Penn Medicine
Abramson Cancer Center

Hereditary Marrow Failure Syndromes

Daria Babushok, MD PhD
Assistant Professor of Medicine, Hematology-Oncology
University of Pennsylvania

January 23, 2025

Learning Objectives

- To develop a practical approach to the recognition and diagnosis of bone marrow failure syndromes
- To review the presenting features, prognosis, and treatment of selected hereditary marrow failure and predisposition syndromes:
  - GATA2 deficiency
  - Fanconi Anemia
  - Telomere Biology Disorders
  - Diamond Blackfan Anemia
  - Shwachman Diamond Syndrome

Patient case #1: 45 yo F referred for a new dx of MDS

Hematologic history:

- No prior documented normal CBC
- Late teens: cytopenias and infections, BM biopsy hypocellular w/mild mega dysplasia and normal karyotype
- 20s: recurrent bacterial infections; another BM biopsy; moderate neutropenia, diagnosed with T-LGL
- 30s: worsening pancytopenia, 1.4>9<72. Diagnosed with acquired AA, treated with horse ATG+CSA. Persistent cytopenias.
- Age 45: progressive cytopenias and transfusion dependence.

  0.6>6.5<25, ANC 0.48, AMC 0.02, ALC 0.04.

Patient case #1: 45 yo F referred for a new dx of MDS

Past medical history

- Recurrent genital warts, with vaginal, cervical, anal dysplasia, and vulvar cancer. First LEEP procedure at 25.
- Multiple miscarriages
- Chronic non-pitting bilateral leg swelling (similar to her maternal side of the family).

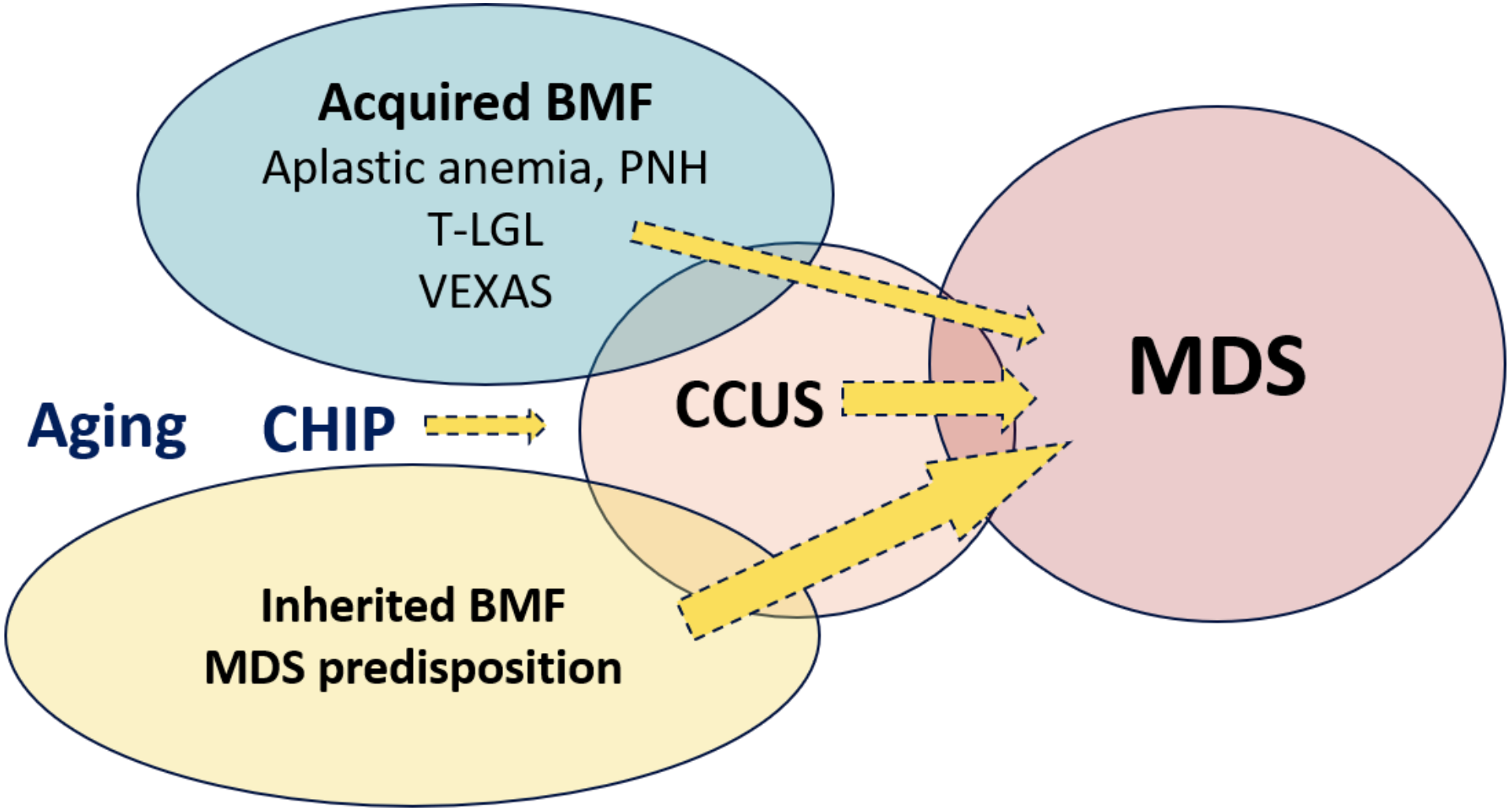
Bone marrow biopsy: Normocellular (50%). Mega atypia (focally clustered, hypo- and abnormally lobated) (20% of lineage). No increased blasts.

Cytogenetics: monosomy 7

Somatic molecular NGS panel: disease-associated variants in RUNX1 (VAF 7%), GATA2 (VAF 51%). VUS in ETV6 (VAF 8%).

Diagnosis → MDS in a patient with germline predisposition (GATA2 deficiency)

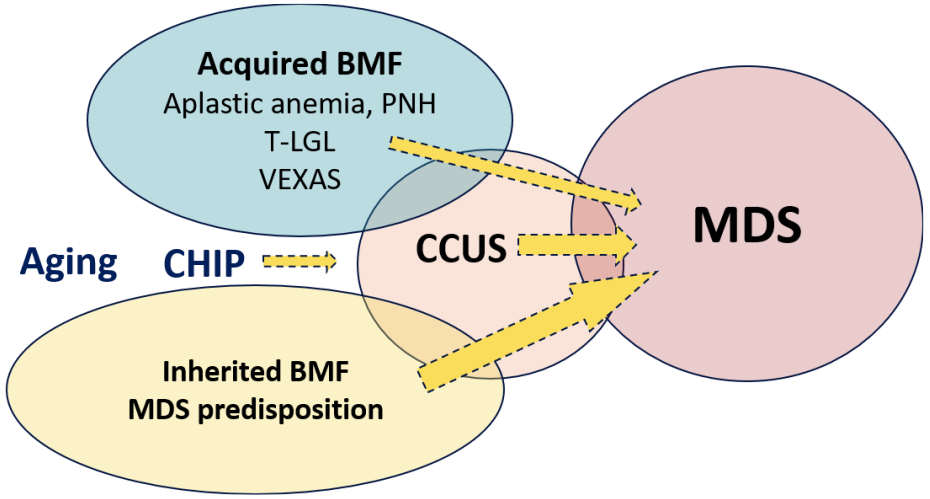
Differential diagnosis of cytopenias and BMF



Cytopenic syndromes and clonal hematopoiesis

<u>Exclusion of secondary causes:</u>

- *Nutritional*
- *Infectious*
- *Rheumatologic*
- *Medications/toxins*
- *Endocrine*
- *Organ dysfunction (cirrhosis, CKD)*
- *Peripheral destruction*
- *Sequestration*



<u>ICUS:</u>

- Requires BM biopsy to exclude malignancies, and an evaluation for acquired and inherited BMF and other defined syndromes

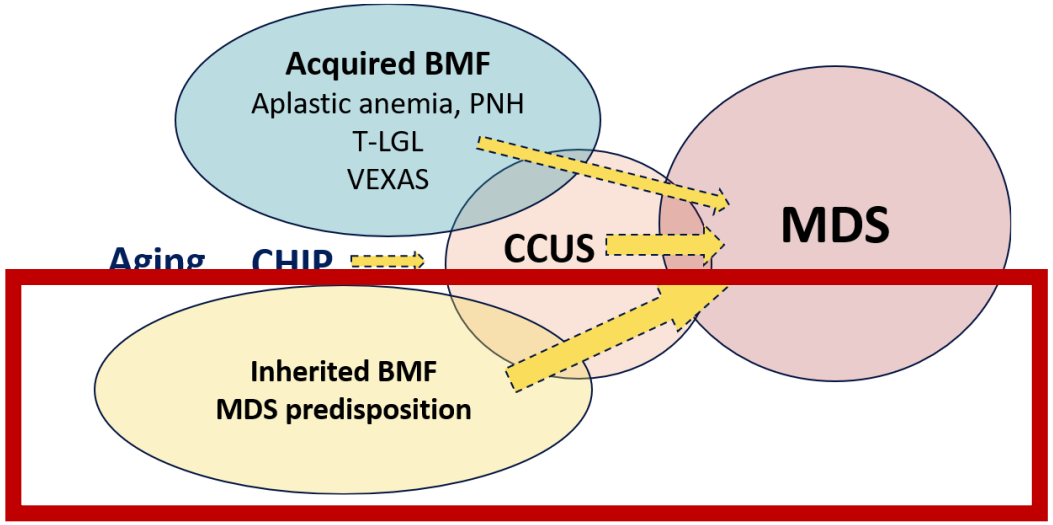
<u>CCUS:</u>

- Requires BM biopsy to exclude malignancies, and an evaluation for acquired and inherited BMF and other defined syndromes
- Additionally, requires findings of clonality

Cytopenic syndromes and clonal hematopoiesis

Exclusion of secondary causes:

- *Nutritional*
- *Infectious*
- *Rheumatologic*
- *Medications/toxins*
- *Endocrine*
- *Organ dysfunction (cirrhosis, CKD)*
- *Peripheral destruction*
- *Sequestration*

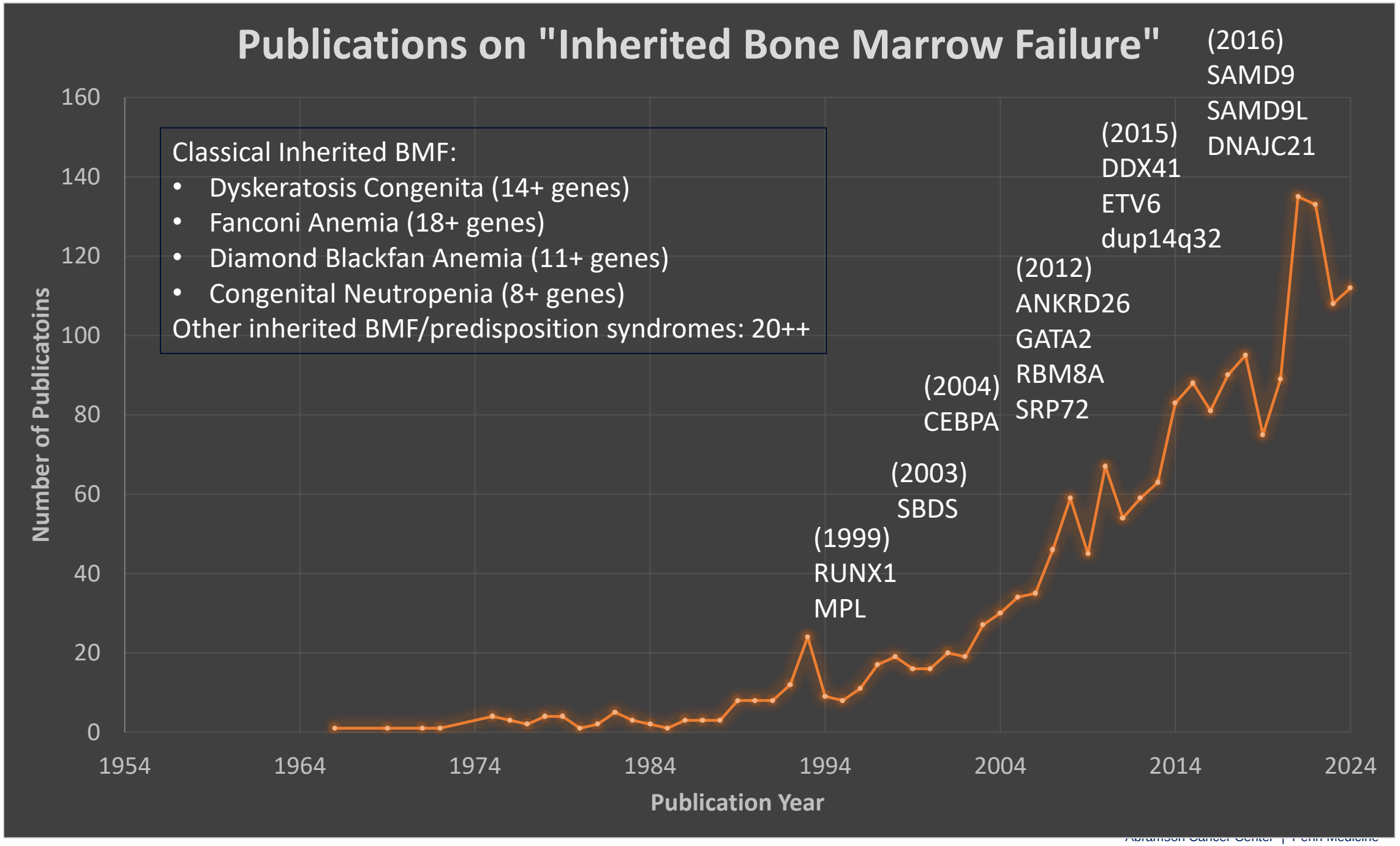


ICUS:

- Requires BM biopsy to exclude malignancies, and an evaluation for acquired and inherited BMF and other defined syndromes

CCUS:

- Requires BM biopsy to exclude malignancies, and an evaluation for acquired and inherited BMF and other defined syndromes
- Additionally, requires findings of clonality


Publications on "Inherited Bone Marrow Failure"
Classical Inherited BMF:
• Dyskeratosis Congenita (14+ genes)
• Fanconi Anemia (18+ genes)
• Diamond Blackfan Anemia (11+ genes)
• Congenital Neutropenia (8+ genes)
Other inherited BMF/predisposition syndromes: 20++
(1999)
RUNX1
MPL
(2003)
SBDS
(2004)
CEBPA
(2012)
ANKRD26
GATA2
RBM8A
SRP72
(2015)
DDX41
ETV6
dup14q32
(2016)
SAMD9
SAMD9L
DNAJC21
Number of Publicatoins
Publication Year
0
20
40
60
80
100
120
140
160
1954
1964
1974
1984
1994
2004
2014
2024

NCCN guidelines on MDS predisposition (1.2025)

Germline predisposition for myeloid neoplasms *with* pre-existing cytope

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy
ANKRD26[17]	*ANKRD26*	Moderate thrombocytopenia with mild bleeding manifestations; platelet size is usually not enlarged; dysmegakaryopoiesis[18]/AML, MDS
ETV6[21,22]	*ETV6*	Thrombocytopenia and mild bleeding manifestations; platelet size is usually not enlarged[23]/AML, MDS
MECOM-associated syndrome	*MECOM (MDS1 and EVI1 complex locus) on 3q26.2*	Amegakaryocytic thrombocytopenia; B-cell deficiency; hypocellular marrow failure/ MDS[24,25]
GATA2 deficiency syndrome[27,28]	*GATA2*	Bone marrow failure; monocytopenia/AML, MDS; B-/NK-/ CD4-cell lymphocytopenia; highly penetrant[29]

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES[a]

Germline predisposition for myeloid neoplasms *without* cytopenia(s), dysplasia, or other organ dysfunction prior to myeloid malignancy presentation

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy	Lifetime Risk of MDS/AML	Other Phenotypes and Clinical Features
CEBPA[1]	*CEBPA*	AML	~90% for germline N-terminal (frameshift) mutations[1,2,3] and ~50% for germline C-terminal bZIP region mutations[b,4,5]	AML (not associated with MDS development) is typically favorable risk and characterized by acquisition of a second somatic mutation in *CEBPA*. The germline mutation most commonly affects the N-terminus whereas the somatic mutation arises in the C-terminus bZIP region (predominantly missense or in-frame indels) with different somatic mutations occurring with AML recurrence.[2] ~5% to 10% of *CEBPA* double-mutant AML cases harbor germline mutations.[6] Less commonly, familial AML due to germline mutations in the C-terminus bZIP region have also been reported.[4,5]
DDX41-associated predisposition to myeloid malignancy[7]	*DDX41*	AML, MDS, CML	• Estimates vary. Penetrance is higher in males than females • ~50% (estimated by an analysis of 1st degree relatives of patients with germline *DDX41* mutations with MDS/ AML)[8] • ~3% (estimated by a UK Biobank population-based analysis)[9]	Patients often have macrocytosis and/or cytopenias prior to myeloid malignancy development.[10] Median age of onset of myeloid malignancy is ~ 66 y, like sporadic AML/MDS.[11-14] Risk of myeloid malignancy is negligible prior to ~ 40 y.[8] Myeloid malignancy development is associated with biallelic *DDX41* mutations due to acquisition of a somatic mutation in the wild-type allele in ~55% to 70% of AML/MDS cases. Most commonly, the somatic mutation is R525H.[8,12,13] AML is commonly characterized by hypocellularity, low blast percentage, and a normal karyotype.[14,15]
14q32.2 genomic duplicatio				

Germline predisposition for myeloid neoplasms *with* pre-existi

Disorder	Gene	Hematologic Findin Myeloid Malignanc
SAMD9/SAMD9L syndromes[31,43-45]	*SAMD9 SAMD9L*	Transient or permanent cytopenias and hypocellular marrow failure/AML, MDS
SRP72[46]	*SRP72*	Marrow failure/MDS

Germline predisposition for myeloid neoplasms *with* pre-existing cytopenia(s) and/or other organ dysfunction prior to myeloid malignancy presentation

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy	Lifetime Risk of MDS/AML	Other Phenotypes and Clinical Features
Familial platelet disorder with associated myeloid malignancy[b,34,35]	*RUNX1*	Thrombocytopenia and abnormal platelet function/AML, MDS; highly penetrant[c]	35%-40%[36]	Typical age of onset of AML/MDS is 20–40 y. Anticipation may lead to occurrence in younger individuals in subsequent generations; eczema; ALL also seen.
LIG-4 syndrome[37]	*LIG4*	Marrow failure, lymphoid malignancy	Not established	Short stature, microcephaly, combined immunodeficiency.
Xeroderma pigmentosum C (XPC)[38,39]	*XPC^{delTG}*	Increased myeloid malignancies and T-cell ALL in people aged 7–29 y.	Not established	Sensitivity to ultraviolet light, experiencing severe sunburns within minutes of exposure, dry skin (xeroderma), freckling (pigmentosum), hearing loss, poor coordination, loss of intellectual function, seizures, and development of squamous cell carcinomas and melanomas often as early as 10 y in sun-exposed areas.
ERCC6L2[40-42]	*ERCC6L2*	Marrow failure/AML, MDS	Not established	Skeletal/cardiac abnormalities, neurological defects also associated with somatic *TP53* mutations and erythroleukemia. Pre-existing cytopenias, microcephaly, developmental delay, and other congenital abnormalities.

NCCN guidelines on MDS predisposition (1.2025)

Germline predisposition for myeloid neoplasms *with* pre-existing cytope

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy
ANKRD26[17]	*ANKRD26*	Moderate thrombocytopenia with mild bleeding manifestations; platelet size is usually not enlarged; dysmegakaryopoiesis[18]/AML, MDS
ETV6[21,22]	*ETV6*	Thrombocytopenia and mild bleeding manifestations; platelet size is usually not enlarged[23]/AML, MDS
MECOM-associated syndrome	*MECOM (MDS1 and EVI1 complex locus) on 3q26.2*	Amegakaryocytic thrombocytopenia; B-cell deficiency; hypocellular marrow failure/ MDS[24,25]
GATA2 deficiency syndrome[27,28]	*GATA2*	Bone marrow failure; monocytopenia/AML, MDS; B-/NK-/ CD4-cell lymphocytopenia; highly penetrant[29]

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES[a]

Germline predisposition for myeloid neoplasms *without* cytopenia(s), dysplasia, or other organ dysfunction prior to myeloid malignancy presentation

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy	Lifetime Risk of MDS/AML	Other Phenotypes and Clinical Features
CEBPA[1]	*CEBPA*	AML	~90% for germline N-terminal (frameshift) mutations[1,2,3] and ~50% for germline C-terminal bZIP region mutations[b,4,5]	AML (not associated with MDS development) is typically favorable risk and characterized by acquisition of a second somatic mutation in *CEBPA*. The germline mutation most commonly affects the N-terminus whereas the somatic mutation arises in the C-terminus bZIP region (predominantly missense or in-frame indels) with different somatic mutations occurring with AML recurrence.[2] ~5% to 10% of *CEBPA* double-mutant AML cases harbor germline mutations.[6] Less commonly, familial AML due to germline mutations in the C-terminus bZIP region have also been reported.[4,5]
DDX41-associated predisposition to myeloid malignancy[7]	*DDX41*	AML, MDS, CML	• Estimates vary. Penetrance is higher in males than females • ~50% (estimated by an analysis of 1st degree relatives of patients with germline *DDX41* mutations with MDS/ AML)[8] • ~3% (estimated by a UK Biobank population-based	Patients often have macrocytosis and/or cytopenias prior to myeloid malignancy development.[10] Median age of onset of myeloid malignancy is ~ 66 y, like sporadic AML/MDS.[11-14] Risk of myeloid malignancy is negligible prior to ~ 40 y.[8] Myeloid malignancy development is associated with biallelic *DDX41* mutations due to acquisition of a somatic mutation in the wild-type allele in ~55% to 70% of AML/MDS cases. Most commonly, the somatic mutation is R525H.[8,12,13] AML is commonly characterized by hypocellularity, low blast percentage, and a normal karyotype.[14,15]
14q32.2 genomic duplicatio				

Germline predisposition for myeloid neoplasms *with* pre-existi

Disorder	Gene	Hematologic Findin Myeloid Malignanc
SAMD9/SAMD9L syndromes[31,43-45]	*SAMD9 SAMD9L*	Transient or permanent cytopenias and hypocellular marrow failure/AML, MDS
SRP72[46]	*SRP72*	Marrow failure/MDS

Germline predisposition for myeloid neoplasms *with* pre-existing cytopenia(s) and/or other organ dysfunction prior to myeloid malignancy presentation

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy	Lifetime Risk of MDS/AML	Other Phenotypes and Clinical Features
Familial platelet disorder with associated myeloid malignancy[b,34,35]	*RUNX1*	Thrombocytopenia and abnormal platelet function/AML, MDS; highly penetrant[c]	35%-40%[36]	Typical age of onset of AML/MDS is 20–40 y. Anticipation may lead to occurrence in younger individuals in subsequent generations; eczema; ALL also seen.
LIG-4 syndrome[37]	*LIG4*	Marrow failure, lymphoid malignancy	Not established	Short stature, microcephaly, combined immunodeficiency.
Xeroderma pigmentosum C (XPC)[38,39]	*XPC^{delTG}*	Increased myeloid malignancies and T-cell ALL in people aged 7–29 y.	Not established	Sensitivity to ultraviolet light, experiencing severe sunburns within minutes of exposure, dry skin (xeroderma), freckling (pigmentosum), hearing loss, poor coordination, loss of intellectual function, seizures, and development of squamous cell carcinomas and melanomas often as early as 10 y in sun-exposed areas.
ERCC6L2[40-42]	*ERCC6L2*	Marrow failure/AML, MDS	Not established	Skeletal/cardiac abnormalities, neurological defects also associated with somatic *TP53* mutations and erythroleukemia. Pre-existing cytopenias, microcephaly, developmental delay, and other congenital abnormalities.

Whom to evaluate for inherited BMF diseases

- Lifelong cytopenias, aplastic anemia and hypocellular MDS
- MDS in the young(er) [*e.g., <50 years**]
- Family history of MDS/AML or associated conditions
- "Red flag" conditions associated with BMF syndomes:

- monosomy 7 or chromosome 1q gain in young patient w/ MDS
- congenital malformations and dysmorphology incl. abnl thumbs
- solid tumors at a young age
- failure to recover counts after chemotherapy/radiation
- immune deficiency, lymphedema
- cirrhosis, pulmonary fibrosis, early graying, mucocutaneous findings

Estimated prevalence of predisposition syndromes in MDS patients

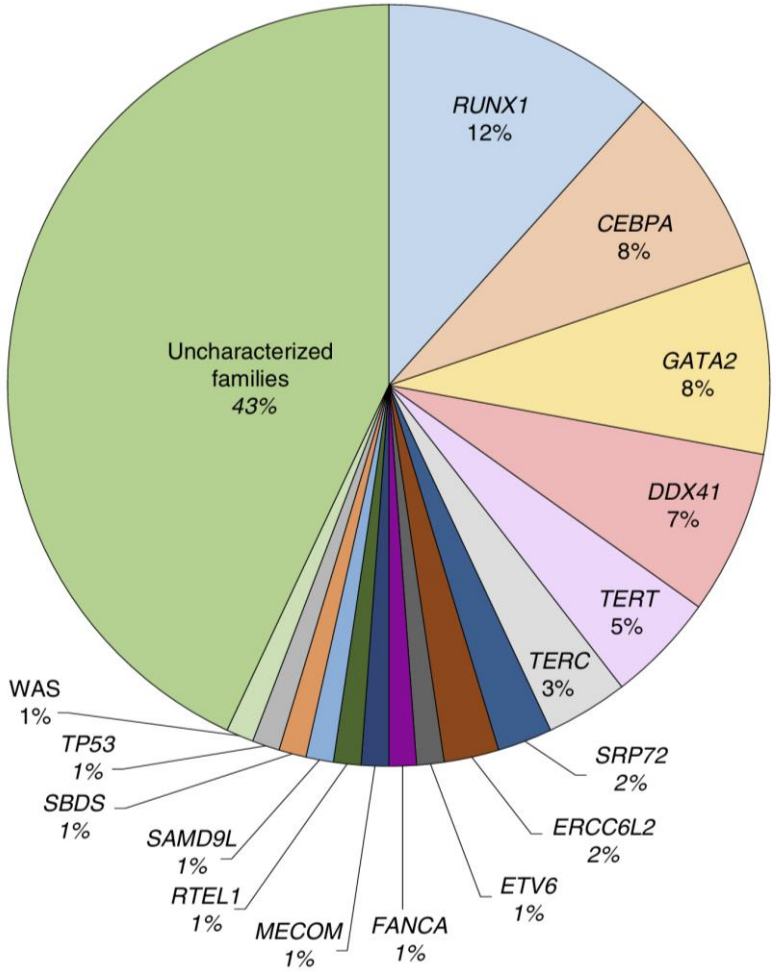
All-comer MDS patients:

- Estimated ~15% with hereditary syndromes

Patients with known familial MDS: ⟶

~60% with defined diagnosis

40% without defined diagnosis



NATURECOMMUNICATIONS | (2020) 11:1044 Abramson Cancer Center | Penn Medicine

Clinical case #1: 45 yo F referred for a new dx of MDS

Hematologic history:

- No prior documented normal CBC
- Late teens: cytopenias and infections, BM biopsy hypocellular w/mild mega dysplasia and normal karyotype
- 20s: recurrent bacterial infections; another BM biopsy; moderate neutropenia, diagnosed with T-LGL
- 30s: worsening pancytopenia, 1.4>9<72. Diagnosed with acquired AA, treated with horse ATG+CSA. Persistent cytopenias.
- Age 45: progressive cytopenias and transfusion dependence.

  0.6>6.5<25, ANC 0.48, AMC 0.02, ALC 0.04.

Clinical case #1: 45 yo F referred for a new dx of MDS

Past medical history

- Recurrent genital warts, with vaginal, cervical, anal dysplasia, and vulvar cancer. First LEEP procedure at 25.
- Multiple miscarriages
- Chronic non-pitting bilateral leg swelling=lymphedema (similar to her maternal side of the family).

Bone marrow biopsy: Normocellular (50%). Mega atypia (focally clustered, hypo- and abnormally lobated) (20% of lineage). No increased blasts.

Cytogenetics: monosomy 7

Somatic molecular NGS panel: disease-associated variants in RUNX1 (VAF 7%), GATA2 (VAF 51%). VUS in ETV6 (VAF 8%).

Diagnosis → MDS in a patient with germline predisposition (GATA2 deficiency)

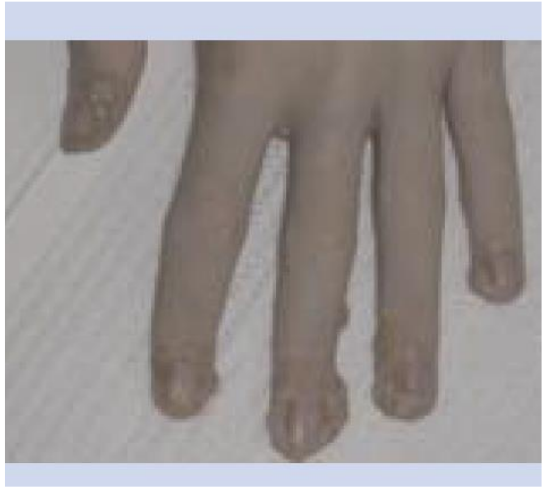
CLINICAL REPORT

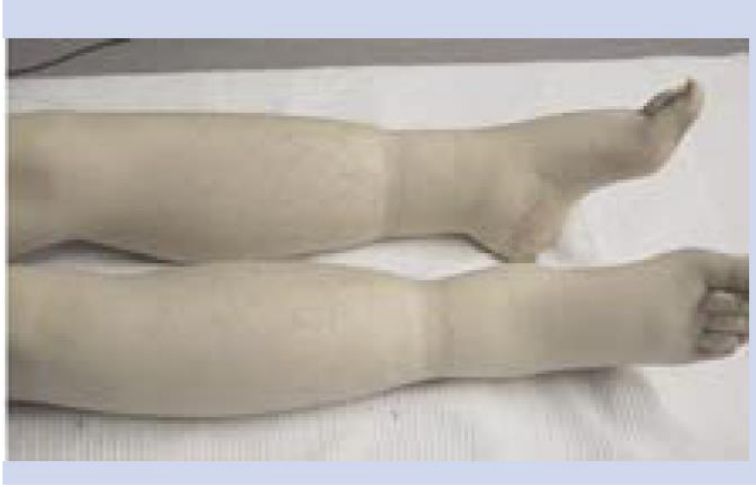
AMERICAN JOURNAL OF medical genetics

Emberger Syndrome—Primary Lymphedema With Myelodysplasia: Report of Seven New Cases

Autosomal-dominant

- Lymphedema
- Predisposition to MDS/AML
- Warts
- Sensorineural deafness





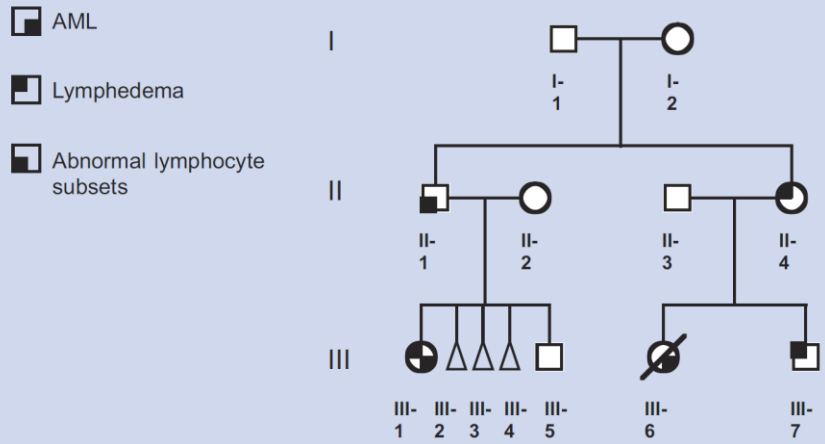


FIG. 1. Pedigree for patient 1.

Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency

Rachel Emma Dickinson,[1] Helen Griffin,[2] Venetia Bigley,[1,3] Louise N. Reynard,[1] Rafiqul Hussain,[2] Muzlifah Haniffa,[1,3] Jeremy H. Lakey,[4] Thahira Rahman,[2] Xiao-Nong Wang,[1] Naomi McGovern,[1] Sarah Pagan,[1] Sharon Cookson,[1] David McDonald,[1] Ignatius Chua,[5] Jonathan Wallis,[3] Andrew Cant,[1,3] Michael Wright,[2,3] Bernard Keavney,[2] Patrick F. Chinnery,[2] John Loughlin,[1] Sophie Hambleton,[1,3] Mauro Santibanez-Koref,[2] and Matthew Collin[1,3]

Mutations in *GATA2* are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome

Amy P. Hsu,[1] Elizabeth P. Sampaio,[1] Javed Khan,[2] Katherine R. Calvo,[3] Jacob E. Lemieux,[4] Smita Y. Patel,[5] David M. Frucht,[6] Donald C. Vinh,[1] Roger D. Auth,[6] Alexandra F. Freeman,[1] Kenneth N. Olivier,[1] Gulbu Uzel,[1] Christa S. Zerbe,[1] Christine Spalding,[1] Stefania Pittaluga,[7] Mark Raffeld,[7] Douglas B. Kuhns,[8] Li Ding,[1] Michelle L. Paulson,[1,8] Beatriz E. Marciano,[1] Juan C. Gea-Banacloche,[9] Jordan S. Orange,[10] Jennifer Cuellar-Rodriguez,[1] Dennis D. Hickstein,[9] and Steven M. Holland[1]

Loss-of-function germline *GATA2* mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature

*Jan Kazenwadel,[1] *Genevieve A. Secker,[1] *Yajuan J. Liu,[2] Jill A. Rosenfeld,[3] Robert S. Wildin,[4] Jennifer Cuellar-Rodriguez,[5] Amy P. Hsu,[5] Sarah Dyack,[6] Conrad V. Fernandez,[7] Chan-Eng Chong,[8,9] Milena Babic,[8] Peter G. Bardy,[1] Akiko Shimamura,[10,11] Michael Y. Zhang,[10,12] Tom Walsh,[12] Steven M. Holland,[5] Dennis D. Hickstein,[13] Marshall S. Horwitz,[2] *Christopher N. Hahn,[8,9] Hamish S. Scott,[8,9,14] and Natasha L. Harvey[1,9]

Heritable *GATA2* mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia

Christopher N Hahn[1,2], Chan-Eng Chong[1,2,14], Catherine L Carmichael[3,14], Ella J Wilkins[3,13], Peter J Brautigan[1], Xiao-Chun Li[1], Milena Babic[1], Ming Lin[1], Amandine Carmagnac[3], Young K Lee[1], Chung H Kok[4,5], Lucia Gagliardi[1], Kathryn L Friend[6], Paul G Ekert[7], Carolyn M Butcher[4,5], Anna L Brown[5], Ian D Lewis[2,5], L Bik To[2,5], Andrew E Timms[8], Jan Storek[9], Sarah Moore[1], Meryl Altree[10], Robert Escher[3,13], Peter G Bardy[5], Graeme K Suthers[10,11], Richard J D'Andrea[2,4,5,15], Marshall S Horwitz[8] & Hamish S Scott[1–3,12,15]

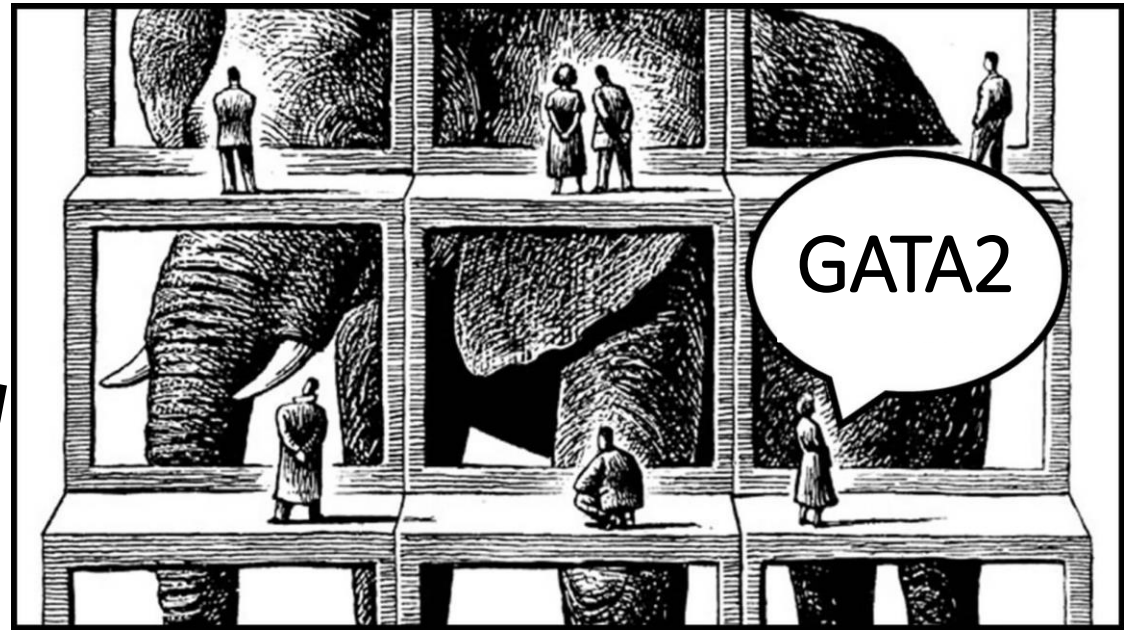
Mutations in *GATA2* cause human NK cell deficiency with specific loss of the CD56^{bright} subset

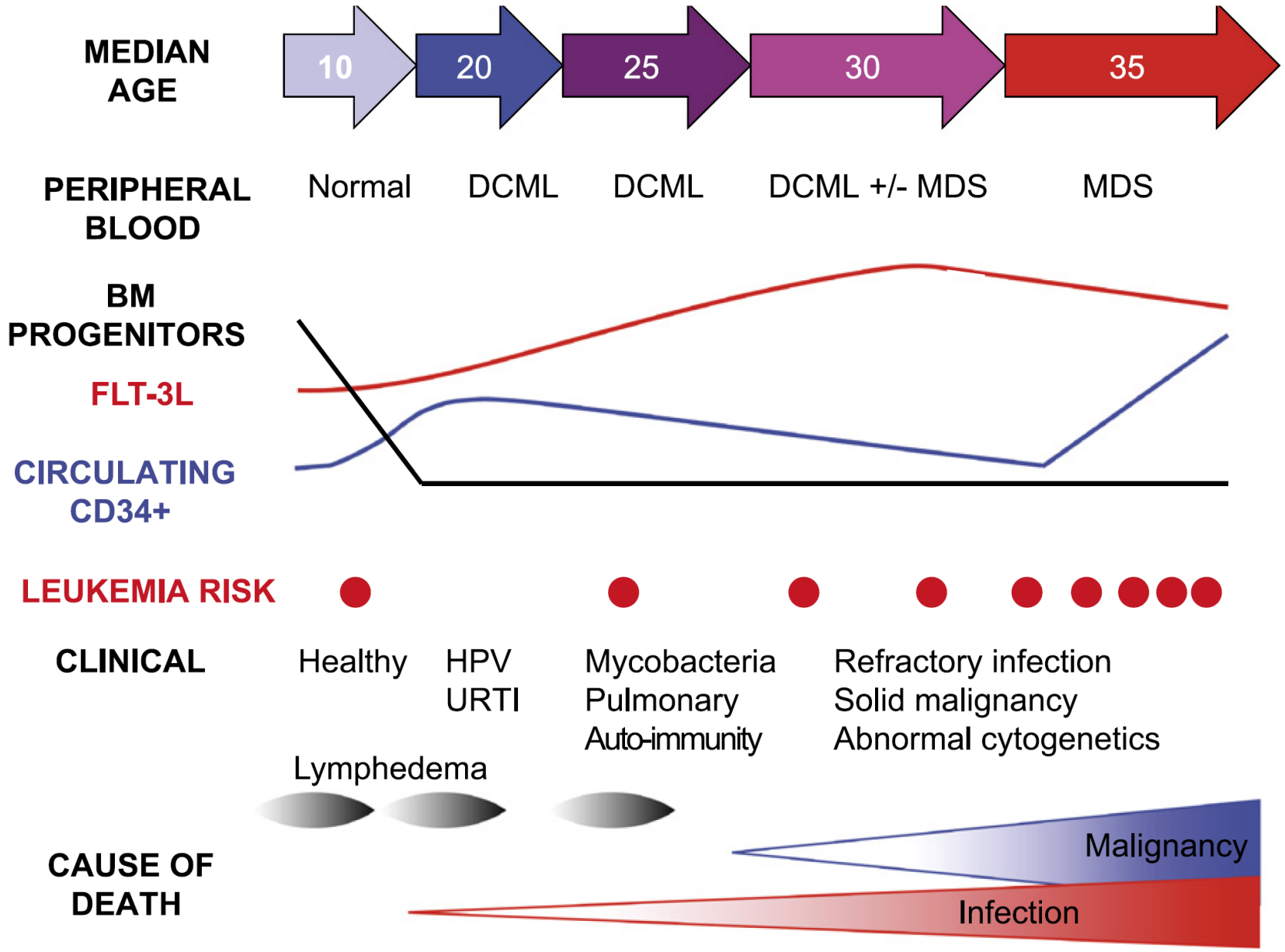
Emily M. Mace,[1,2] Amy P. Hsu,[3] Linda Monaco-Shawver,[4] George Makedonas,[1,2] Joshua B. Rosen,[4] Lesia Dropulic,[5] Jeffrey I. Cohen,[5] Eugene P. Frenkel,[6] John C. Bagwell,[6] John L. Sullivan,[7] Christine A. Biron,[8] Christine Spalding,[3] Christa S. Zerbe,[3] Gulbu Uzel,[3] Steven M. Holland,[3] and Jordan S. Orange[1,2]

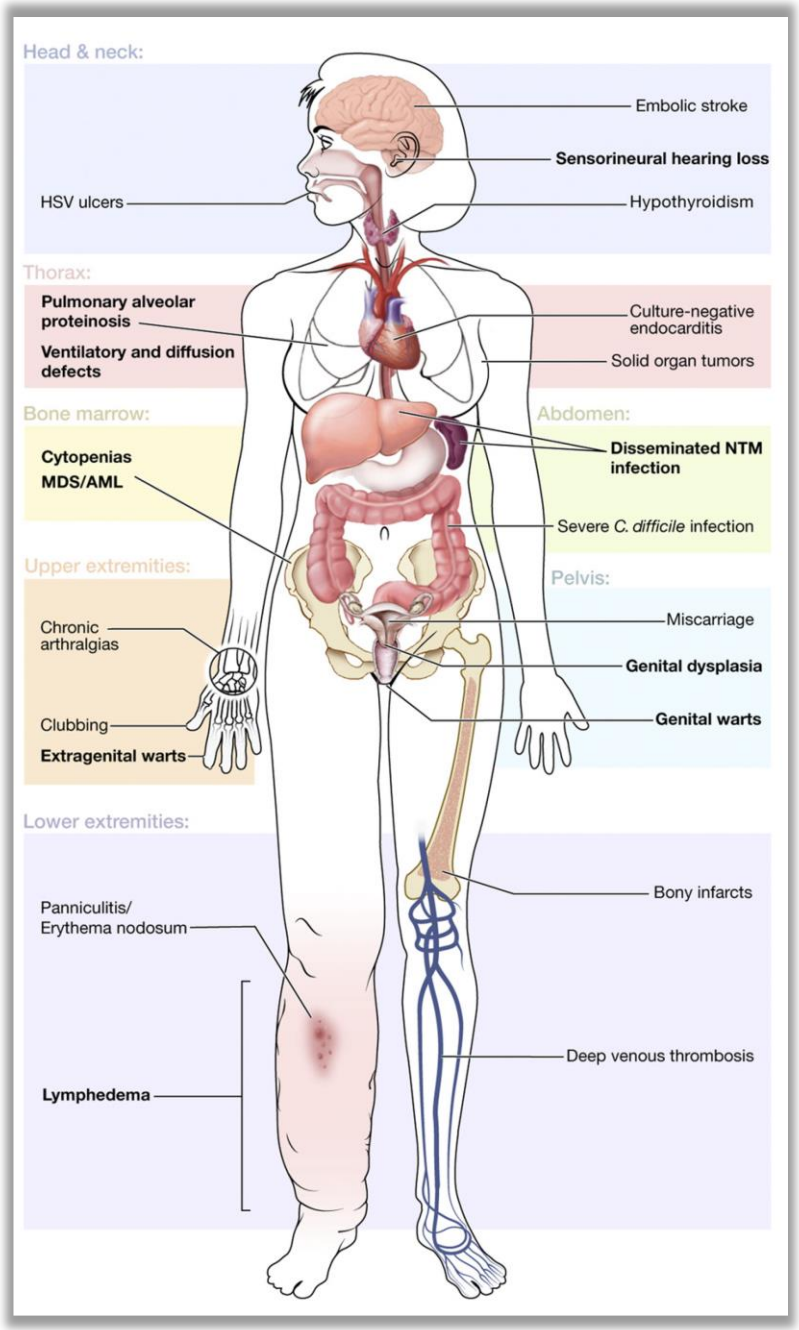
Mutations in *GATA2* cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome)

Pia Ostergaard[1,13], Michael A Simpson[2,13], Fiona C Connell[3], Colin G Steward[4], Glen Brice[5], Wesley J Woollard[2], Dimitra Dafou[2], Tatjana Kilo[6], Sarah Smithson[7], Peter Lunt[7], Victoria A Murday[8], Shirley Hodgson[5], Russell Keenan[9], Daniela T Pilz[10], Ines Martinez-Corral[11], Taija Makinen[11], Peter S Mortimer[12], Steve Jeffery[1], Richard C Trembath[2] & Sahar Mansour[5]

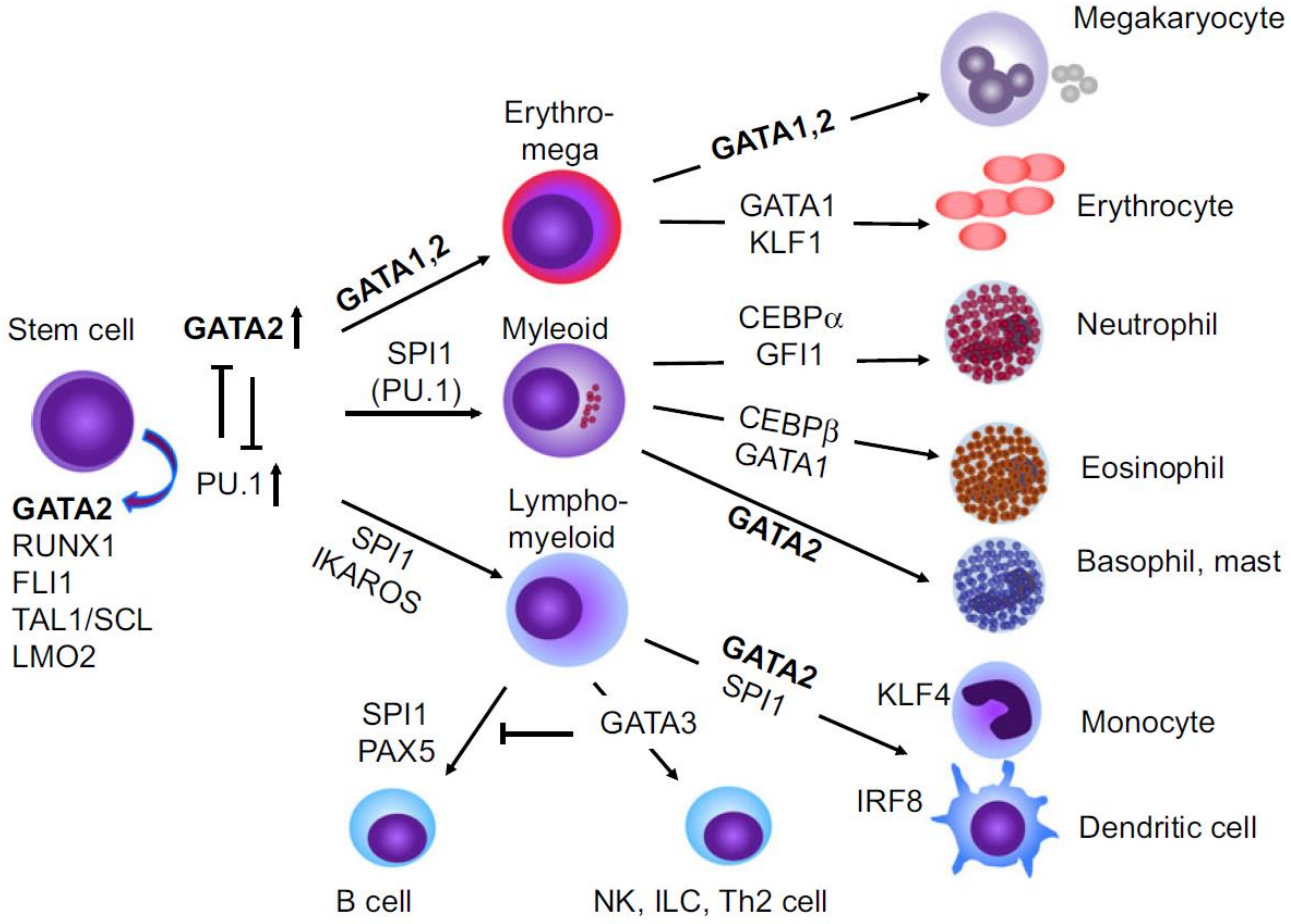
2010-2011




MEDIAN AGE
10
20
25
30
35
PERIPHERAL BLOOD
Normal
DCML
DCML
DCML +/- MDS
MDS
BM PROGENITORS
FLT-3L
CIRCULATING CD34+
LEUKEMIA RISK
CLINICAL
Healthy
HPV URTI
Mycobacteria Pulmonary Auto-immunity
Refractory infection Solid malignancy Abnormal cytogenetics
Lymphedema
CAUSE OF DEATH
Malignancy
Infection


Head & neck:
Embolic stroke
Sensorineural hearing loss
HSV ulcers
Hypothyroidism
Thorax:
Pulmonary alveolar proteinosis
Ventilatory and diffusion defects
Culture-negative endocarditis
Solid organ tumors
Bone marrow:
Cytopenias
MDS/AML
Abdomen:
Disseminated NTM infection
Severe C. difficile infection
Upper extremities:
Chronic arthralgias
Clubbing
Extragenital warts
Pelvis:
Miscarriage
Genital dysplasia
Genital warts
Lower extremities:
Panniculitis/ Erythema nodosum
Bony infarcts
Deep venous thrombosis
Lymphedema

GATA2 is a key transcriptional regulator of hematopoiesis



British Journal of Haematology, 2015, **169,** 173–187

In embryo, regulates endothelial to hematopoietic transition

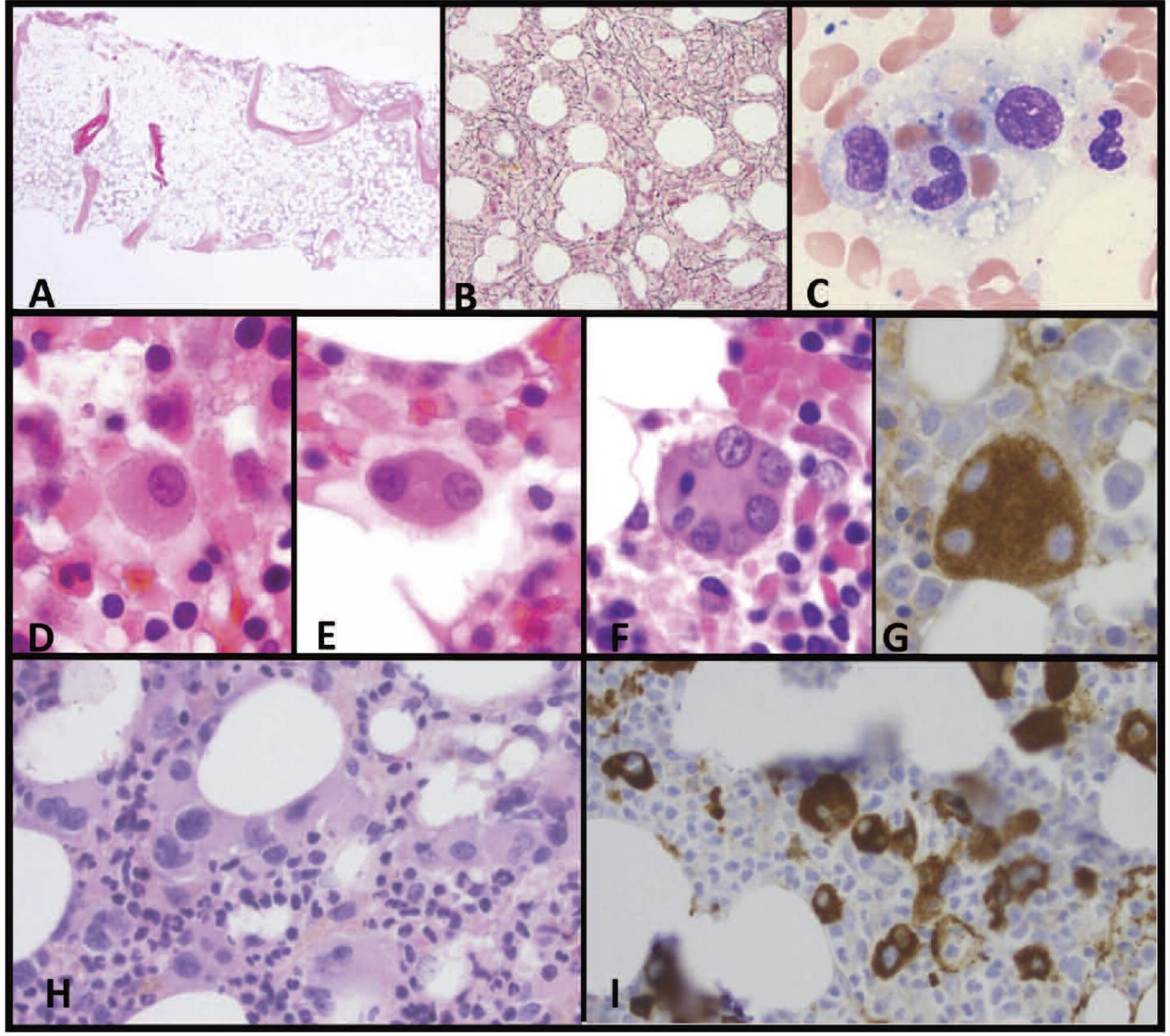
GATA2 KO is embryonic lethal due to failure to establish adult hematopoiesis

In adult hematopoiesis, GATA2 is

- Required for HSC survival and self-renewal
- Interacts with various transcription factors that regulate cell fate

Bone Marrow Features

- Hypocellular
- Fibrosis
- Hemophagocytic histiocytes
- Abnormal megakaryocytes



Clinical management of GATA2 deficiency

- Cytopenias/BMF
  - Supportive management of cytopenias
  - Bone marrow surveillance for MDS/AML evolution
- HSCT is indicated for:
  - Transfusion-dependent BMF
  - Adverse clonal evolution and MDS/AML progression
  - Severe immune deficiency with recurrent opportunistic infections
  - Refractory HPV disease
- HPV vaccination
- Multidisciplinary care including:
  - Infectious disease (for opportunistic infections, e.g. NTM, HSV)
  - Gyn (e.g. for genital warts, malignancy screening)
  - Dermatology (e.g. for EN)
  - Gyn (e.g., for recurrent miscarriage)
- Genetic counseling

NCCN guidelines on classical inherited BMF (1.2025)

Classical inherited bone marrow failure syndromes

Disorder	Gene	Hematologic Findings/ Myeloid Malignancy	Lifetime Risk of MDS/AML	Other Phenotypes and Clinical Features
Diamond-Blackfan anemia[d]	*RPL5, RPL11, RPL15, RPL23, RPL26, RPL27, RPL31, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, TSR2, GATA1*	Anemia and marrow erythroid hypoplasia/AML, MDS	~5% risk by 45–50 y[47,48]	Cardiac anomalies, Cathie facies, genitourinary anomalies, cleft lip/palate, short stature; sarcomas; elevated erythrocyte adenosine deaminase.
Fanconi anemia[e,f]	*FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ/BRIP1/ BACH1, FANCL, FANCM, FANCN/PALB2, FANCO/ RAD51C, FANCP/SLX4, FANCQ/ERCC4, FANCR/ RAD51, FANCS/BRCA1, FANCT/UBE2T, FANCU/ XRCC2, FANCV/REV7/ MAD2L2*	Bone marrow failure/AML, MDS	10% AML 90% bone marrow failure[49]	Short stature, skin pigmentation (café-au-lait or hypopigmented spots), skeletal anomalies (thumbs, arms), multiple other congenital anomalies; squamous cell carcinomas of head/neck/vulva/vagina, liver tumors, additional solid tumors associated with *FANCD1* include brain and Wilms tumors; therapy-related neoplasms may emerge after treatment for solid tumors; increased chromosome fragility. Cumulative incidence of solid cancers is extremely high in patients with bi-allelic *FANCD1/BRCA2* mutations (97% at the age of 7 y).
Shwachman-Diamond syndrome[g]	*SBDS, EFL1, DNAJC21*	Bone marrow failure/AML, MDS	Not established[50]	Pancreatic insufficiency, skeletal abnormalities; low serum trypsinogen or pancreatic isoamylase; somatic mutations in *EIF6* & *TP53*.[51]
Short telomere syndromes[h]	*ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RTEL1, TERC, TERT, TINF2, WRAP53, ZCCHC8*[52]	Bone marrow failure/AML, MDS	10% with the highest risk above the age of 50 y[53-55]	Idiopathic pulmonary fibrosis, emphysema, early hair graying, osteoporosis, pulmonary arteriovenous malformations and hepatopulmonary syndrome, liver fibrosis-cirrhosis, esophageal stricture, enterocolitis, immune deficiency; rare cases manifest as dyskeratosis congenita with nail dystrophy, rash, oral leukoplakia; squamous cell carcinomas of head/neck/GI tract; shortened telomere lengths. Somatic reversion events are possible. 10% lifetime risk has a competing risk of mortality due to pulmonary fibrosis.
Congenital neutropenia	*ELANE, G6PC3, GFI1, HAX1*	Neutropenia/AML, MDS	Not established	*G6PC3* mutations can be associated with congenital anomalies.[56] *HAX1* mutations can be associated with neurologic manifestations including seizures.[57]
Myeloid neoplasms associated with Down syndrome	*Trisomy 21, GATA1*	Transient abnormal myelopoiesis/AML, MDS	Not established	Down syndrome; acute megakaryoblastic leukemia.

References on MDS-E 8 of 10

- **SYNDROMIC**
- **HIGH POTENTIAL FOR TOXICITY**
- **LIFETIME RISK OF AML VARIES**
- **~10% FOR FANCONI ANEMIA AND TBD PATIENTS BY AGE 50 YEARS**
- **HIGHER FOR OTHER SYNDROMES (~50% BY AGE 50 FOR SDS)**

Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	15 (into late adulthood)	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	15 (into late adulthood)	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	15 (into late adulthood)	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	15 (into late adulthood)	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	15 (into late adulthood)	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

Hereditary BMF Syndromes

BMF Syndrome	Median age at dx (yrs)	Incidence	Molecular Pathogenesis	Inheritance	Malignancy predisposition
Fanconi Anemia (FA)	~6	~1 in 130,000	DNA Repair	AR, XR	MDS/AML + solid tumor (HIGH)
Telomere Biology Disorders (TBD)	15 (into late adulthood)	~1 in 1 million for DC; other forms unknown	Telomere Maintenance	AD,AR, XR	MDS/AML + solid tumor (HIGH)
Diamond-Blackfan Anemia (DBA)	<1	~1 in 200,000	Ribosomal Biogenesis	AD	MDS/AML + solid tumor (moderate)
Shwachman-Diamond Syndrome (SDS)	1	~1 in 100,000	Ribosomal Biogenesis (SBDS)	AR	MDS/AML (HIGH)
Severe Congenital Neutropenia (SCN)	3	~1 in 200,000	Heterogeneous (ELA2, HAX1, other)	AD, AR	MDS/AML (moderate)
SAMD9/SAMD9L syndromes	childhood	Unknown (~200 reported cases)	Gain of function in SAMD9 or SAMD9L, anti-proliferative effect	AD	MDS/AML (moderate)
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	<1	n/a	Defective thrombopoietin Receptor (MPL)	AR	None
Thrombocytopenia Absent Radii (TAR)	<1	< 1 in 100,000	Defective RNA pre-processing, exon –junction complex (RBM8A)	AR	MDS/AML (rare)

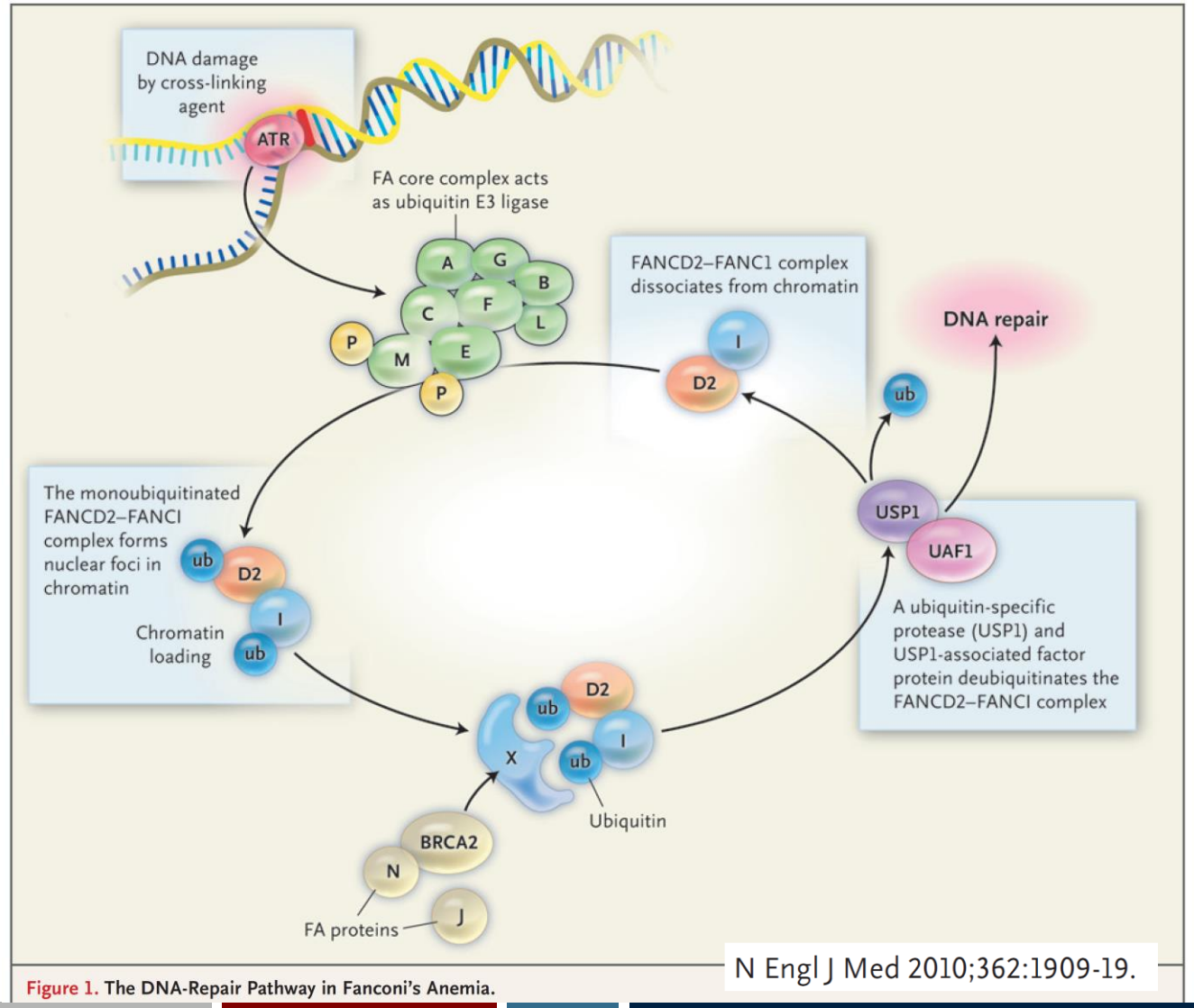
Patient Case #2

HPI: 30 yo F diagnosed with vulvar carcinoma
Physical exam: 5'1'' female, no lymphadenopathy, no organomegaly. Small thumb with a surgical scar overlying thumb.
Labs: mild pancytopenia.
Imaging: incidental finding of congenital absence of one kidney.

Clinical course:
- Following diagnosis of vulvar cancer, patient received cisplatin and radiation from her gyn oncologist.
- Following the first cycle of therapy, she developed profound pancytopenia with marrow aplasia.
- Hematology is consulted.

What is the likely diagnosis?
What testing should be ordered?

Fanconi Anemia (FA): Pathogenesis



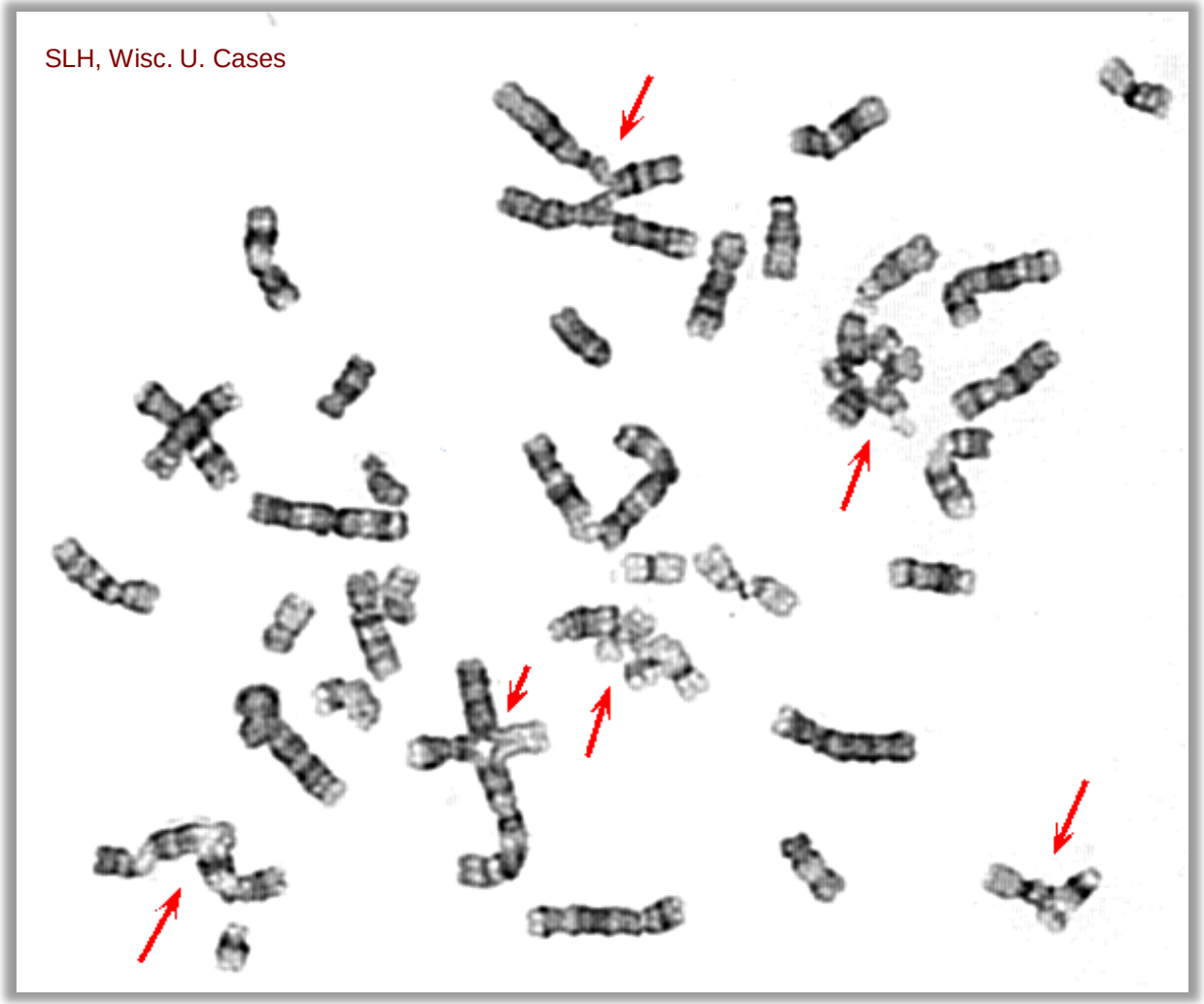
N Engl J Med 2010;362:1909-19.

Figure 1. The DNA-Repair Pathway in Fanconi's Anemia.

- One of the most common causes of inherited BMF
- FA incidence 1 in 130,000 live births in the US

- Genetic defect in one of 22 known FA complex genes
- Defect in homologous DNA repair
- Hypersensitivity to DNA crosslinking agents
  - DEB, mitomycin C
  - Others (cisplatin, radiation)

Diagnostic test: Chromosome Breakage Analysis



- PHA-stimulated peripheral blood lymphocytes cultured with crosslinking agents, mitomycin C and diepoxybutane (DEB).

- Increased chromosomal breaks and radials in FA.

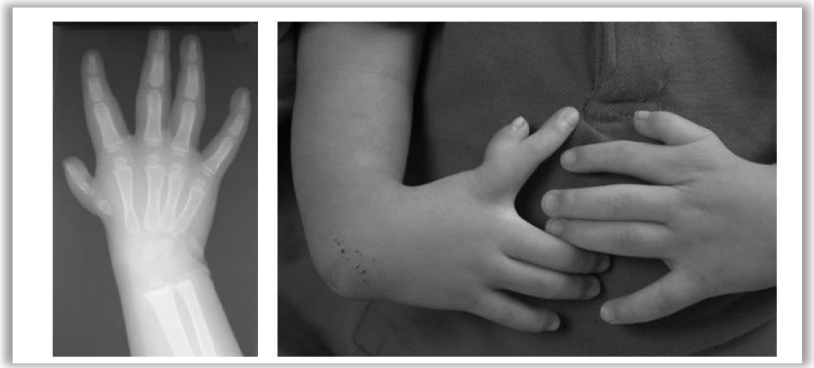
- Note: *In cases with a high suspicion of FA, but an apparent negative test in blood, testing should be repeated in skin fibroblasts, due to ~10-15% rate of reversion mosaicism and false-negative results in blood.*

Multisystem disease diagnosed in children and adults

Short stature
Café a lait spots
Thumb abnormalities
Microcephaly
Triangular face
Congenital hip dislocation
Hyper- and hypopigmentation
Imperforate anus
GU anomalies

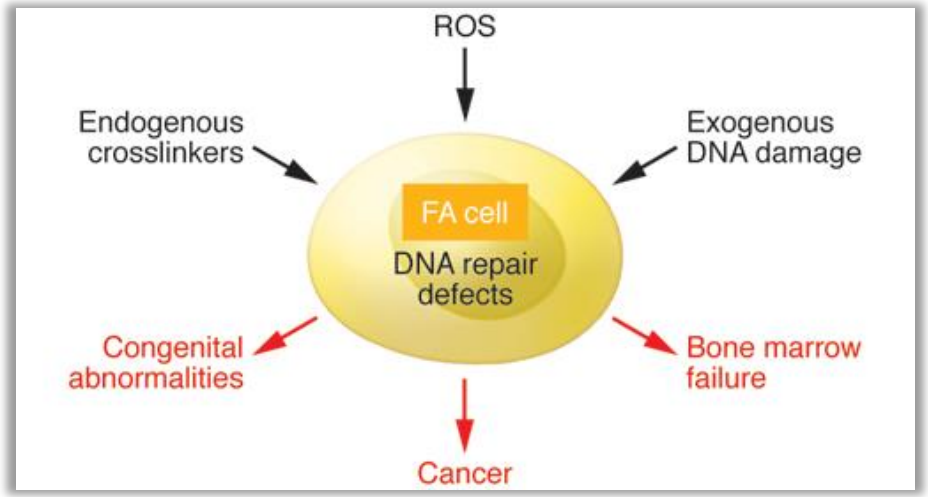
30% have no apparent extrahematopoietic findings

Blood Reviews 2010, 24, 101

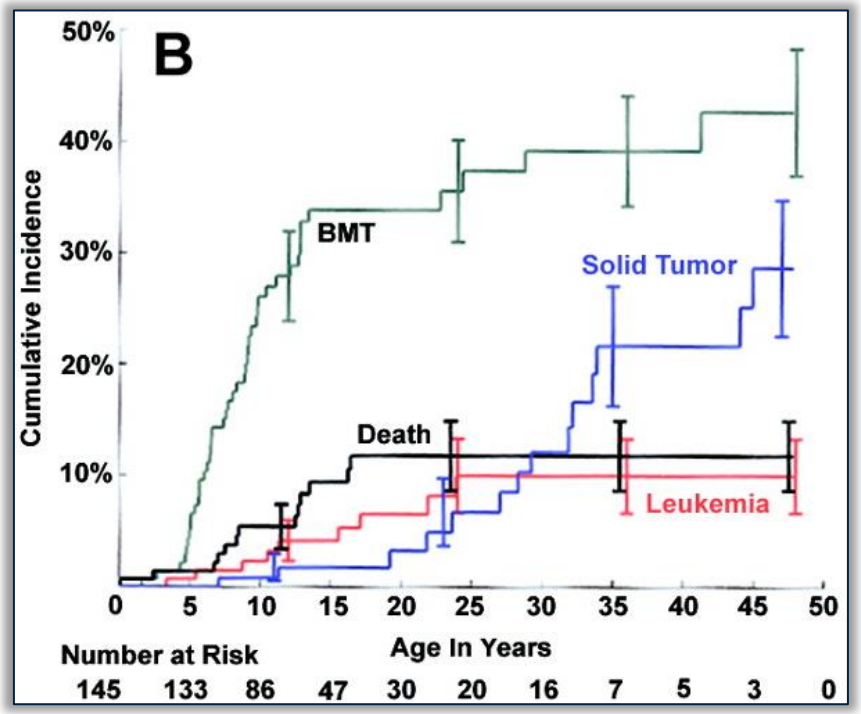


FA Handbook, Version 4, 2014

Predisposition to BMF, MDS/AML and solid tumors

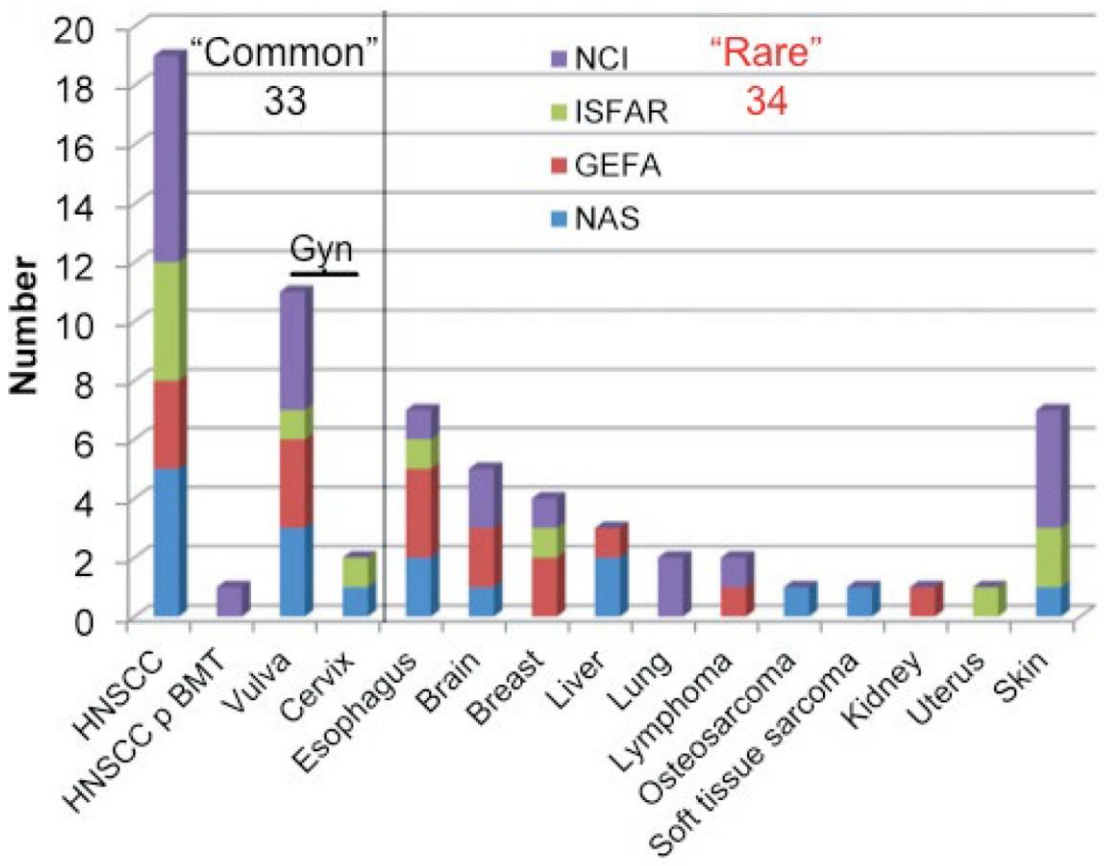


~80% develop BMF by age of 20 years
~10% develop MDS/AML by middle age
~30% develop solid tumors by 48 years

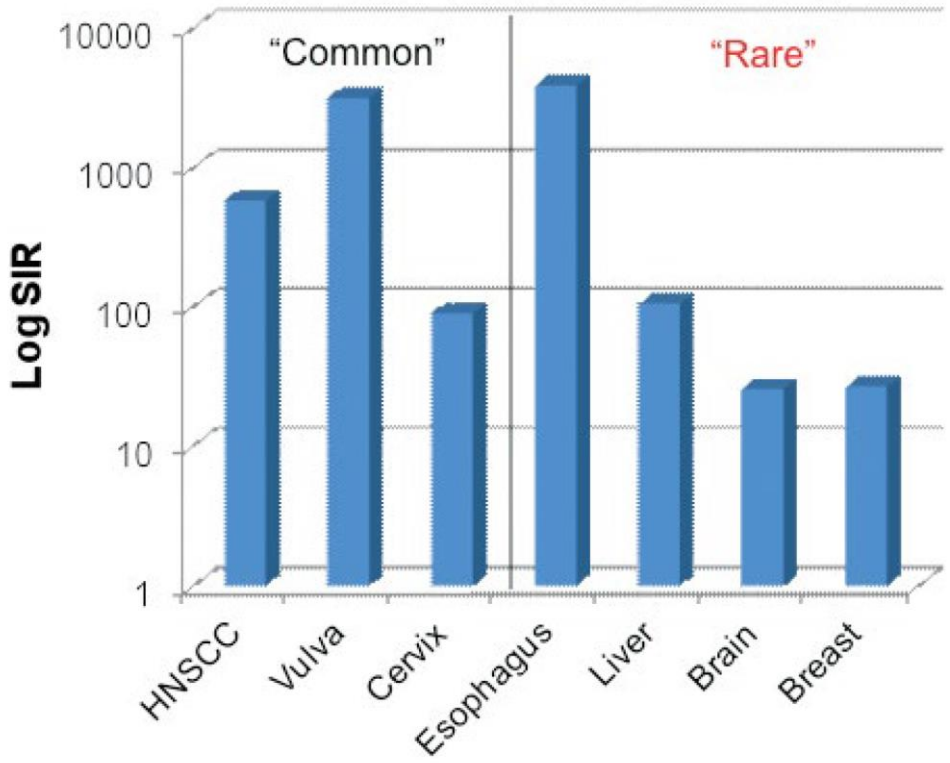


Rosenberg P S et al. Blood 2003;101:822-826

HNSCC and Gyn cancers are most common



Ratio Observed: Expected



FA Handbook, Version 4, 2014

Management of Fanconi Anemia

- Multimodality approach focused on management of cytopenias and cancer surveillance
  - BMF:
    - Bone marrow transplant is the only curative therapy for BMF
      - Requires lower intensity conditioning regimen
    - Medical management:
      - Anabolic steroids (e.g., oxymetholone or danazol)
      - Transfusion support
      - Avoidance of radiation and DNA damaging agents
    - *Experimental/emerging: gene therapy, antioxidants.*
  - Multidisciplinary care:
    - Endocrinology, ENT, GU, orthopedics/plastics, genetics.
  - Aggressive cancer surveillance:
    - ENT, gynecological, bone marrow surveillance.

More cases for discussion:

- A 67-year-old previously healthy patient with a recent diagnosis of AML was found to have two *FANCA* gene variants (both at 50% VAF, both VUS) on a somatic NGS panel done on recovery bone marrow after induction chemotherapy. How do you approach this case?

- A 40-year-old M with chronic thrombocytopenia, history of oropharyngeal dysplasia, and family history of a brother who died at a young age of “FA” has a negative chromosome breakage test. What is your next step?

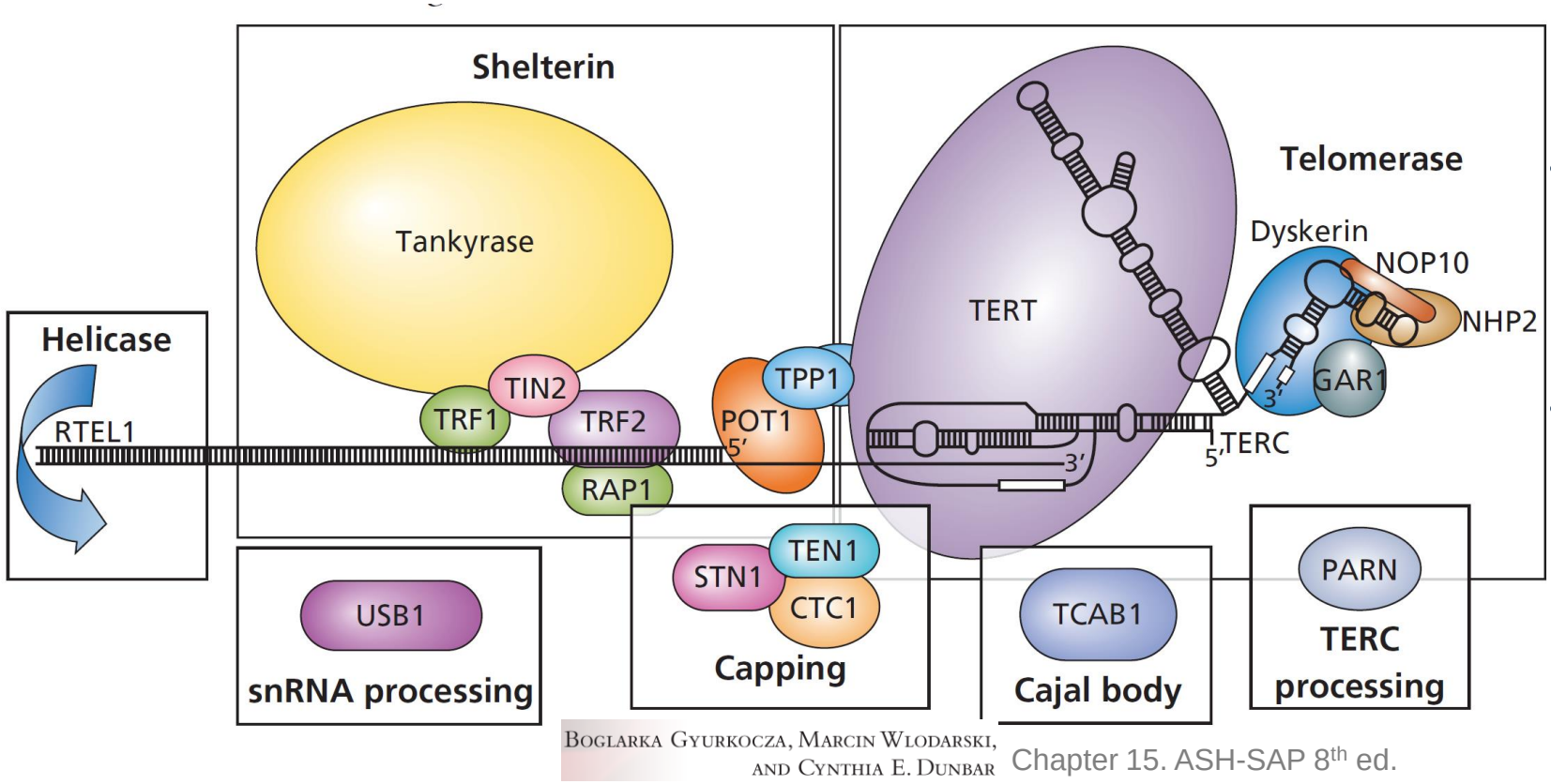
Patient Case 3

HPI: 55 yo M with decades-long thrombocytopenia, referred for evaluation of BMF.
Physical exam: Fit middle-aged male with unremarkable physical exam.
Labs: WBC 2.9, Hgb 10.6, Platelets 29; with 58.9% granulocytes, 6.2% monocytes, and 34.9% lymphocytes. MCV 121.
Family history: brother with thrombocytopenia.
Pathology: Bone marrow hypocellular without dysplastic changes, normal karyotype, and no acquired mutations.

BMF evaluation:

- Chromosome breakage studies were normal.
- Telomere length flow FISH testing showed very low lymphocyte telomere lengths for age
- Panel-based NGS genetic testing for genes mutated in BMF identified a pathogenic variant in *TERC*, confirming the diagnosis of telomere biology disorder (TBD).

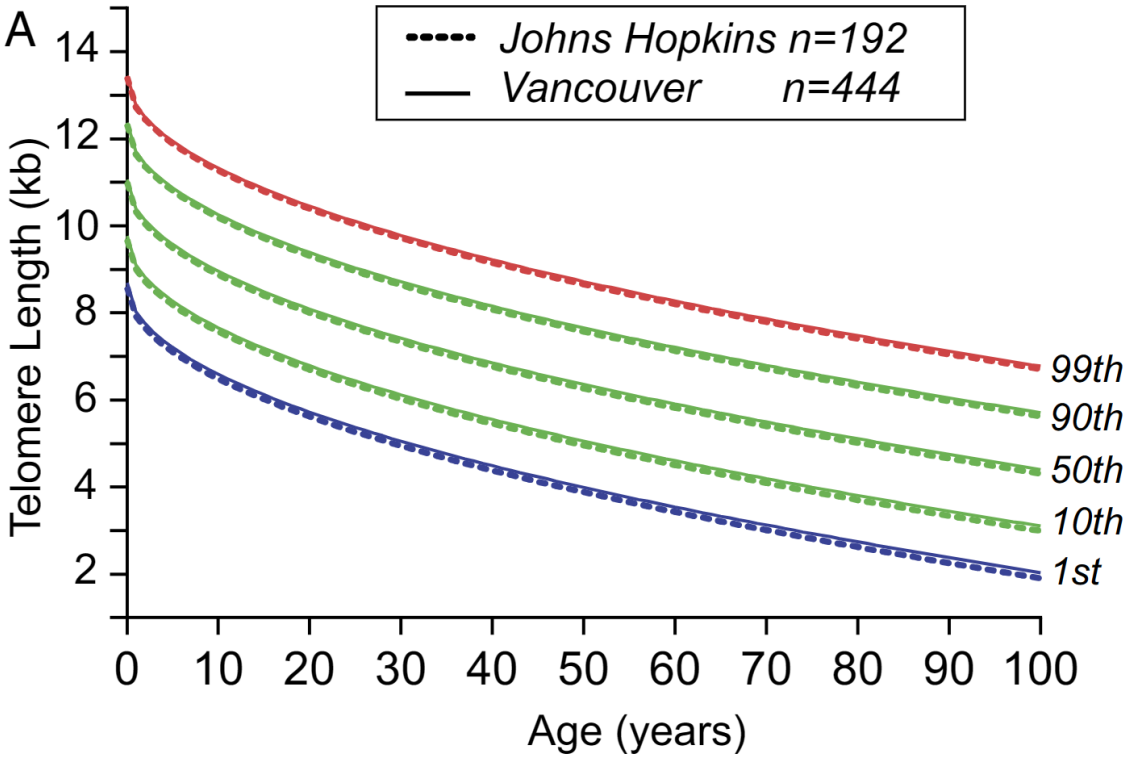
Telomere Biology Disorders



Boglarka Gyurkocza, Marcin Wlodarski, and Cynthia E. Dunbar Chapter 15. ASH-SAP 8th ed.

- Genetic defect in one of 14 genes associated with telomere maintenance
- Leads to abnormal shortening of telomeres

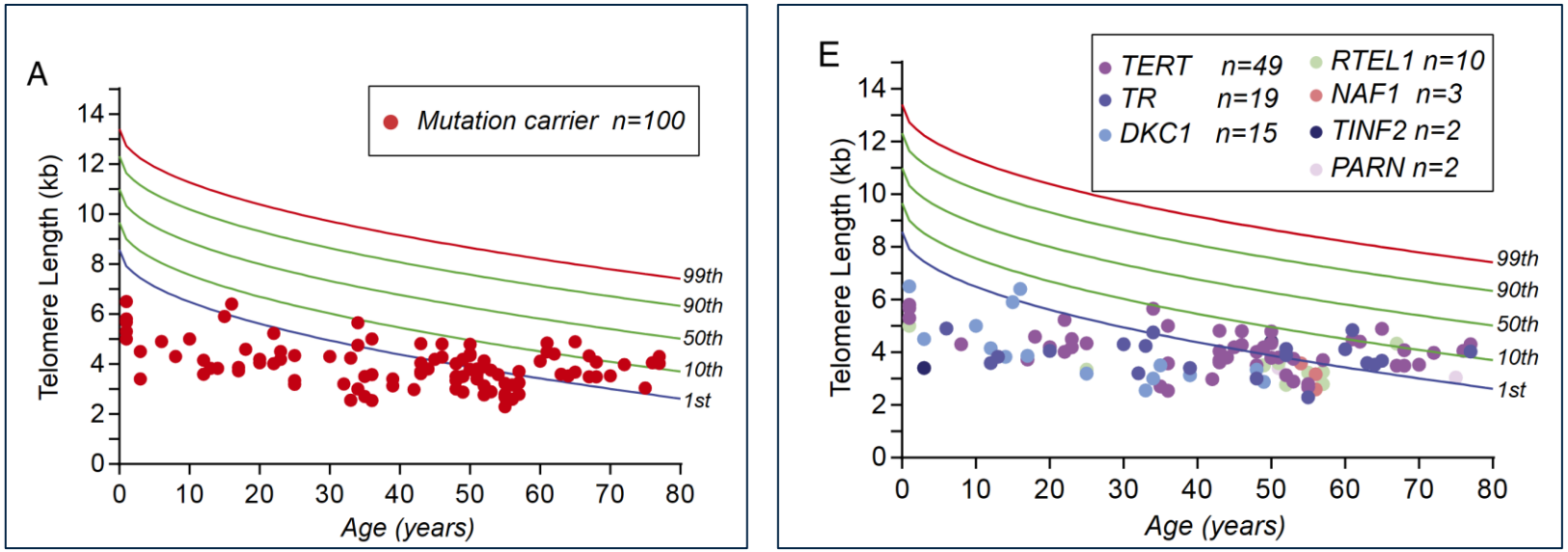
Diagnostic test: Telomere Length Measurement (flow-FISH)



Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365

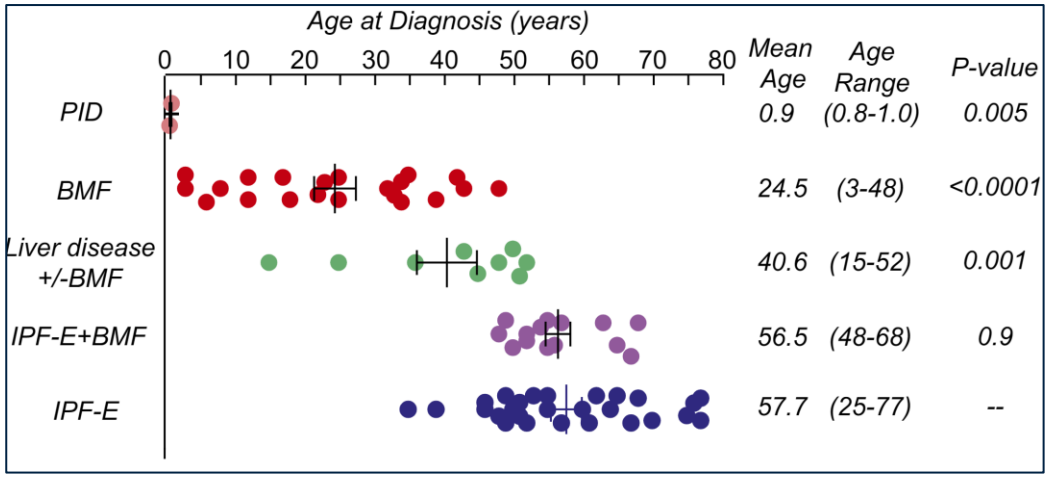
- TL by flow FISH is highly reproducible
- Standardized, age-dependent diagnostic thresholds.
- Low TL test should be followed by genetic testing to establish genetic diagnosis

Lymphocyte TL in genetically confirmed TBD patients

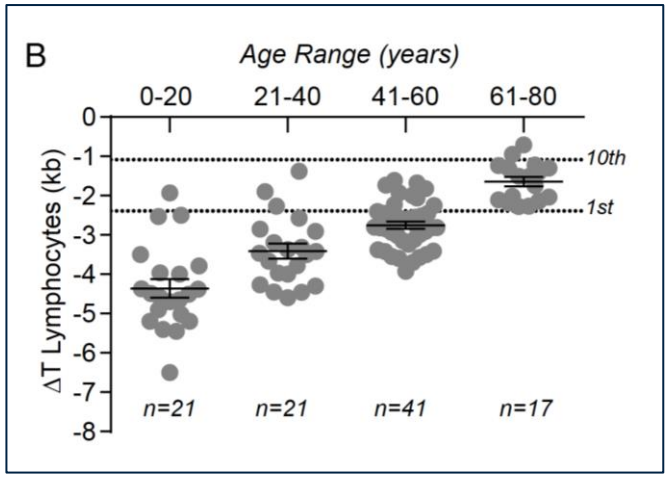


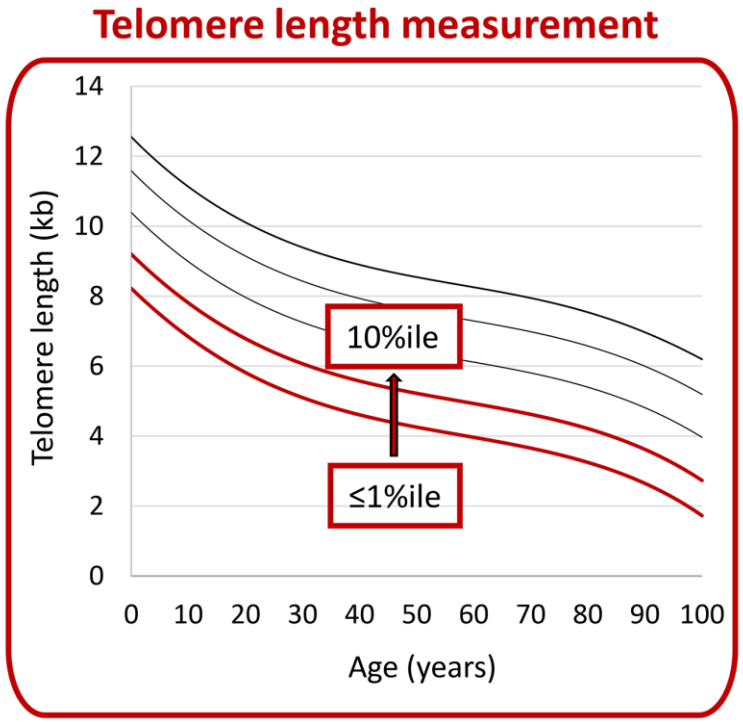
Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365

Age and presentation-dependent TL diagnostic thresholds



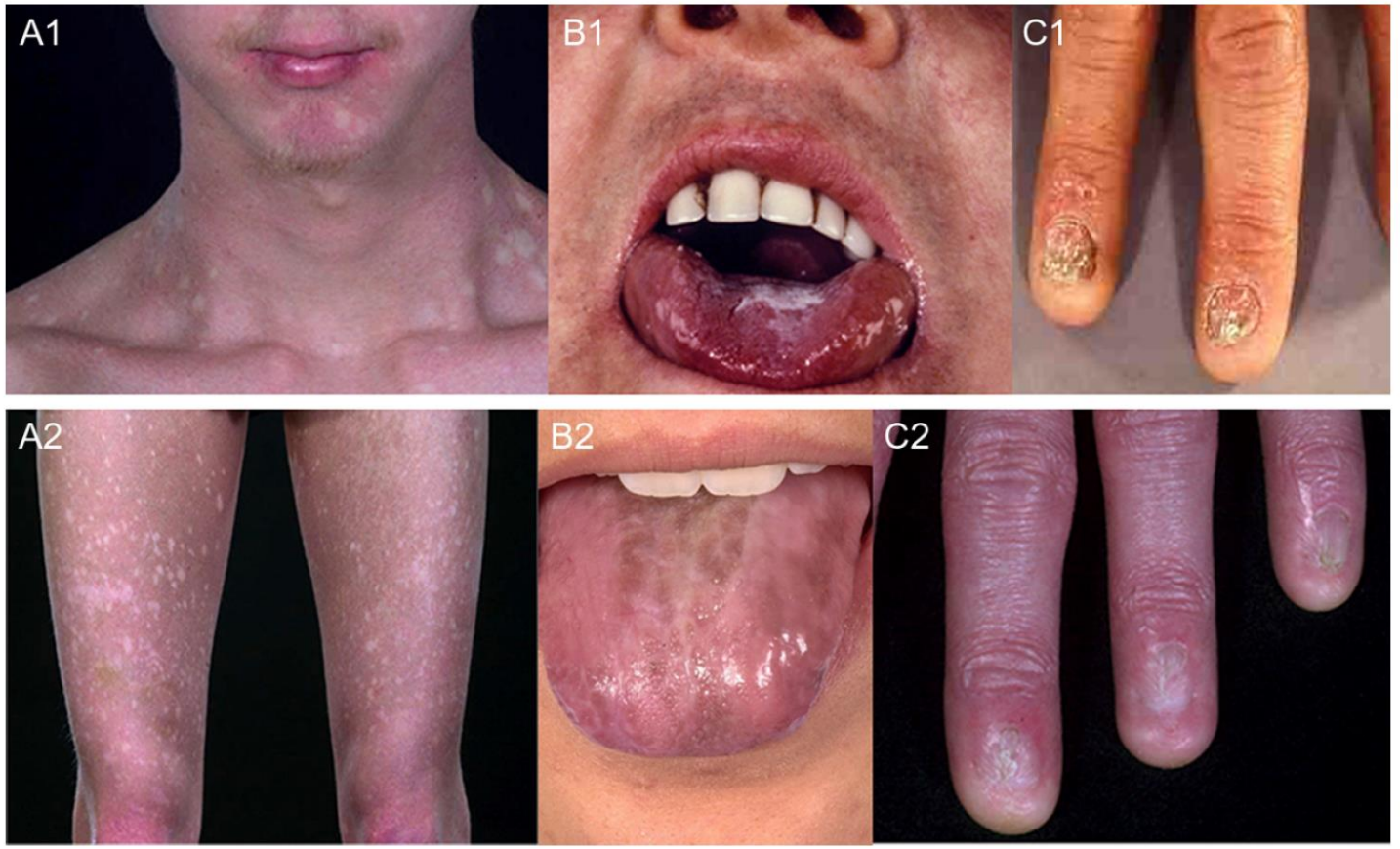
Alder et al. PNAS 2018 Mar 6;115(10):E2358-E2365





Niewisch, et al. Hematology, 2023

Classical mucocutaneous triad



Dokal, Dyskeratosis Congenita, 2014

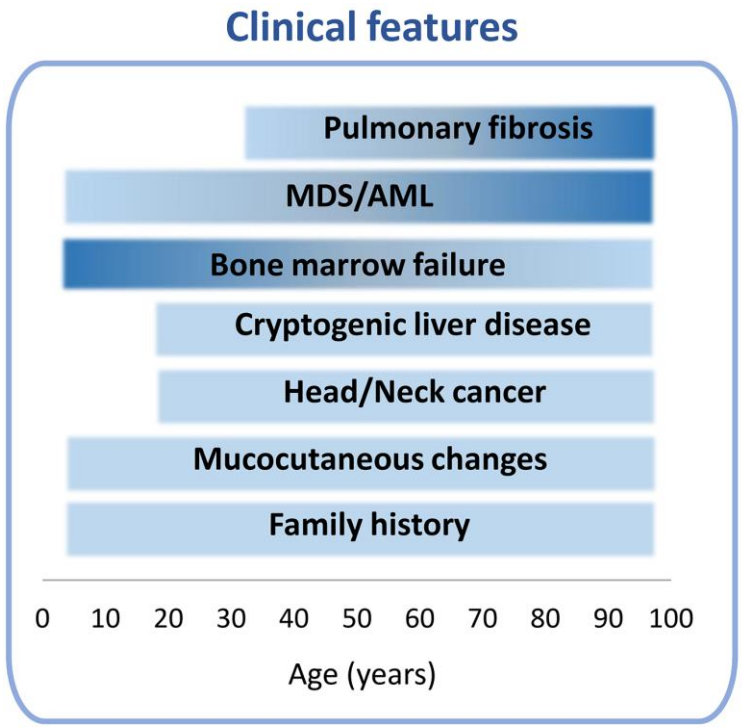
(seen in the historically named dyskeratosis congenita)
skin hypopigmentation, oral leukoplakia, nail dystrophy

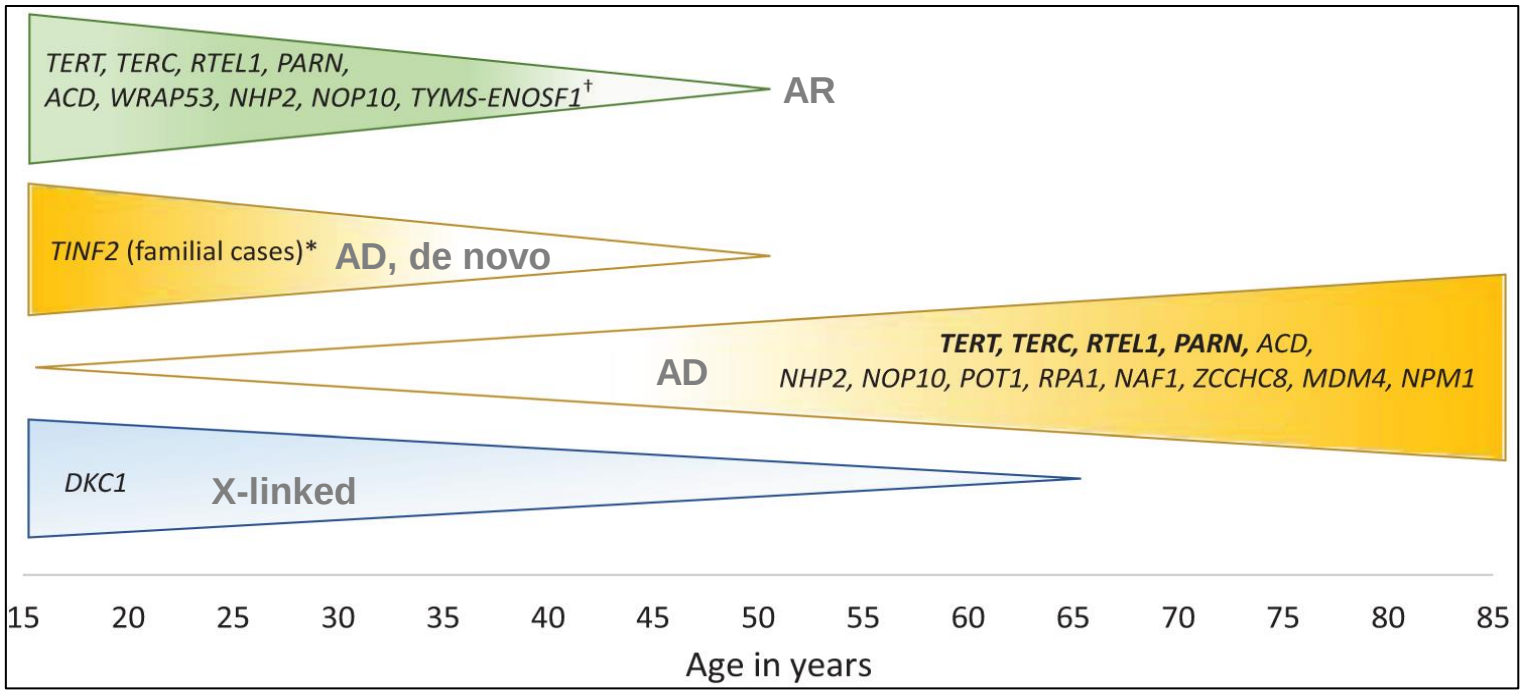
Multisystem disease

- Interstitial lung disease (ILD)
- Liver cirrhosis
- GI/GU
  - Esophageal stricture
  - Urethral stricture
- Dental
- Mucocutaneous
- Early graying
- AVM
- Immunodeficiency
- Increased risk of malignancy
  - MDS/AML
  - Solid tumors

Bokar, Dyskeratosis Congenita, 2014

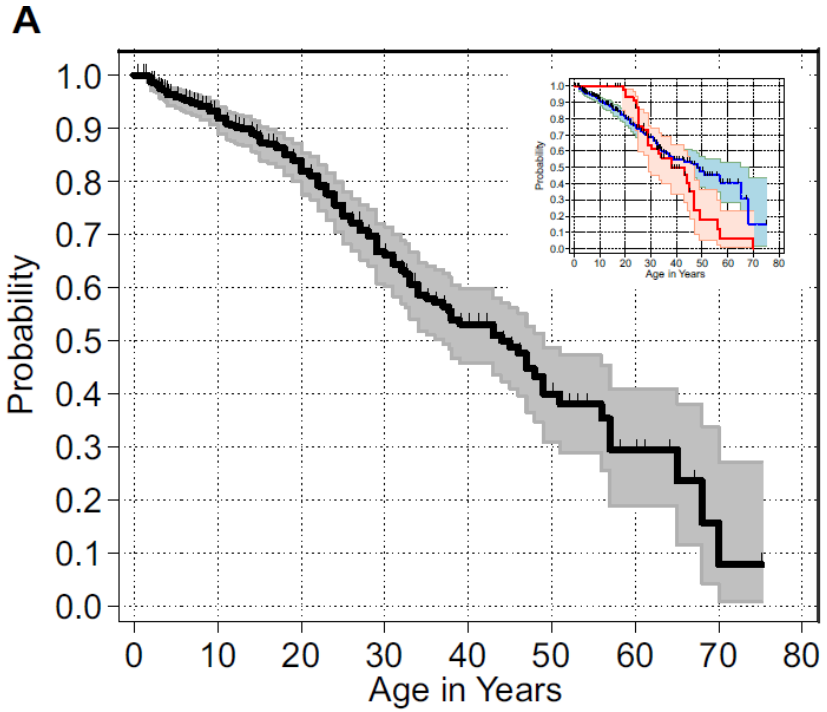
Genes and patterns of inheritance in adult TBD patients





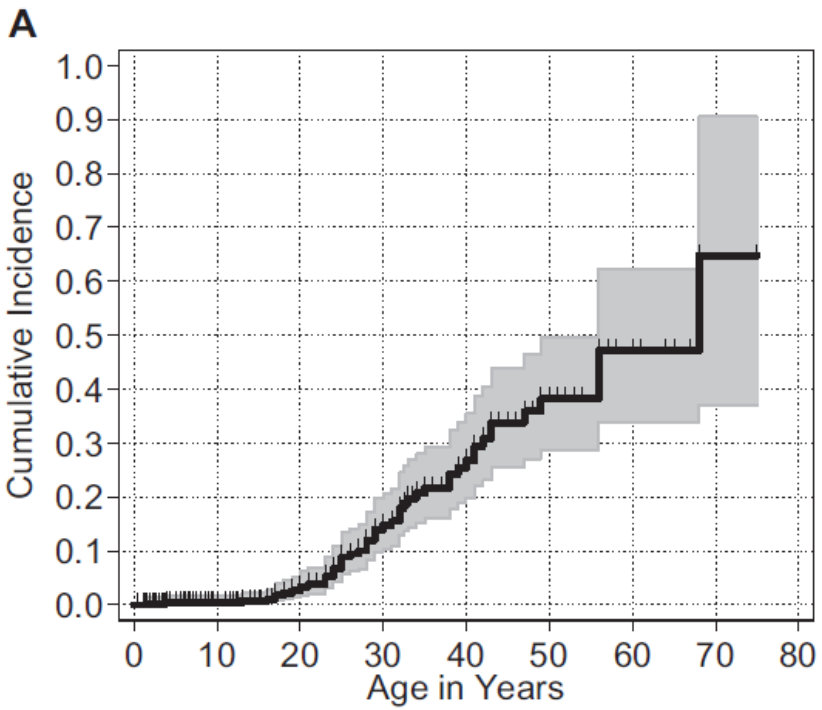
Niewisch, et al. Hematology, 2023

Overall Survival and Cancer Risk



Cumulative Survival N=552

Literature cases through 2008



Incidence of cancer, N=52

Literature cases through 2008

Alter et al. Blood (2009) 113 (26): 6549–6557.

Solid Tumors in TBD Patients

Table 2. Types and ages of solid tumors in DC literature cases

Type of cancer	No. of cancers	Male	Female	Median age, y (range)	Median age in general population, y
All solid tumors	60 in 51 pts	41	10	28 (1.5-68)	67
HNSCC	24 in 22 pts	14	8	32 (17-49)	62
Skin SCC	8	7	1	21 (4-43)	68
Anorectal	6	6	0	28 (17-52)	61
Stomach	4	4	0	23 (16-44)	71
Lung	4	4	0	56 (52-68)	71
Esophagus	3	3	0	25, 38, 41	69
Hodgkin disease	3	3	0	23, 25, 28	38
Colon	2	2	0	20, 25	71
Pancreas	2	2	0	29, 29	72
Liver	1	1	0	32	65
Retinoblastoma	1	1	0	1.5	2
Cervix	1	0	1	31	48
Lymphoma*	1	1	0	43	67

Alter et al. Blood (2009) 113 (26): 6549–6557.

Observed/Expected Cancers in NCI TBD cohort

Table 6. Types of cancers and observed/expected ratio in the NCI IBMFS DC cohort

Cancer	Age, y	Observed	Expected	O/E	95% CI
All sites, median (range)	37 (25-44)	7*	0.6	11†	4-23
All solid tumors, median (range)	37 (25-42)	5*	0.5	8†	2-20
Tongue	25, 25, 42	3	0	1154†	232-3372
AML	28, 44	2	0.01	196†	22-707
Cervical SCC	37	1	0.02	43	0.6-236
Lymphoma, non-Hodgkin	42	1	0.03	34	0.5-191
Basal cell carcinoma, face	29	1*	NA	NA	NA
MDS, median (range)	35 (19-61)	5	0	2663†	858-6215

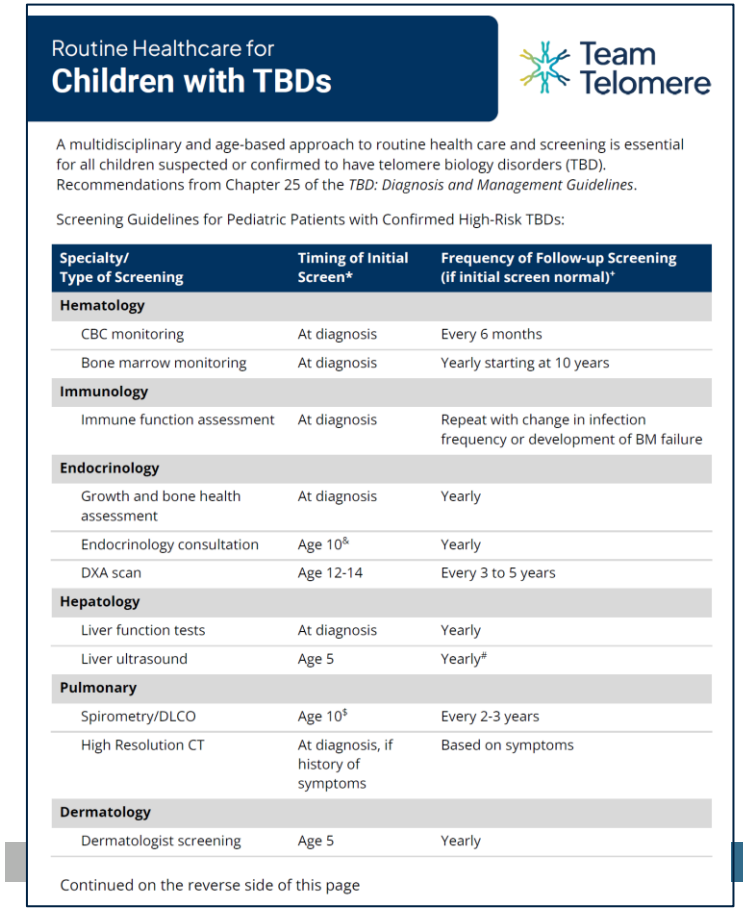
Alter et al. Blood (2009) 113 (26): 6549–6557.

Comprehensive management focused on affected organs and cancer surveillance

- Referral to a center with experience in managing telomere biology disease patients
- BMF/immune deficiency/MDS/AML:
  - Low intensity bone marrow transplant can cure BMF or primary immune deficiency
  - Higher intensity is required for treatment of MDS/AML, but has high rates of TRM.
  - Medical management:
    - Anabolic steroids (e.g., danazol)
    - Transfusion support
    - Avoidance of myelosuppressive agents
    - Clinical trial
- ILD: Antifibrotics, lung transplant
- Cirrhosis: medical management, liver transplant
- AVN: joint replacement
- GI/GU strictures: dilation.
- Mucocutaneous: dermatology/oral medicine
- Cancer surveillance: ENT, GI, bone marrow surveillance.
- Genetics: genetic testing/counseling of patient and family.

A helpful resource: Team Telomere Management Handbook

Team Telomere | A Community for Telomere Biology Disorders



Routine Healthcare for
Children with TBDs

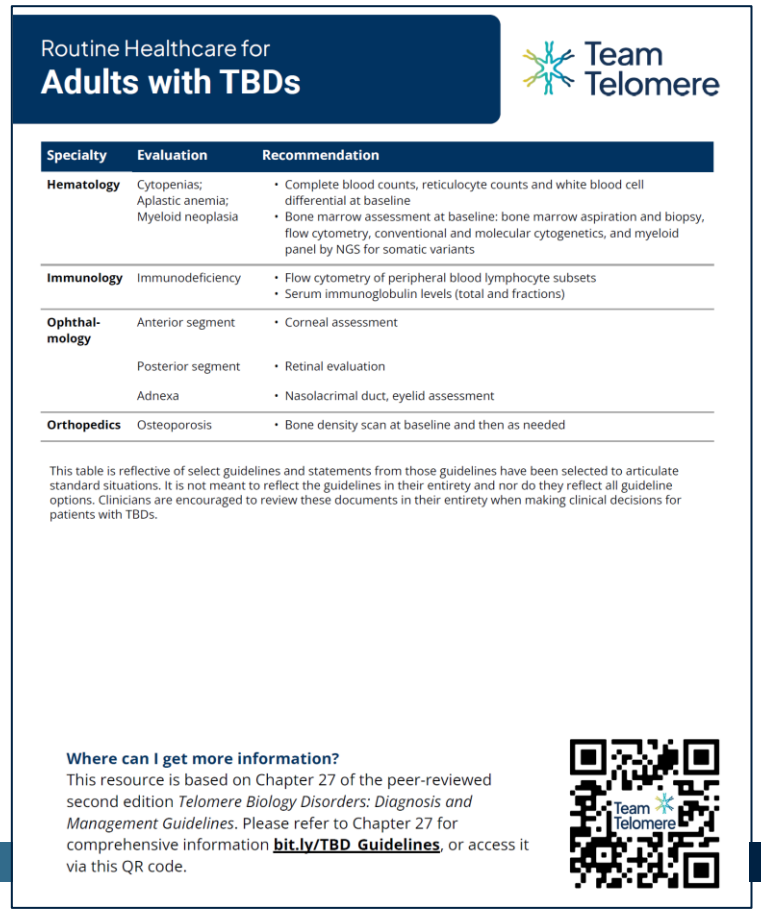
Team Telomere

A multidisciplinary and age-based approach to routine health care and screening is essential for all children suspected or confirmed to have telomere biology disorders (TBD). Recommendations from Chapter 25 of the *TBD: Diagnosis and Management Guidelines*.

Screening Guidelines for Pediatric Patients with Confirmed High-Risk TBDs:

Specialty/ Type of Screening	Timing of Initial Screen*	Frequency of Follow-up Screening (if initial screen normal)*
Hematology		
CBC monitoring	At diagnosis	Every 6 months
Bone marrow monitoring	At diagnosis	Yearly starting at 10 years
Immunology		
Immune function assessment	At diagnosis	Repeat with change in infection frequency or development of BM failure
Endocrinology		
Growth and bone health assessment	At diagnosis	Yearly
Endocrinology consultation	Age 10[&]	Yearly
DXA scan	Age 12-14	Every 3 to 5 years
Hepatology		
Liver function tests	At diagnosis	Yearly
Liver ultrasound	Age 5	Yearly[#]
Pulmonary		
Spirometry/DLCO	Age 10[$]	Every 2-3 years
High Resolution CT	At diagnosis, if history of symptoms	Based on symptoms
Dermatology		
Dermatologist screening	Age 5	Yearly

Continued on the reverse side of this page



Routine Healthcare for
Adults with TBDs

Team Telomere

Specialty	Evaluation	Recommendation
Hematology	Cytopenias; Aplastic anemia; Myeloid neoplasia	• Complete blood counts, reticulocyte counts and white blood cell differential at baseline • Bone marrow assessment at baseline: bone marrow aspiration and biopsy, flow cytometry, conventional and molecular cytogenetics, and myeloid panel by NGS for somatic variants
Immunology	Immunodeficiency	• Flow cytometry of peripheral blood lymphocyte subsets • Serum immunoglobulin levels (total and fractions)
Ophthal-mology	Anterior segment	• Corneal assessment
	Posterior segment	• Retinal evaluation
	Adnexa	• Nasolacrimal duct, eyelid assessment
Orthopedics	Osteoporosis	• Bone density scan at baseline and then as needed

This table is reflective of select guidelines and statements from those guidelines have been selected to articulate standard situations. It is not meant to reflect the guidelines in their entirety and nor do they reflect all guideline options. Clinicians are encouraged to review these documents in their entirety when making clinical decisions for patients with TBDs.

Where can I get more information?
This resource is based on Chapter 27 of the peer-reviewed second edition *Telomere Biology Disorders: Diagnosis and Management Guidelines*. Please refer to Chapter 27 for comprehensive information **bit.ly/TBD_Guidelines**, or access it via this QR code.

Team Telomere

Patient Case 4

HPI: 2 month old previously healthy boy brought to pediatrician with pallor.

Family History: 2 brothers, healthy. No blood conditions in the family.

Labs: Anemia (Hgb 4 g/dl), reticulocytes 0.1%, MCV 103 (macrocytic).

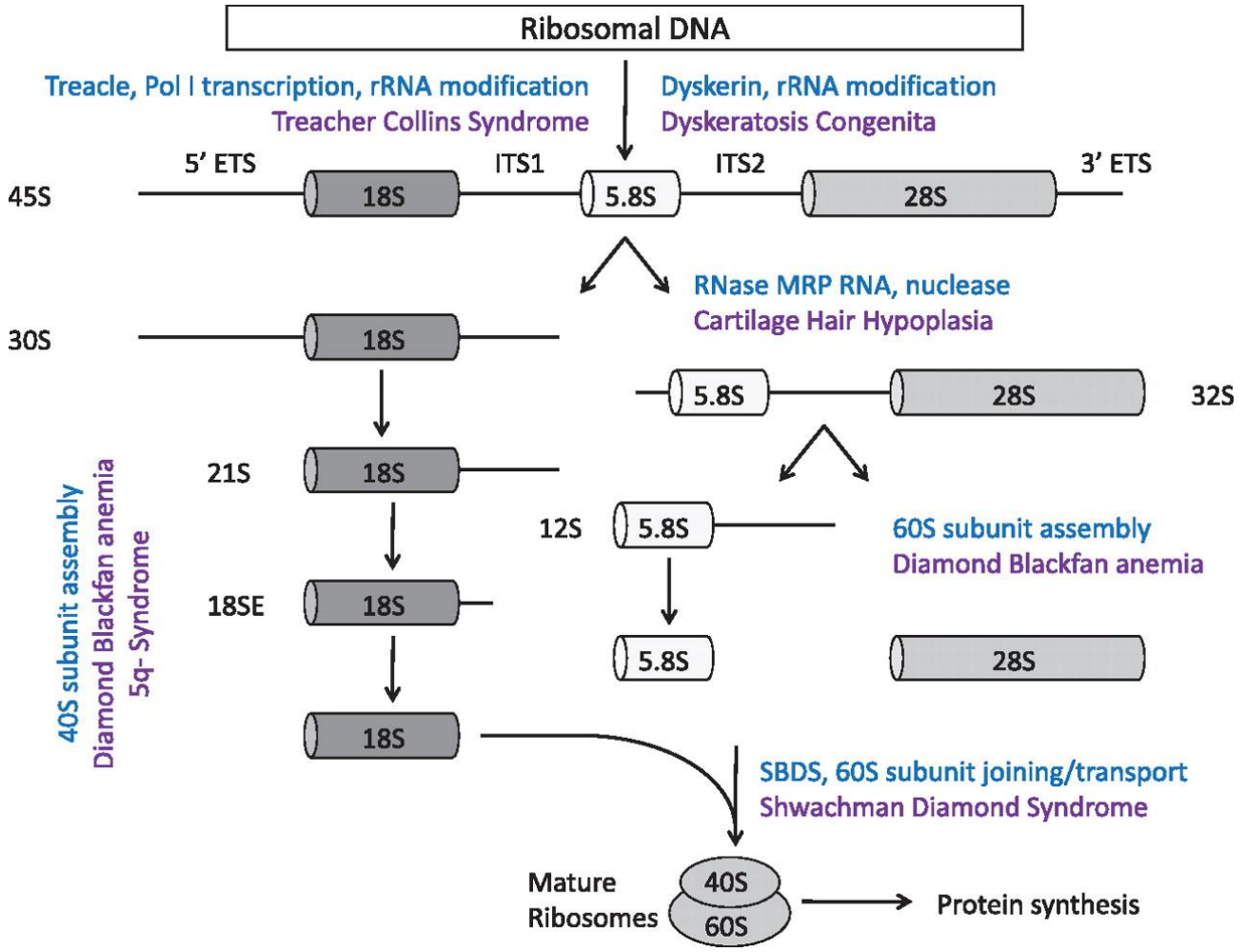
Physical exam: Small for age. Pallor, otherwise no apparent abnormality.
Holosystolic murmur.

Bone marrow aspiration and biopsy: absence of erythroid precursors.

Cytogenetics and somatic molecular testing are normal.

What is the likely diagnosis?
What testing should be ordered?

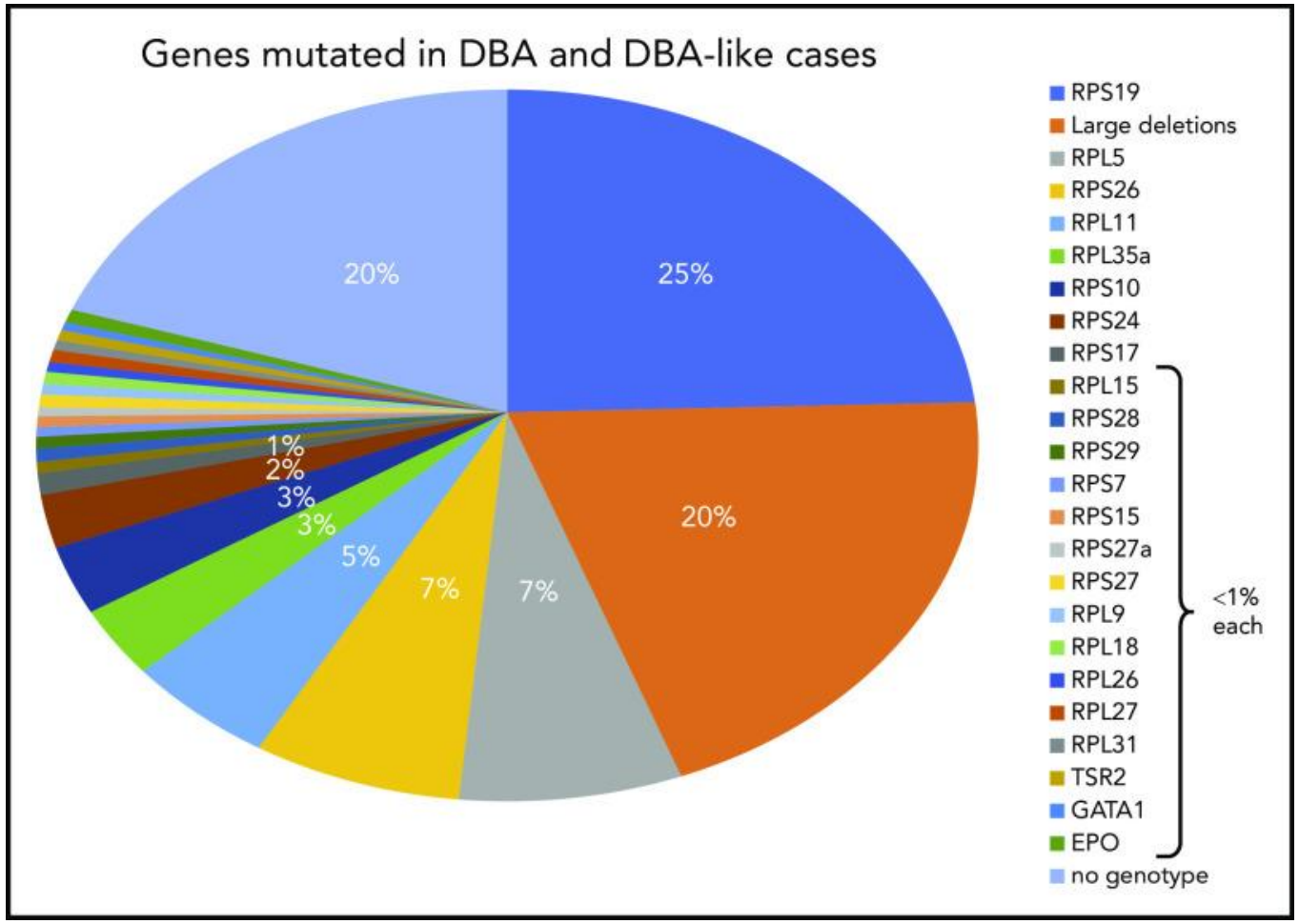
Pathogenesis of Diamond Blackfan Anemia (DBA)



- Genetic defect in >24 genes
  - >20 ribosome protein genes
  - Several non-ribosome genes (e.g. GATA1, EPO)

Narla A , and Ebert B L Blood 2010;115:3196-3205/Liu and Ellis Blood 2006

Genetic causes of DBA



Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

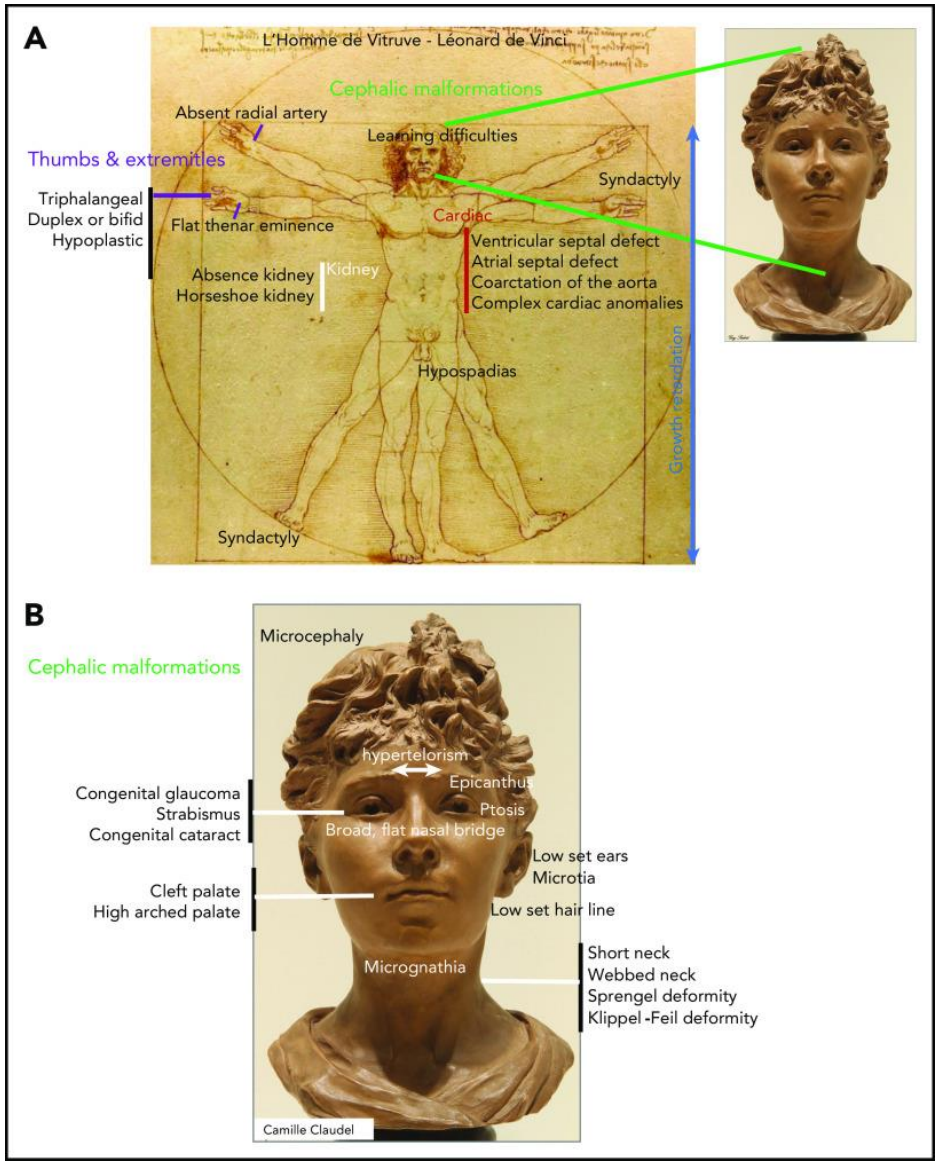
- AD, haploinsufficiency in RP
  - Most common: RPS19, RPL5, RPL11
- X-linked: GATA1, TSR2
- AR: EPO

- Mutations and large deletions

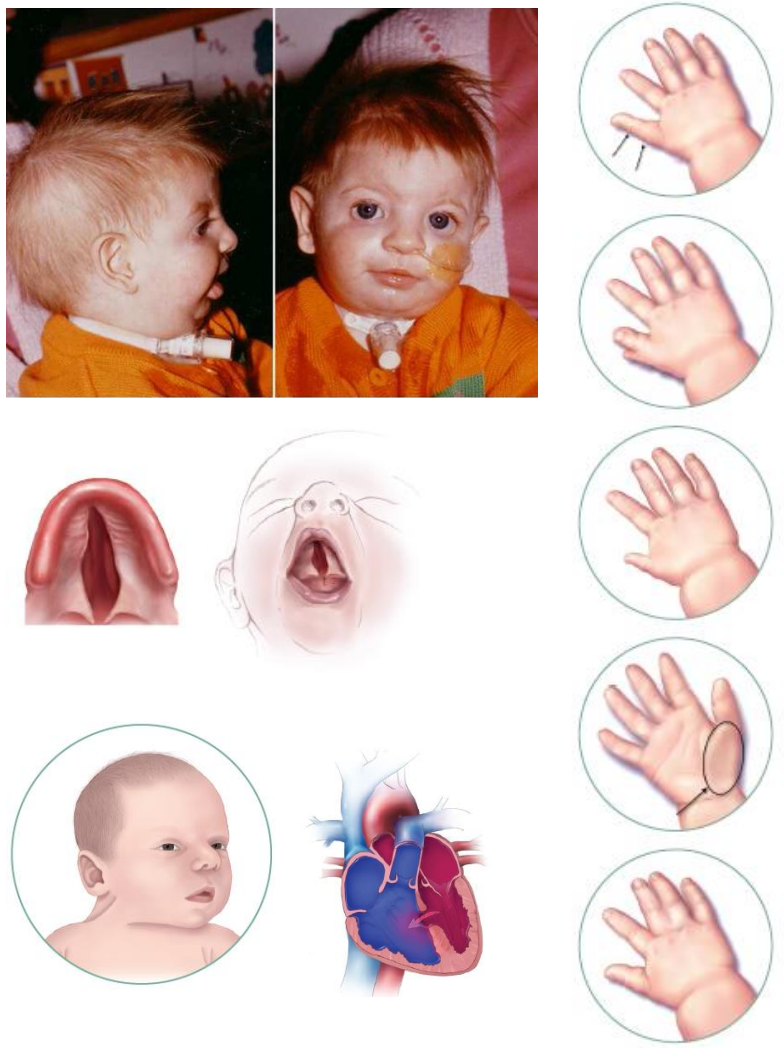
- Diagnosis is established by:
  - Genetic testing
  - Elevated erythrocyte ADA

Diagnosed at 3 months of age: 50%
…….... at 6 months of age: 75%
…….. by 1 year: 92%

Clinical Presentation in DBA



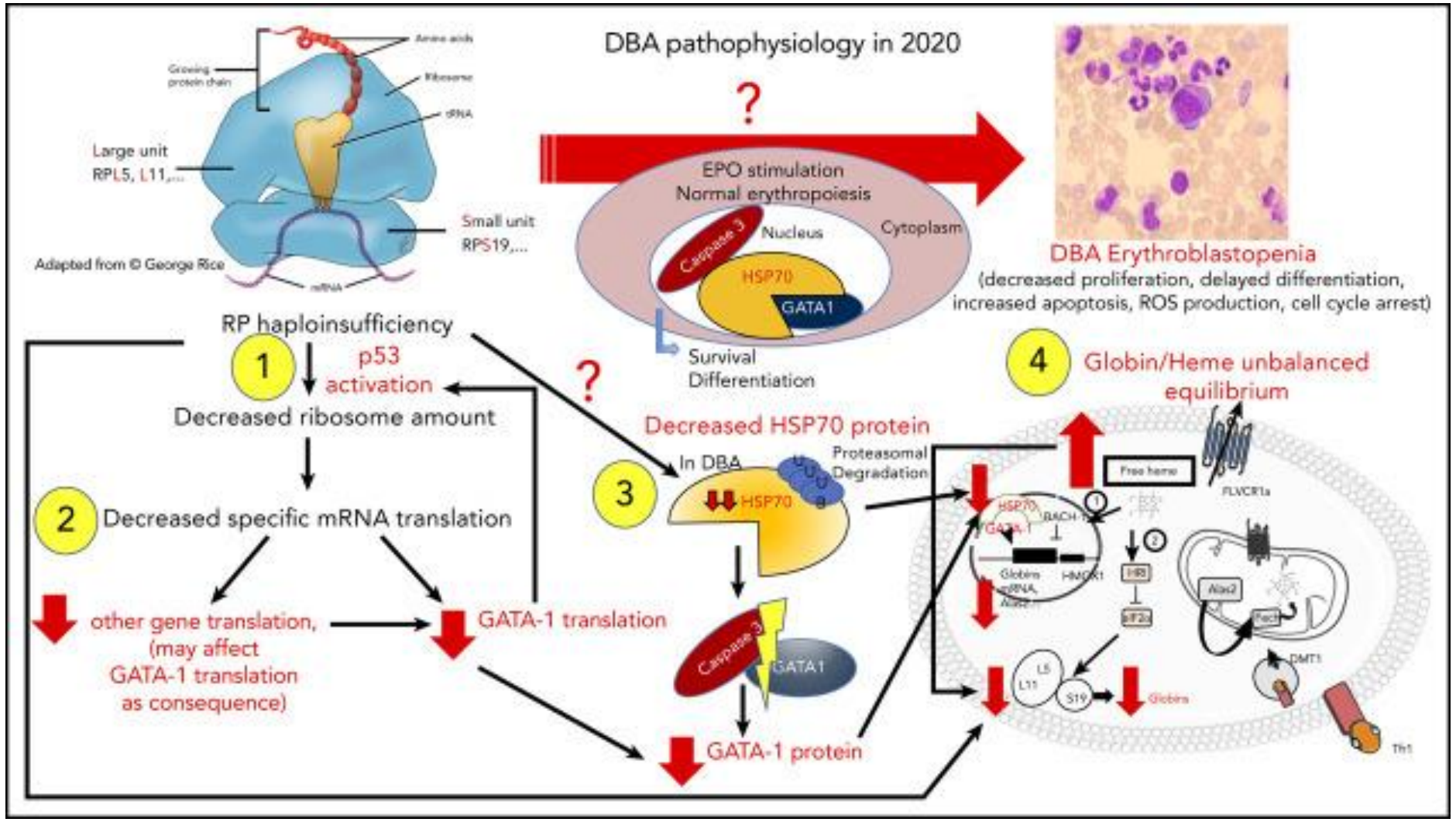
- Macrocytic, hypoproliferative anemia with absence of red cell precursors in bone marrow.
- ~ HALF have congenital anomalies.



Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

Hematol Oncol Clin North Am. 2009 April; 23(2): 261–282.

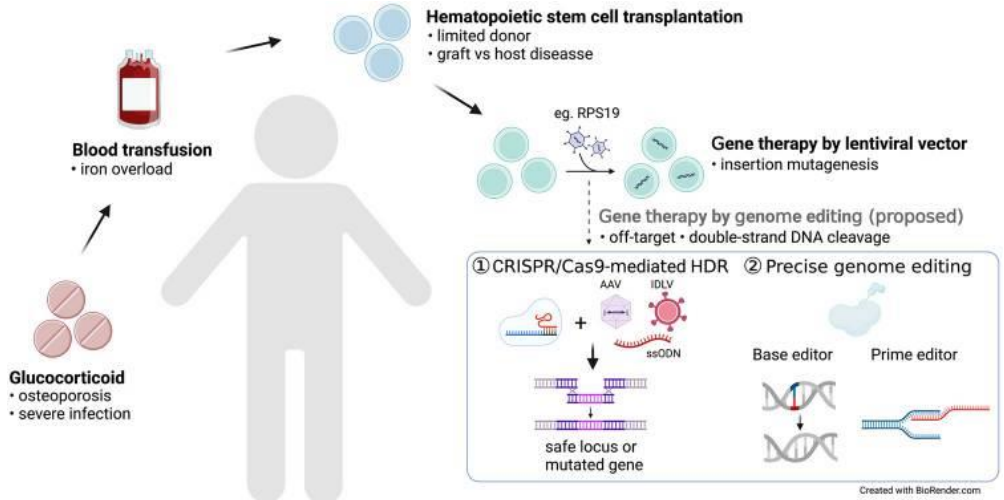
DBA Pathogenesis



Da Costa et al. Blood. 2020 Sep 10; 136(11): 1262–1273.

Clinical Management

- Anemia:
  - Transfusion support
  - Most patients respond to corticosteroids (high dose, 2mg/kg daily x 4 weeks, then taper slowly to some maintenance dose of corticosteroid)
  - Leucine (low efficacy)
  - BMT
  - Clinical trial
- Mitigation of corticosteroid toxicities:
  - PJP prophylaxis while on high dose steroids
  - Calcium/vitamin D + bone density surveillance
- Management of iron overload:
  - Chelation therapy
- Cancer screening:
  - Colonoscopy
  - Age-appropriate cancer screening
- Multidisciplinary care of affected organ systems (e.g. Cardiology, endocrinology, orthopedics)
- Genetic counseling

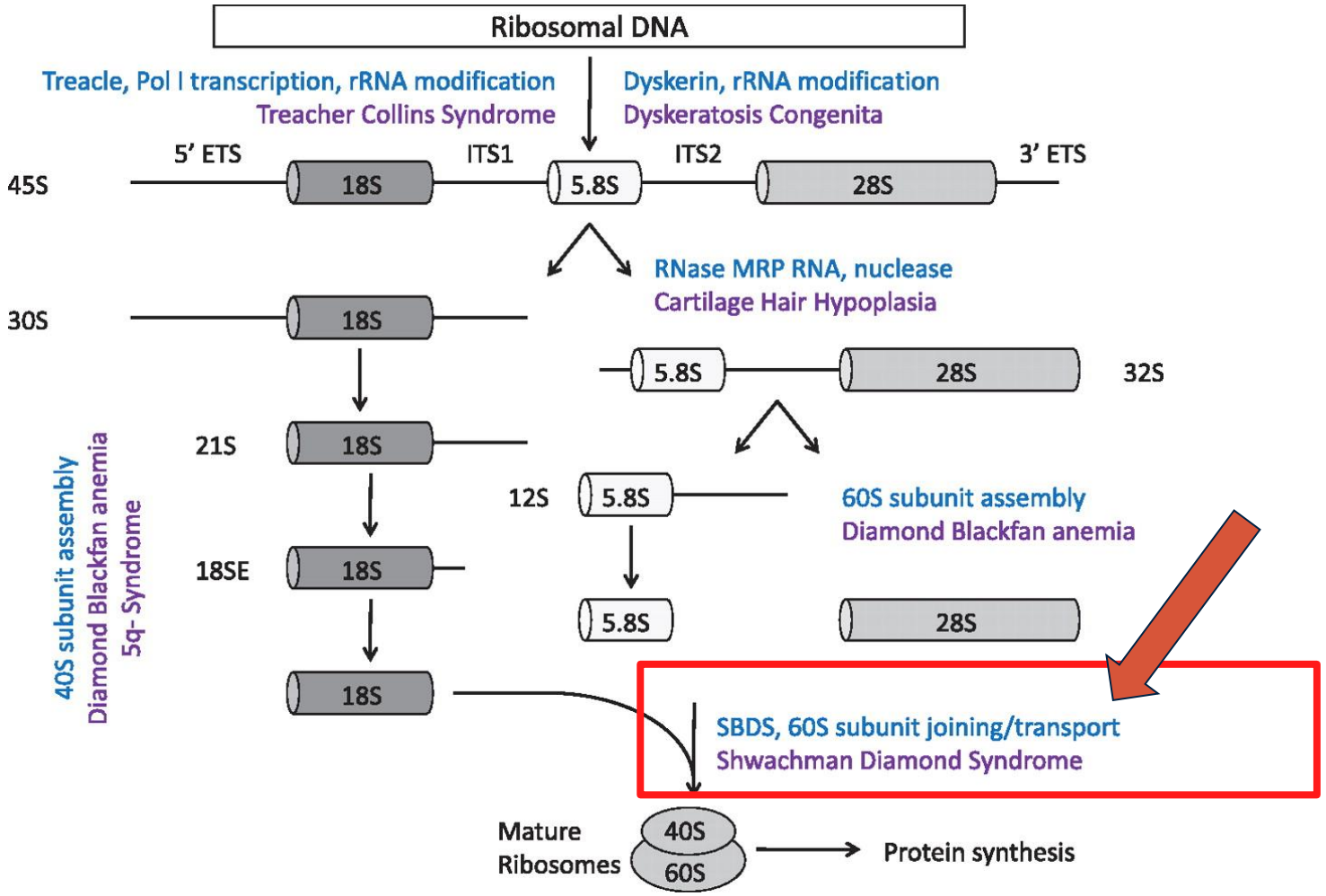


Liu et al. Leukemia. 2024; 38(1): 1–9.

A helpful resource: 2024 DBA International Consensus Statement

- Diagnosis, treatment, and surveillance of Diamond-Blackfan anaemia syndrome: international consensus statement - The Lancet Haematology

Shwachman-Diamond Syndrome (SDS)



Narla A , and Ebert B L Blood 2010;115:3196-3205/Liu and Ellis Blood 2006

Shwachman-Diamond Syndrome (SDS) Clinical Presentation

- Cytopenias:
  - Neutropenia
  - Other cell lines can also be affected
- Short stature (unexplained height <3rd percentile)
- Skeletal abnormalities
- Pancreatic insufficiency
  - Low levels fecal elastase
  - Abnormal pancreatic imaging
  - Elevated fecal fat excretion
- ~30-50% rate of transformation to MDS/AML by age 50 (median age of MDS/AML of 18 years)
  - Biallelic TP53 inactivation is associated with leukemic progression
  - Isochromosome 7q, del 20 q are common but are not associated with poor prognosis

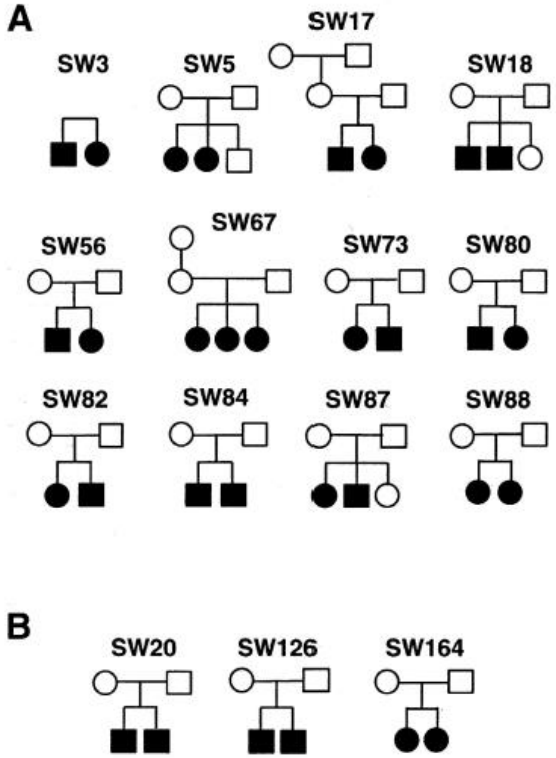
Diagnosis

- A combination of clinical criteria and genetic testing

- Biallelic mutation in SBDS (90%)

- Other rare causes of SDS-like syndrome:
- *SRP54 (AD)*
- *DNAJC21 (AR)*
- *EFL1 (AR)*

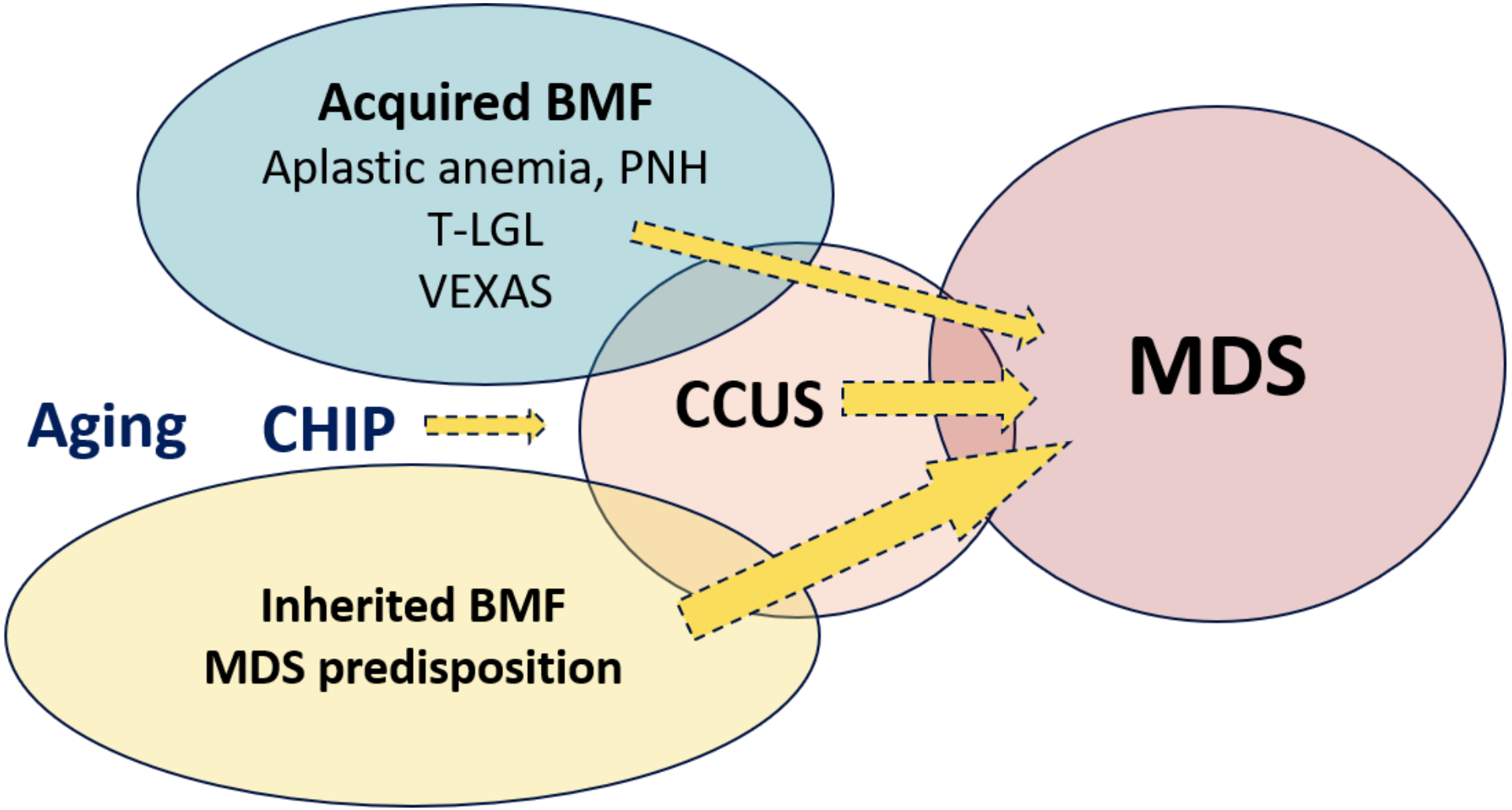
Autosomal recessive inheritance (SBDS)



Clinical Management of SDS

- Cytopenias/BMF
  - Without infections, neutropenia can be followed supportively
  - If needed, G-CSF can be used
  - Annual bone marrow surveillance for adverse clonal evolution
  - HSCT for transfusion-dependent BMF, MDS/AML, and for high risk features
- Endocrinology and orthopedics evaluation
- Pancreatic insufficiency responds to pancreatic enzymes
- Genetic counseling

Summary and Take Home Points: Differential Diagnosis



Take Home Points: whom to evaluate for hereditary BMF

- Lifelong cytopenias, aplastic anemia and hypocellular MDS
- MDS in the young(er) [*e.g., <50 years**]
- Family history of MDS/AML or associated conditions
- "Red flag" conditions associated with BMF syndomes:
  - monosomy 7 or chromosome 1q gain in young patient w/ MDS
  - congenital malformations and dysmorphology incl. abnl thumbs
  - solid tumors at a young age
  - failure to recover counts after chemotherapy/radiation
  - immune deficiency, lymphedema
  - cirrhosis, pulmonary fibrosis, early graying, mucocutaneous findings

Thank you!

Questions?