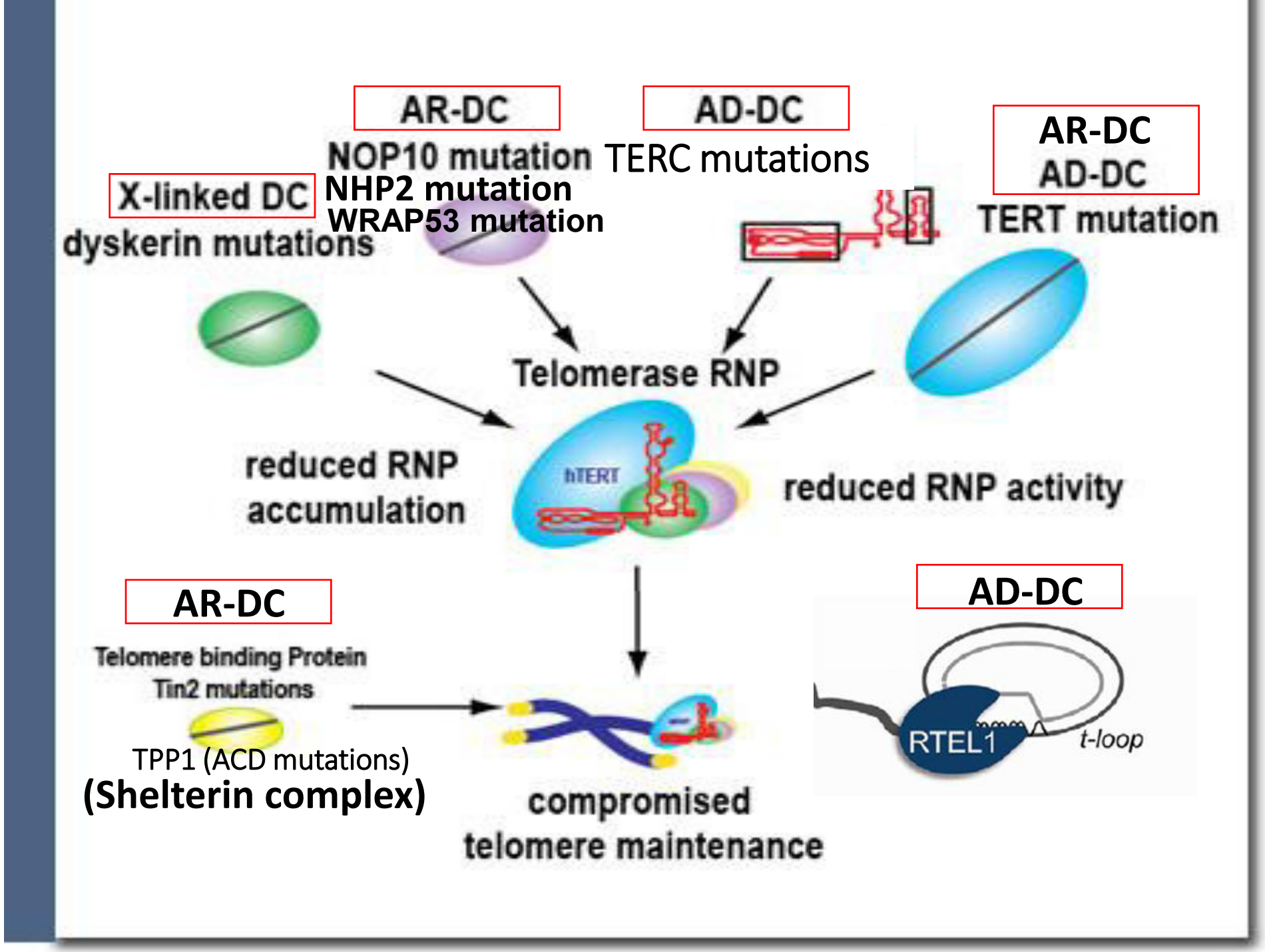


NEJM Calado & Young, 2009

Factors influencing telomere length maintenance and associated with telomere biology disorders

Gramatges & Bertuch *Transl Res* 2013




AR-DC
NOP10 mutation
AD-DC
TERC mutations
AR-DC
AD-DC
TERT mutation
X-linked DC
dyskerin mutations
NHP2 mutation
WRAP53 mutation
Telomerase RNP
hTERT
reduced RNP
accumulation
reduced RNP activity
AR-DC
Telomere binding Protein
Tin2 mutations
TPP1 (ACD mutations)
(Shelterin complex)
AD-DC
RTEL1
t-loop
compromised
telomere maintenance

Telomere length measurement

- Southern blotting is considered the “gold standard”
- More commonly used –
  - flow-FISH - use peptide nucleic acid probes for the telomeric repeat sequence
  - qPCR – (monochrome multiplex qPCR) – determines amount of telomeric DNA relative to a single copy genomic DNA locus

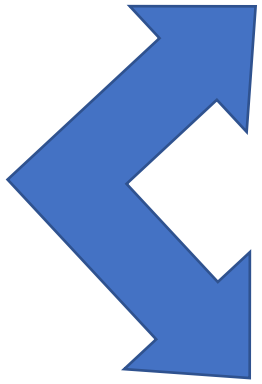
Telomere biology disorders-TBD

- 14 genes have been identified as causes of disorders of telomere maintenance:

ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, RTEL1, TERC, TERT, TINF2, STN1, WRAP53, ZCCHC8

- Telomeropathy, short telomere syndrome

Broad clinical spectrum



- **Can present in infancy** – bone marrow failure, immune deficiency, GIT and neurological dysfunctions
- **Adult presentation** – mild to severe cytopenias, interstitial lung disease (ILD), cryptogenic cirrhosis, hematologic malignancies, solid tumors

Dyskeratosis Congenita

- Extremely short telomeres (<1st %-ile for age in lymphocytes is 97% sensitive and 91% specific)
- Bone marrow failure > 90% penetrance by age 30 yrs
- Severe clinical syndromes
  - Revez – cerebral calcifications, exudative retinopathy
  - Hoyeraal Hreidarsson – cerebral calcifications, IUGR, short stature, developmental delay, immunodeficiency, cerebellar hypoplasia

Gramatges & Bertuch *Transl Res* 2013
Savage GeneReviews® [Internet] 2019

Case

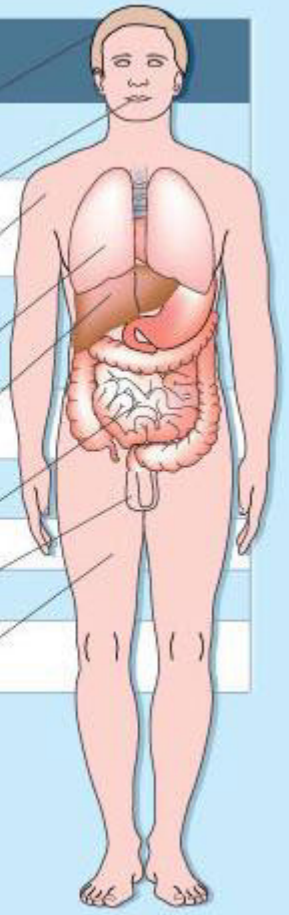
- 17 y/o referred due to splenomegaly, worsening thrombocytopenia, mild neutropenia and increased LFTs
- Celiac disease, paternal uncle died of esophageal cancer
- Auto/Immune work-up – neg
- WES (another center) - neg
- BM aspiration- reduced cellularity
- BM biopsy – cellularity 30%, no increased blasts
- BMF targeted panel – *TERC* mutation (not recognized in WES since it is an RNA!)

Case

- Familial segregation –
  - Twin brother, sister also carriers of the AD TERC mutation
    - Have normal CBCs and LFTs
  - Father and paternal grandfather also carriers of the AD TERC mutation
    - Father had gray hair at a young age
    - Grandfather is 77 and healthy
  - Genetic counselling!!
  - Referred father to adult hematologist
  - Siblings starting hematology follow-up in our clinic
  - Children of the diseased uncle – mother refuses to check

TBD – spectrum of multi-system disorders

Organ system	Cells expressing telomerase	Defect in dyskeratosis congenita
Hair	Hair follicle	Alopecia
Oral cavity	Squamous epithelium	Leukoplakia (precancerous oral lesions)
Skin	Basal layer of epidermis	Abnormal pigmentation Nail dystrophy
Lungs	Type 2 alveolar epithelial cells	Fibrosis
Liver	?	Cirrhosis
Intestine	Intestinal crypts	Gut disorders
Testes	Spermatogonia	Hypogonadism
Bone marrow	Progenitor stem cells	Failure to produce blood cells



Treatment -BMF

- HB < 8g/dl, PLT < 30,000/mm^3, ANC < 1000/mm^3
- Androgen – proven to elongate telomeres
  - danazol, oxymetholone, nandrolone
    - More sensitive the Fanconi patients
    - May take 2-3 months to see response
    - Need to monitor liver – adenomas, carcinoma
- Growth factors –
  - G-CSF, r-EPO: need to monitor spleen (splenic pliosis, rupture)

Vieri et al *Int J Mol Sci* 2020
Kirschner et al *BJH* 2020
Savage *GeneReviews [Internet]* 2020

Treatment-BMF

- Stem cell transplantation – only curative treatment for **BMF or leukemia**
- **Important to perform in experienced centers**
- Major complications = graft failure, GVHD, pulmonary fibrosis, hepatic cirrhosis, VOD, infections
- Poor long-term survival
- RIC – important improvement
- Donor selection – use genetic testing

Savage *GeneReviews [Internet]* 2020

Treatment - Cancer

- At risk for prolonged cytopenias (poor marrow reserve)
- At risk for pulmonary and hepatic toxicity
- May be at risk for radiotherapy-related complications

Treatment – Pulmonary Fibrosis

- Primarily supportive care
- Transplant???

Savage *GeneReviews [Internet]* 2020

Prevention/Surveillance

- No cigarette smoking or alcohol ingestion

BMF –

consider yearly CBC, BM aspirate and biopsy

Androgen therapy

LFTs prior to starting treatment + every 3 months

Abdominal US 2x/year

Cholesterol and triglycerides 2x/year

Savage *GeneReviews [Internet]* 2020

Prevention/Surveillance

Cancer surveillance

*Monthly self-examination – oral, head and neck cancer

*Annual ENT screening

*Annual OB/GYN exam

*Annual dermatologist exam

*Bi-annual dental hygiene & monitoring for head and neck SCC

Pulmonary fibrosis

Annual pulmonary function tests > age 8yrs

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Genetic counselling

- Diagnose “asymptomatic” relatives!
- Provide information on the mode of inheritance of the specific genetic diagnosis
- Prenatal testing/preimplantation testing
- **Prevention!**

Savage *GeneReviews [Internet]* 2020

Summary

- Dyskeratosis Congenita/telomere biology disorders are extremely varied in clinical presentation (including within families) and in inheritance/genetic diagnoses
- Systemic disease with multiple organ involvement
- Chronic, life-long surveillance, treatment necessary
- Specialized clinics needed!

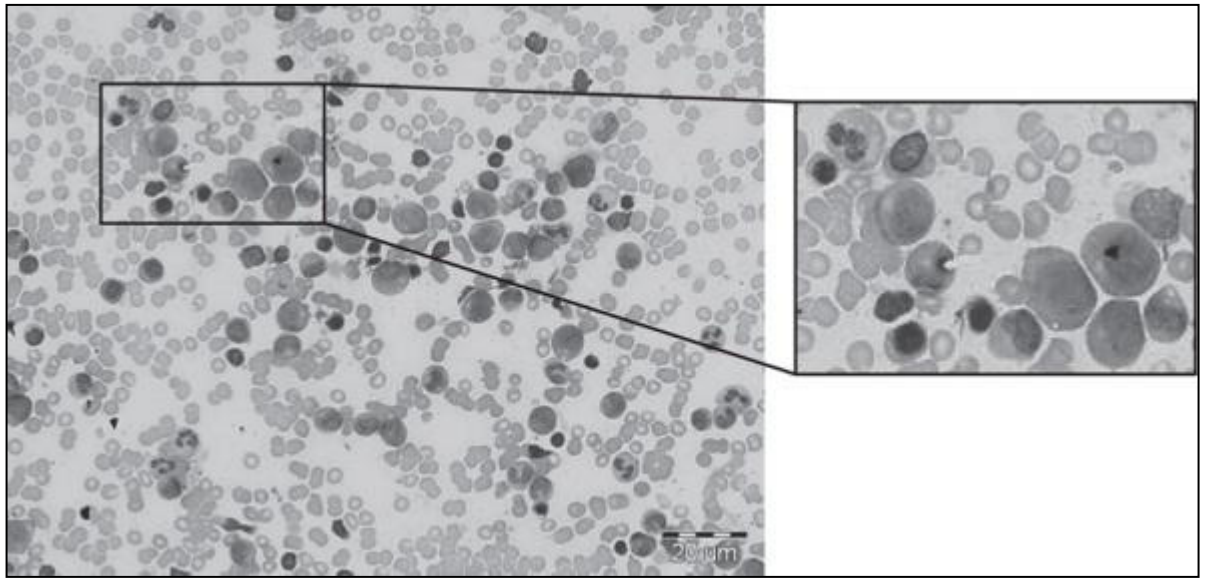
Diamond Blackfan Anemia

DBA-case history

- 15-month-old 1st baby referred to our service for evaluation of anemia
- Healthy non-related parents
- BW = 2200gm, single umbilical artery, right triphalangeal thumb, small PFO
- Age 6 mos - Hb-8.6gr%, MCV - 86.4
- Age 15mos – Hb - 10.9, MCV – 81, ANC = 900
- Peripheral smear - normal
- HbF = 2.4%

DBA-case history

- **BM aspiration- normocellularity, slightly decreased erythroid compartment**



myeloid:erythroid ratio 5:1

Diamond Blackfan Anemia: A Nonclassical Patient With Diagnosis Assisted by Genomic Analysis.
Steinberg-Shemer, Orna; MD, MSc; Keel, Sioban; Dgany, Orly; Walsh, Tom; Noy-Lotan, Sharon; Krasnov, Tanya; Yacobovich, Joanne; Quarello, Paola; Ramenghi, Ugo; King, Mary-Claire; Shimamura, Akiko; MD, PhD; Tamary, Hannah

Journal of Pediatric Hematology/Oncology. 38(7):e260-e262, October 2016.
DOI: 10.1097/MPH.0000000000000587

FIGURE 1 . Bone marrow aspiration of the patient. Left, a representative field. A scale bar is located in the right lower corner. Right, a higher magnification of the marked field. Photographs were taken with a light microscope (BX51; Olympus, x50 magnification).

DBA-case history

- BM aspiration- normocellularity, slightly decreased erythroid compartment
- Over 3 years: HB = 9.2-11.4gr%, MCV 80-84fl, occasional neutropenia around 900/mcl
- Chromosomal fragility, telomere length – normal
- *ELANE* and *SBDS* – normal sequencing

- **Targeted-capture next generation sequencing → RPL5 c.527(+ 1)G> A**

“Classic” Diamond Blackfan Anemia (DBA)

- Anemia before 1 year of age
- Macrocytosis, reticulopenia
- Normal marrow cellularity with paucity of erythroid precursors
- Elevated HbF, increase RBC adenosine deaminase (85% of patients)
- Congenital anomalies
- Increased risk for cancer but still rare– MDS/AML, osteosarcoma, colon, and lung cancer (distinct from the other IBMFS)

Annals of Medicine, 2014; 46: 353–363

Haematologica. 2018 Jan; 103(1): 30–39.

Diamond Blackfan Anemia

- Ribosomal proteins: 22 genes, *RSP19*, *RSP24* = 25% of patients
- Autosomal dominant inheritance
  - *GATA1* or *TSR2* – x-linked
- Steroid therapy ~ 80% initially responsive
- 20% may have spontaneous remission, not consistent
- Transfusion dependent + chelation
- Stem cell transplantation

Diamond Blackfan Anemia

- *Pregnancy management:*
  - Management by an obstetrician with expertise in high-risk pregnancies and hematologists with experience in bone marrow failure syndromes.
  - During pregnancy the maternal hemoglobin level must be monitored.
  - Use of low-dose aspirin up to 37 weeks' gestation may help prevent vasculo-placental complications in women with a history of a problematic pregnancy.

Shwachman-Diamond Syndrome (SDS)

- 18 month-old:
  - boy presented with recurrent AOM, pneumonia
  - Neutropenia found at time of infections
  - Mother reports chronic diarrhea with oily secretions
- Family history:
  - 10 children, eldest is 18y/o –FTT, history of recurrent lung infections, repeated genetic work-up for CF was negative, WES pending
- Genetic work-up
  - 18 month-old – *SDS* **258+2T->C/ 183-184TA->CT** cmpd het
  - Older sibling – WES recognized only one mutation, sanger sequence identified both

Shwachman-Diamond Syndrome (SDS)

- Pancreatic insufficiency (low trypsinogen and isoamylase) and neutropenia
- Neutropenia and aplastic anemia
- Skeletal anomalies, pigeon chest
- >95% mutations in *SBDS* gene
- High risk for leukemia and MDS

Shwachman-Diamond Syndrome-genetics

- 2000 Ginzberg and Ellis reported a segregation analysis with evidence for recessive inheritence
- 2003 Popovic - compound heterozygous mutations in the *SBDS* gene on chromosome 7 associated with the syndrome
- 2005 Shimamura showed intranuclear localization of the protein possible role in rRNA processing

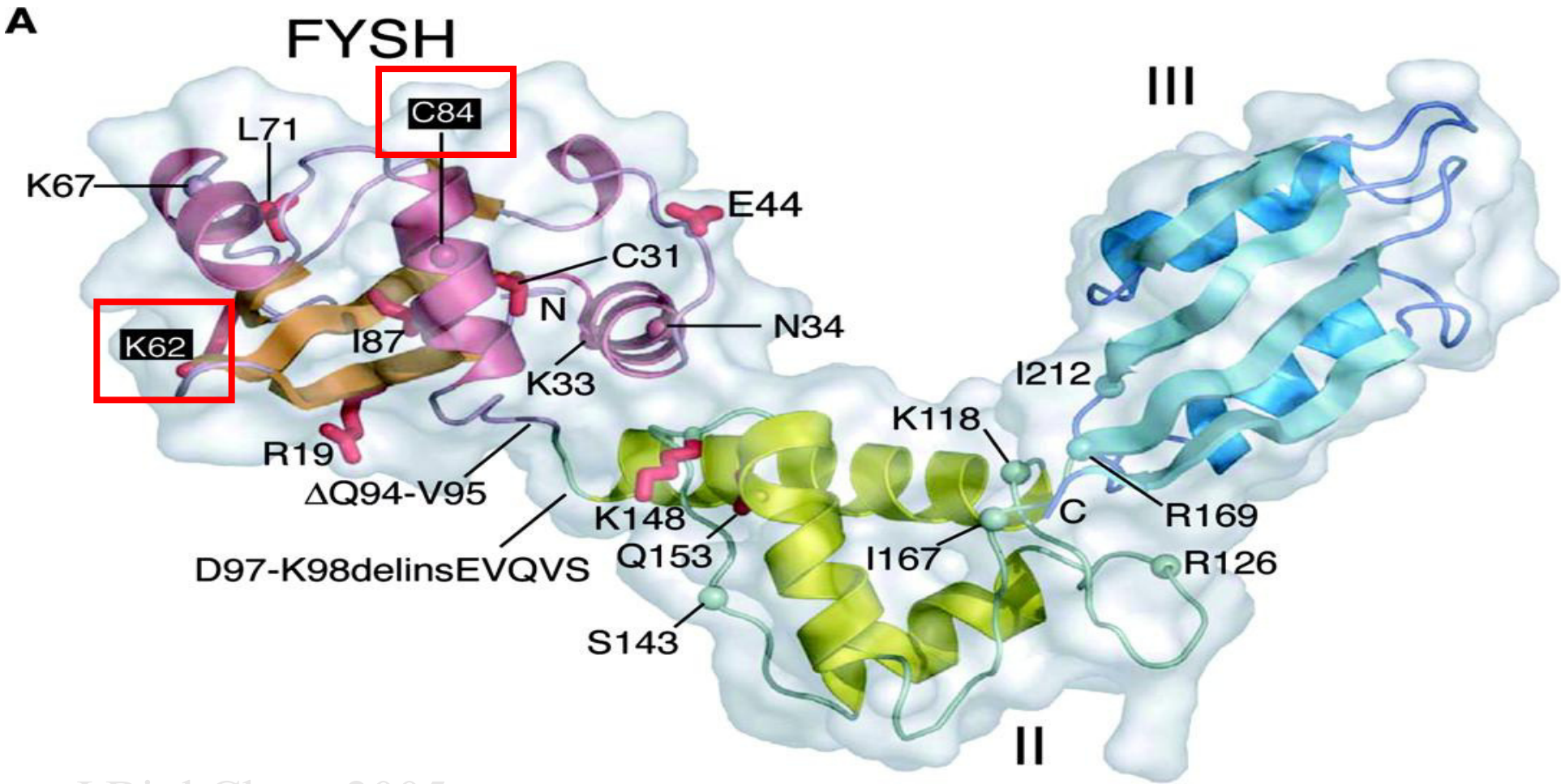
Shwachman-Diamond Syndrome - genetics

- Highly conserved through evolution
- Also highly conserved pseuodogene located distally-97% transcript identity but no protein translation
- 89% of mutations are due to conversion mutations between *SBDS* gene and the pseudogene

Shwachman-Diamond Syndrome - genetics

- **258+2T->C** is most common gene mutation arising from conversion, frameshift & premature protein truncation
- **183-184TA->CT** also common, introduces stop codon (K62X)
- Majority of mutations cause major reduction in protein expression
- Majority of patients are compound heterozygotes

SDS-associated mutations



J Biol Chem 2005

Shwachman-Diamond Syndrome - malignancy

- High propensity to develop MDS/AML
- 30% by the age of 30 years
- Usually present with complex clonal cytogenetics
- Commonly involving monosomy chr7
- Very poor response to treatment
- common cytogenetic abnormality seen in patients with SDS, del(20)(q11) - is not associated with a high risk of malignant transformation
- isochromosome i(7)(q10) can come and go over years of time without progression to MDS/AML (Myers KC, Hematol Oncol Clin N Am 27 (2013) 117–128)

Shwachman-Diamond Syndrome – treatment & F/U

- Hematological manifestations-treat supportively (GCSF, P.C.)
- Pancreatic insufficiency – enzyme replacement, ADEK, yearly trypsinogen
- Yearly BM aspiration & biopsy-screening for malignancy
- Dental, developmental, orthopedic-clinics

Shwachman-Diamond Syndrome – treatment & F/U

- Update –
  - 2 additional siblings were identified by Dor Yesharim testing
  - Now starting follow-up

Severe Congenital Neutropenia

- Early onset of neutropenia(<500/mm^3)
- 70-90% mutations in *Elastase2* gene (*ELANE*), dominant inheritance
- G6PC3 – includes other clinical manifestations (syndromatic)
- Rare – *GFI-1, WAS*
- Few including original Kostman's family (*HAX-1*)- autosomal recessive
- Therapy G-CSF higher dosages
- 40% AML/MDS

Amegakaryocytic Thrombocytopenia

- Early thrombocytopenia
- Reduced number of megakaryocytes
- Mutations in *c-mpl* TPO receptor
- Complications: AA and AML/MDS

Thrombocytopenia and absent radii (TAR)

- **Thrombocytopenia appears early resolves by age of 1 year**
- **Absent radii, may also have additional anomalies**
- **Rare reports of AML**

Rare causes of BMF/MDS

Case 1

- 9-year-old with new-onset pancytopenia
- Severely hypoplastic bone marrow
- 2 prior CBCs with neutropenia – 1: 4 months prior to diagnosis
- NGS bone marrow failure panel – c.1186C>T Ht mutation in *GATA2*
  - Familial segregation – 2 more siblings and the father have same mutation
  - Sister and father have BM dysplasia without cytopenias
- Child 1st received ATG , after the molecular diagnosis→ BMT from MUD

GATA2 Haploisufficiency

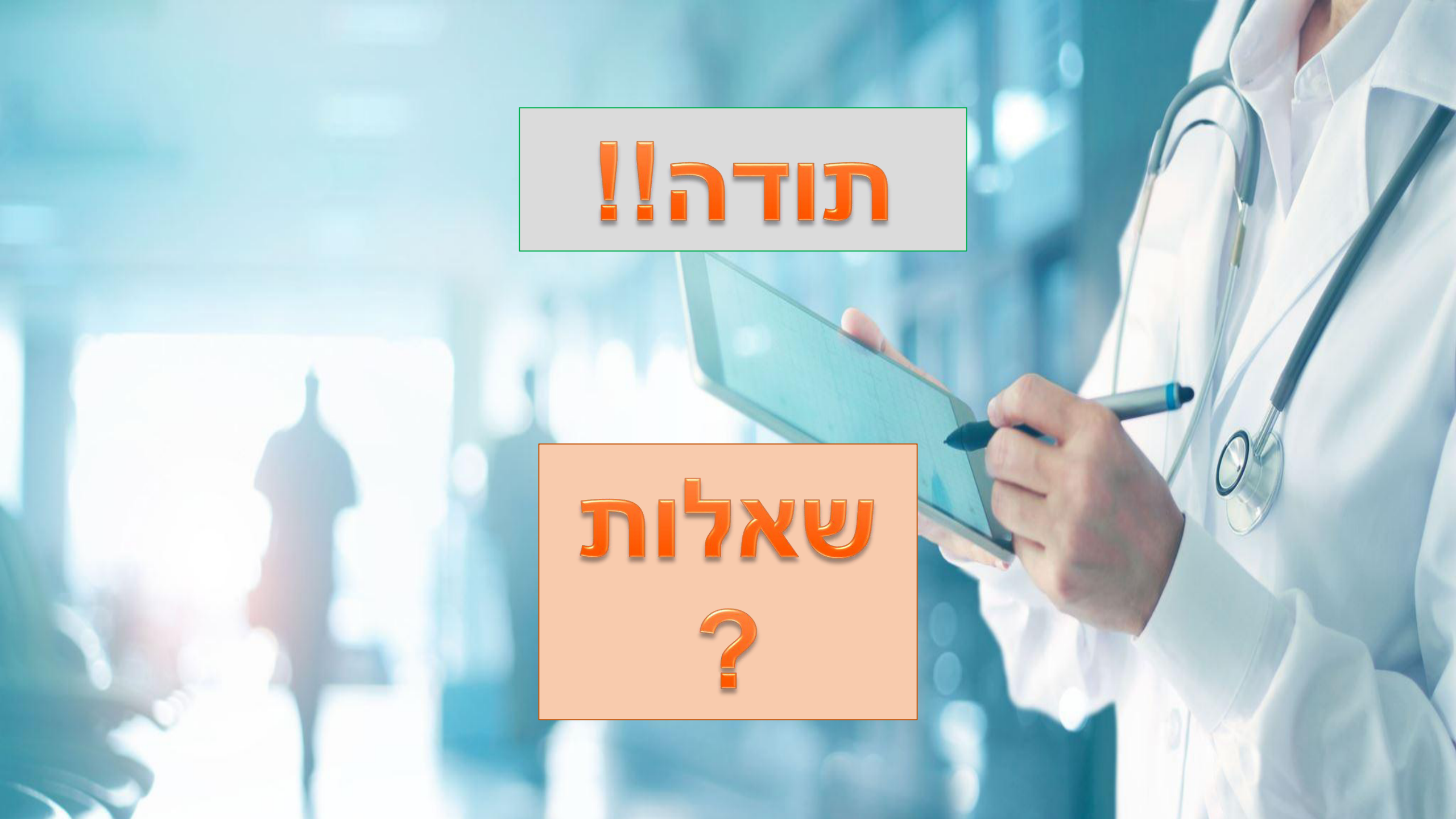
- Germline immunodeficiency
- Germline Constitutional Syndromes (also SAMD9/SAMD9L)
- Difficult to diagnose
- High lifetime risk for MDS/AML
- MonoMac syndrome, Emberger syndrome (primary lymphedema, MDS), DCML deficiency (dendritic, monocyte B&NK lymphoid)
- 72% of adolescents with MDS and Mo7 have *GATA2* deficiency

Case 2

- Father followed for chronic ITP, severe bleeding manifestations, abnormal aggregation
- 1st daughter – thrombocytopenia, bleeding manifestations
- Son – less severe thrombocytopenia, severe atopic dermatitis
- NGS bone marrow panel – AD c.532+1_532+10delGTAAGTGCAT in *RUNX1 = MPD/MP*

RUNX1

- FPD/MP disorder (also – ETV6, ANKD26)
- Most mutations are unique per family
- Pt. mutations, small indels, large intragenic deletions and duplications
- Can have haploinsufficiency or dominant negative effect
- DN effect → higher propensity for MDS/AML
- Germline mutation is insufficient for mutagenesis, need 2nd somatic mutation
- Commonly see platelet dysfunction – collagen, ADP, EPI (more severe bleeding compared to the PLT count
- Lifetime risk of 40% for MDS/AML, also T-ALL, hairy cell leukemia, CMML


תודה!!
שאלות
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