Penn Medicine
Abramson Cancer Center

Hereditary Marrow Failure Syndromes

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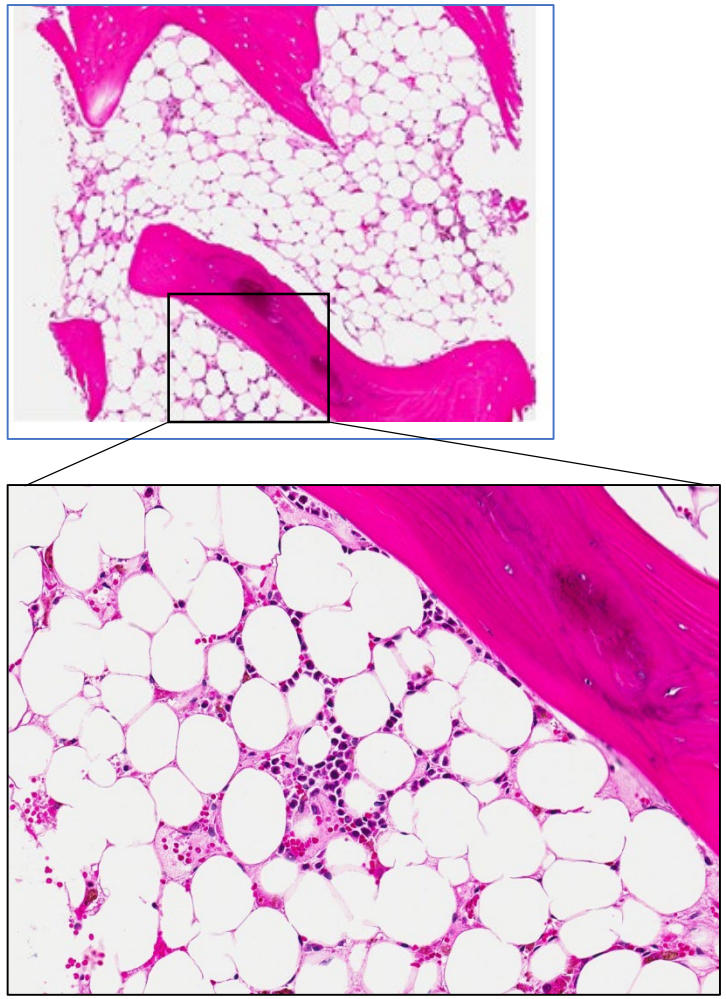
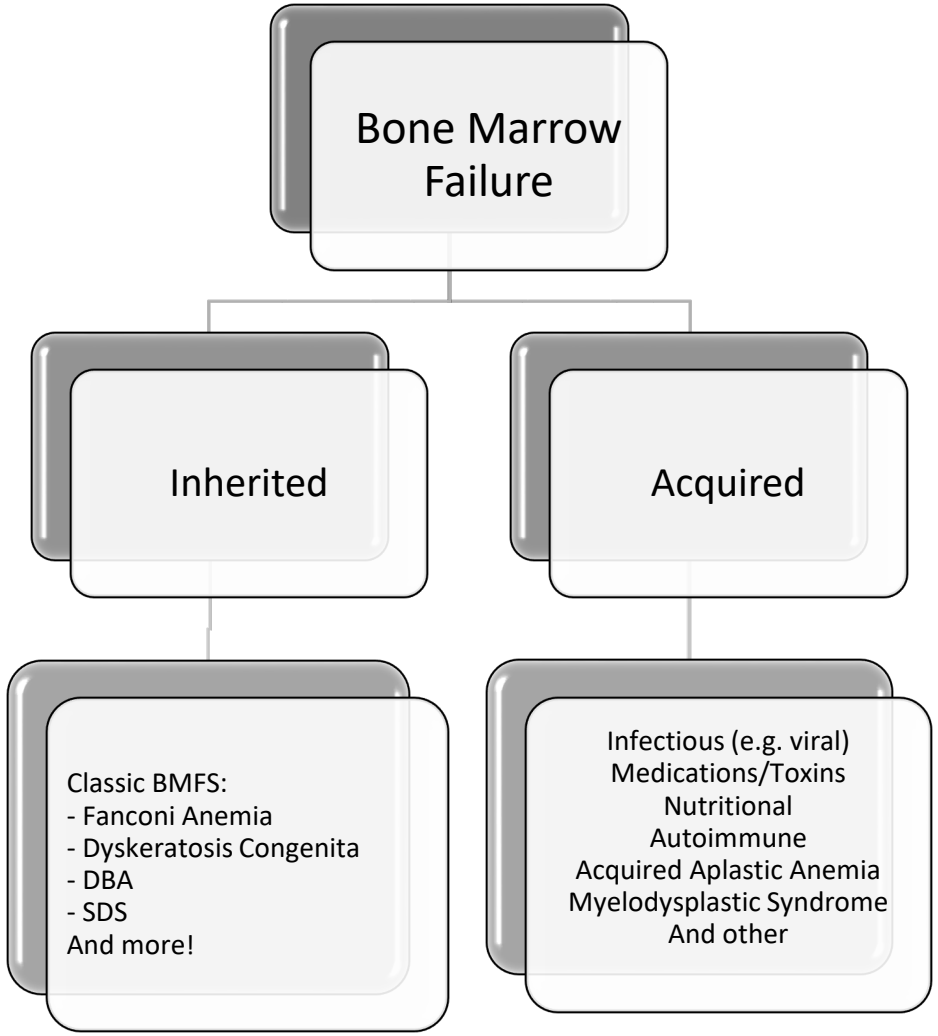
Learning Objectives

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

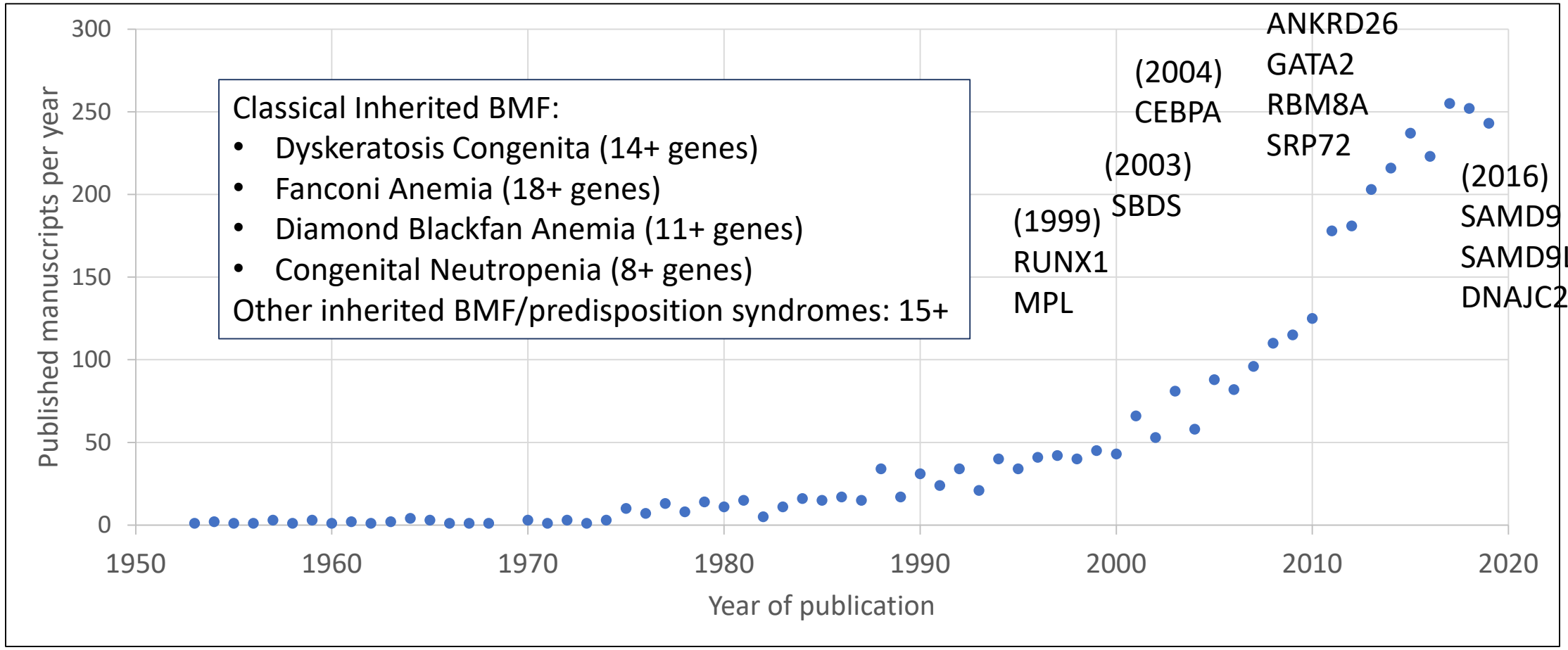
Bone marrow failure (BMF)

Inability of the bone marrow to produce sufficient healthy blood cells to support normal hematopoiesis





Bone Marrow Failure Syndromes



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)
GATA2 deficiency	~20s	Unknown (~500 reported cases)	Haploinsufficiency of GATA2 transcription factor	AD	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)

When to Suspect an Inherited BMF Syndrome?

- **Age at diagnosis** (younger>older)
- **Duration of cytopenias** (life-long cytopenias)
- **Associated conditions and congenital malformations:**
  - pulmonary fibrosis (e.g., in TBD)
  - genitourinary malformation (e.g., in FA, DBA)
  - liver cirrhosis (e.g., in TBD)
  - avascular necrosis (e.g., in TBD)
  - recurrent pre-eclampsia/pregnancy loss (e.g., in TBD, GATA2 deficiency)
  - congenital heart defect (e.g., in DBA)
  - vascular malformation (e.g., in TBD)
  - lymphedema (e.g., in GATA2 deficiency)
  - warts, NTM, EN (e.g., in GATA2 deficiency)
  - thumb and upper limb abnormalities (e.g., in FA, DBA, TAR)
  - café au lait (e.g., in FA)
  - nail abnormalities, early graying (e.g., in TBD)
  - skeletal abnormalities (e.g. hip dysplasia, very short stature) (e.g., in SDS, FA)
- **Personal history of cancers (particularly, at young age)**
- **Sensitivity to chemotherapy/radiotherapy**
- **Classical somatic abnormalities, including**
  - isochromosome 7q (e.g., in SDS)
  - gain 1q (e.g., in FA, TBD)
- **Family history**
  - consanguinity (autosomal recessive conditions)
  - blood disorders
  - associated conditions and congenital malformations
  - cancers
  - death at an early age

Patient Case 1

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?

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Fanconi Anemia (FA): Pathogenesis

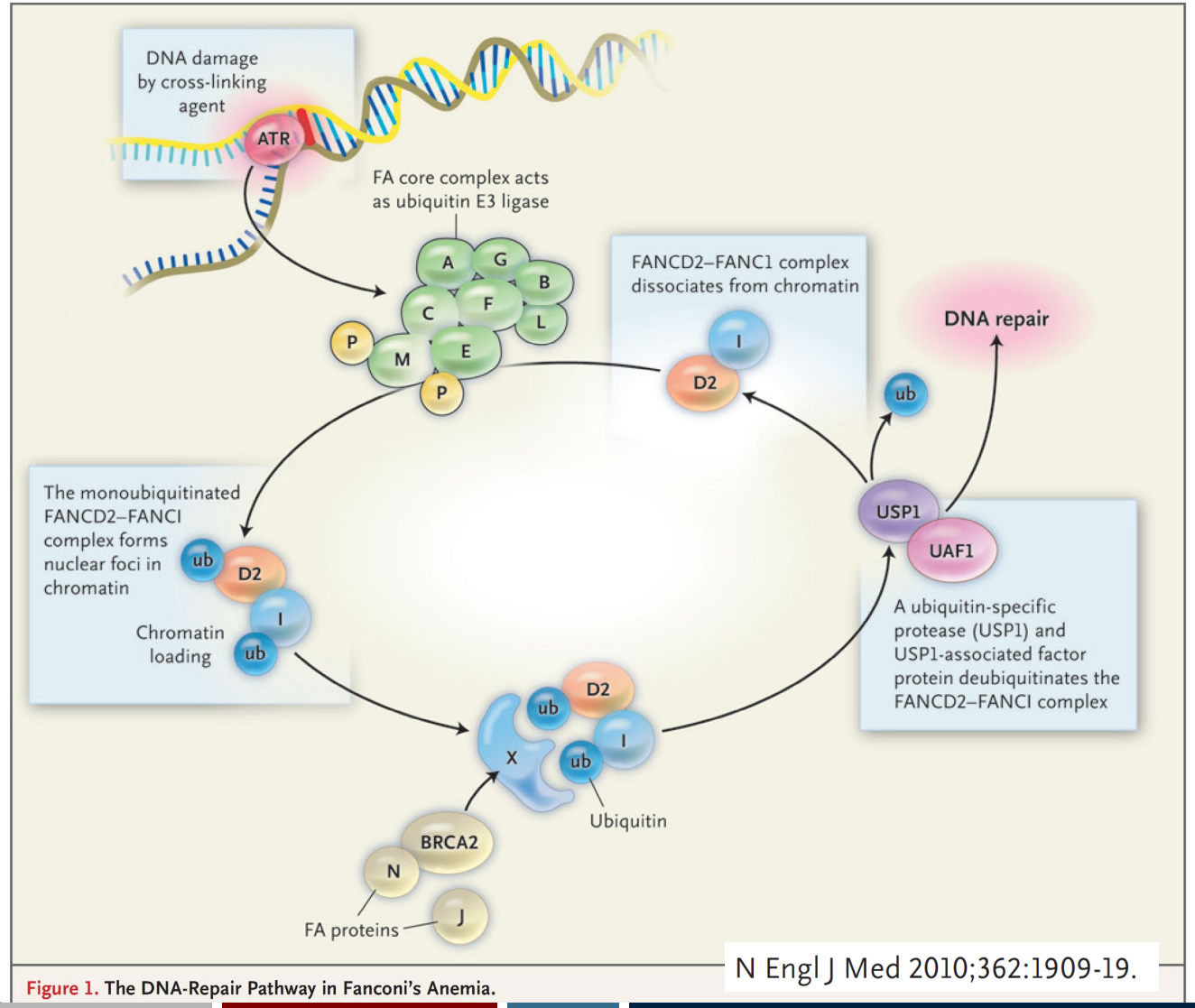
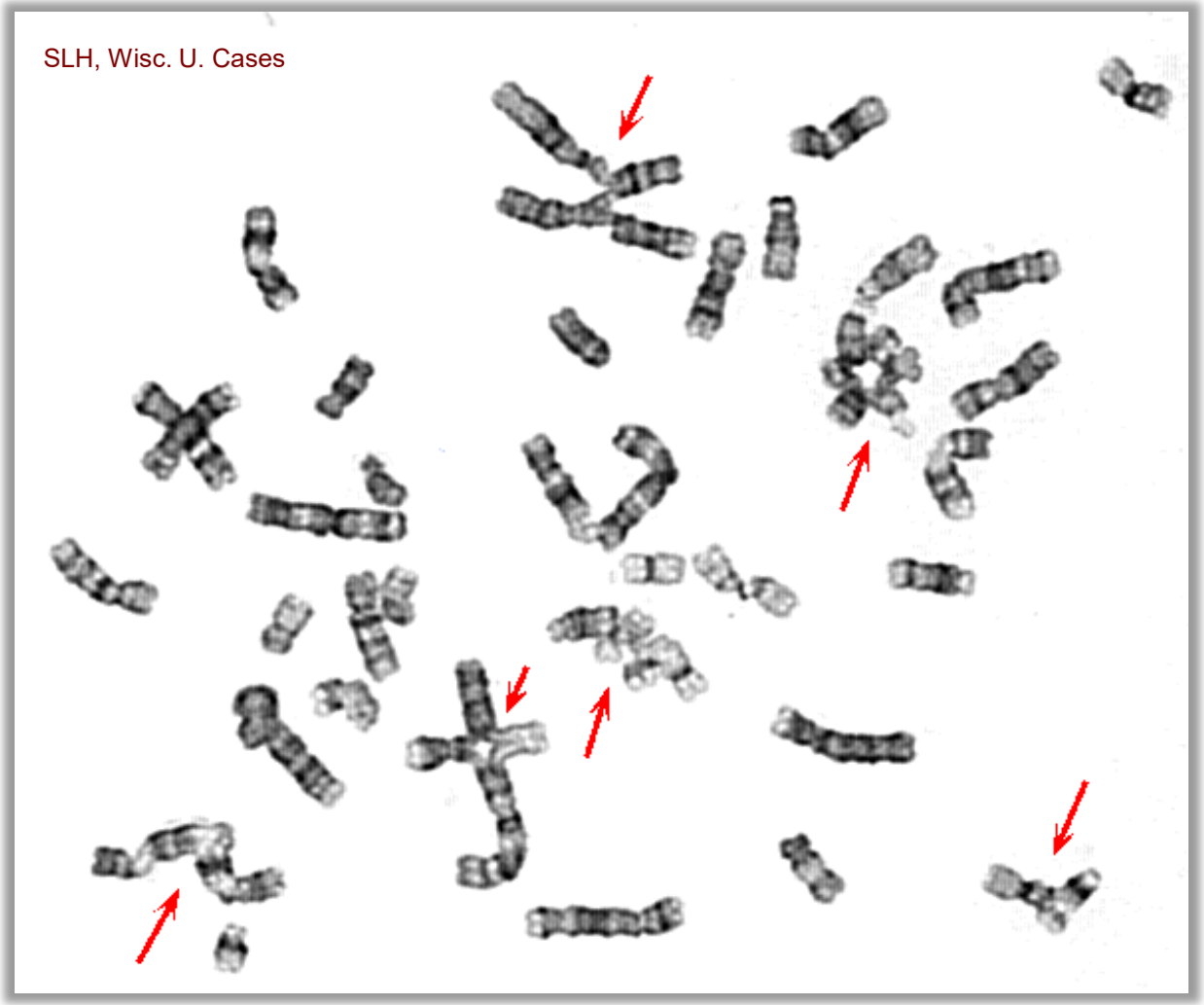


Figure 1. The DNA-Repair Pathway in Fanconi's Anemia.

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

- 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).

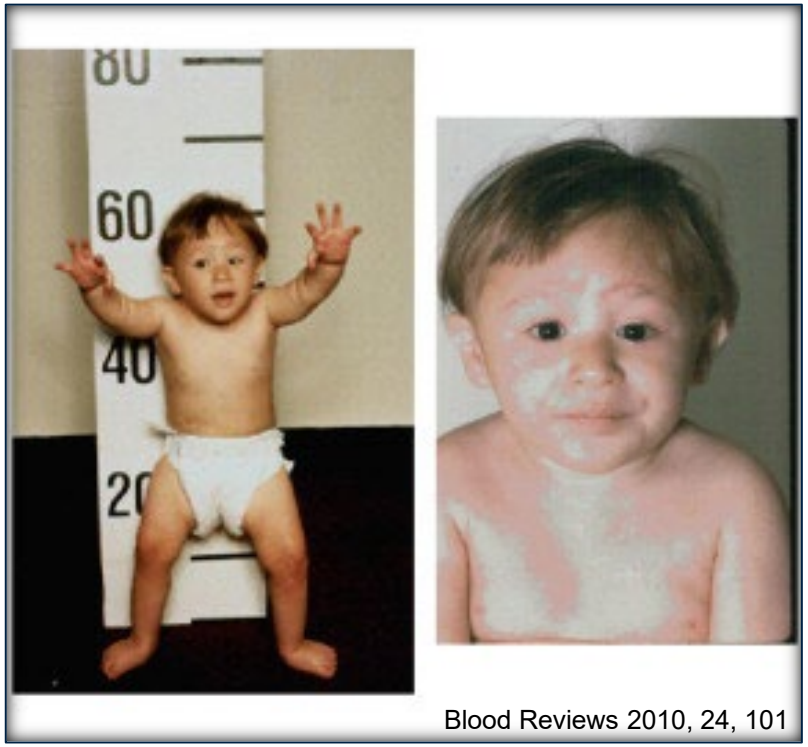
- Increased chromosomal breaks and radials in FA.

- 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.*

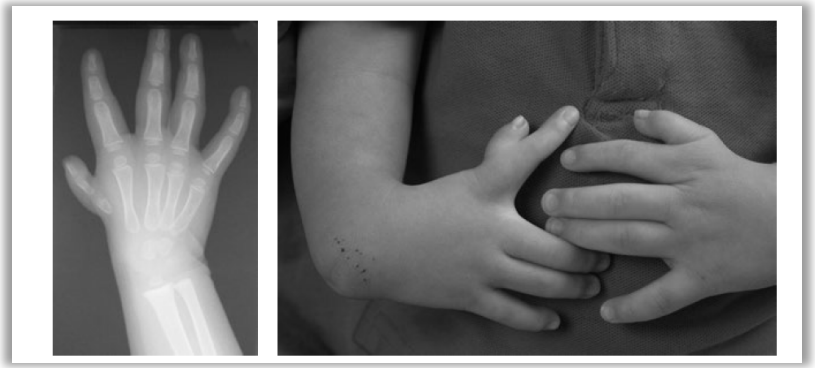
Multisystem disease diagnosed in children and adults

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

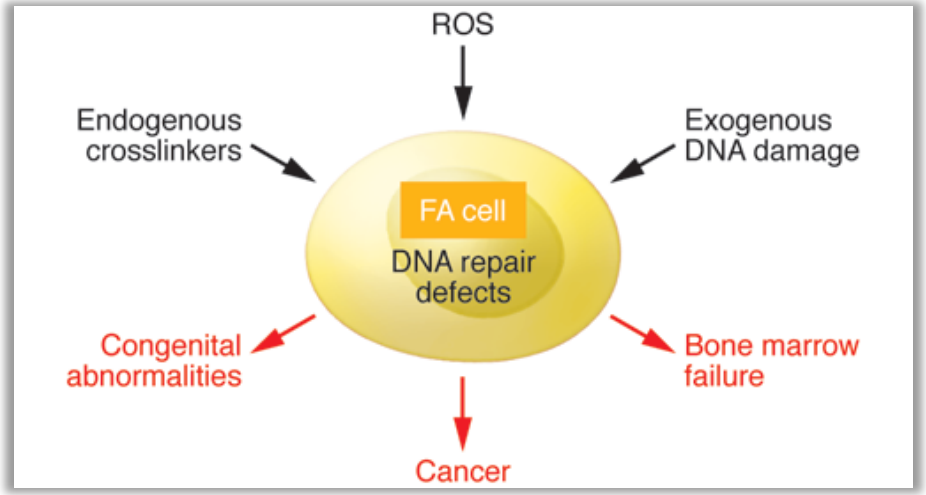


Blood Reviews 2010, 24, 101

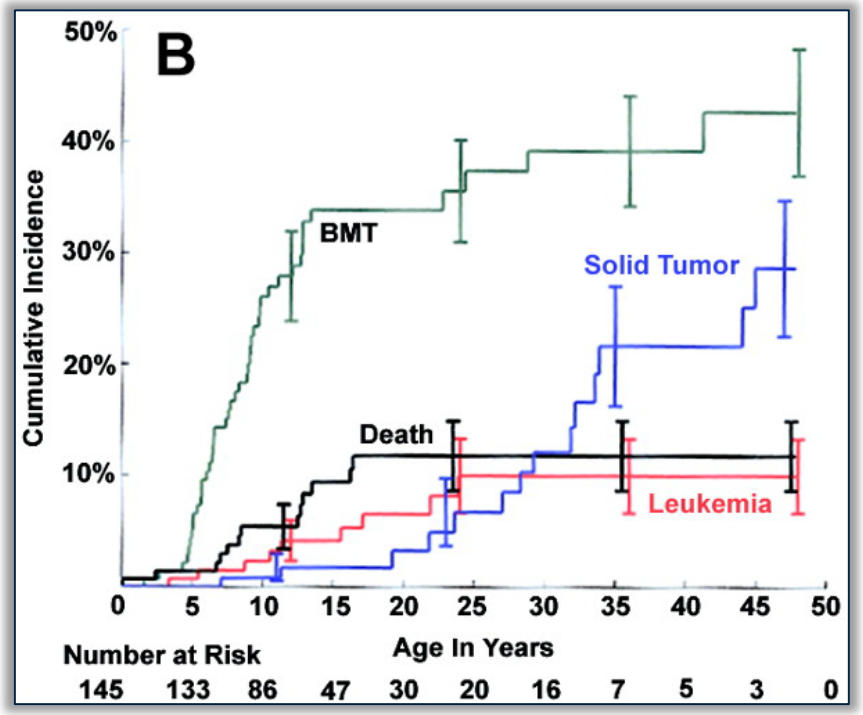


FA Handbook, Version 4, 2014

Predisposition to BMF, MDS/AML and solid tumors

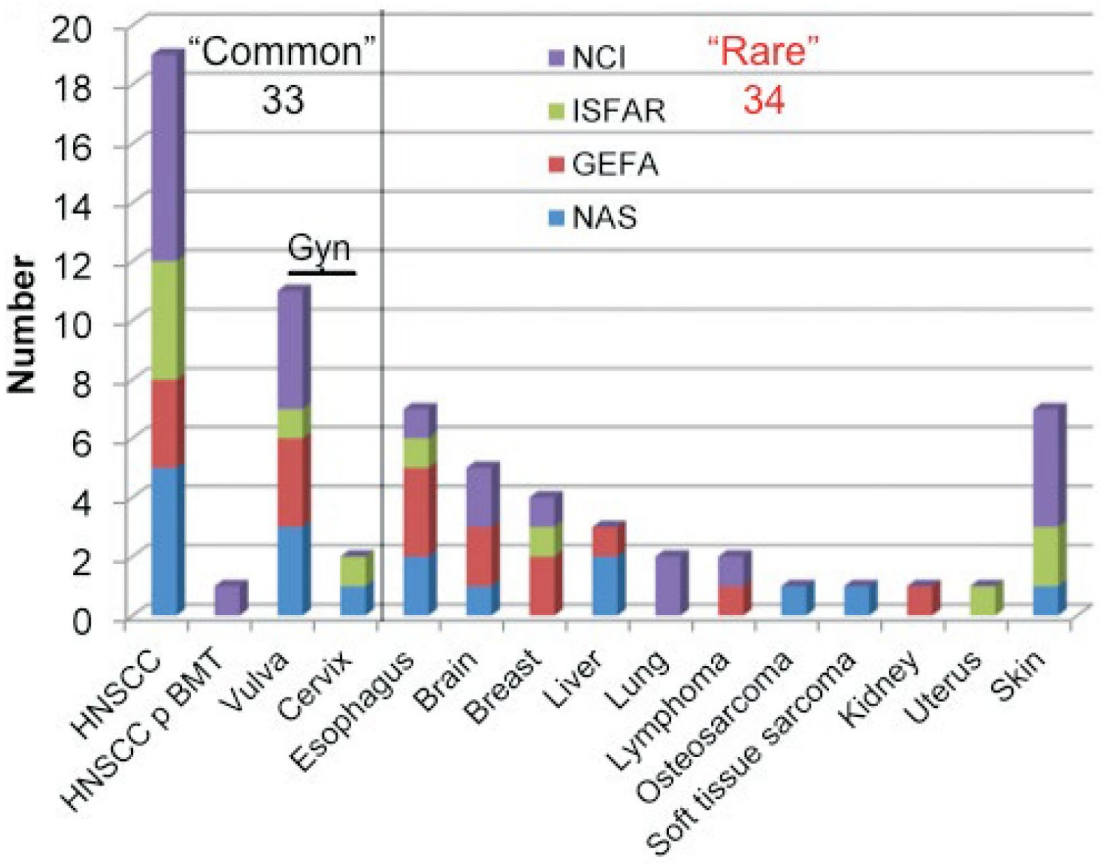


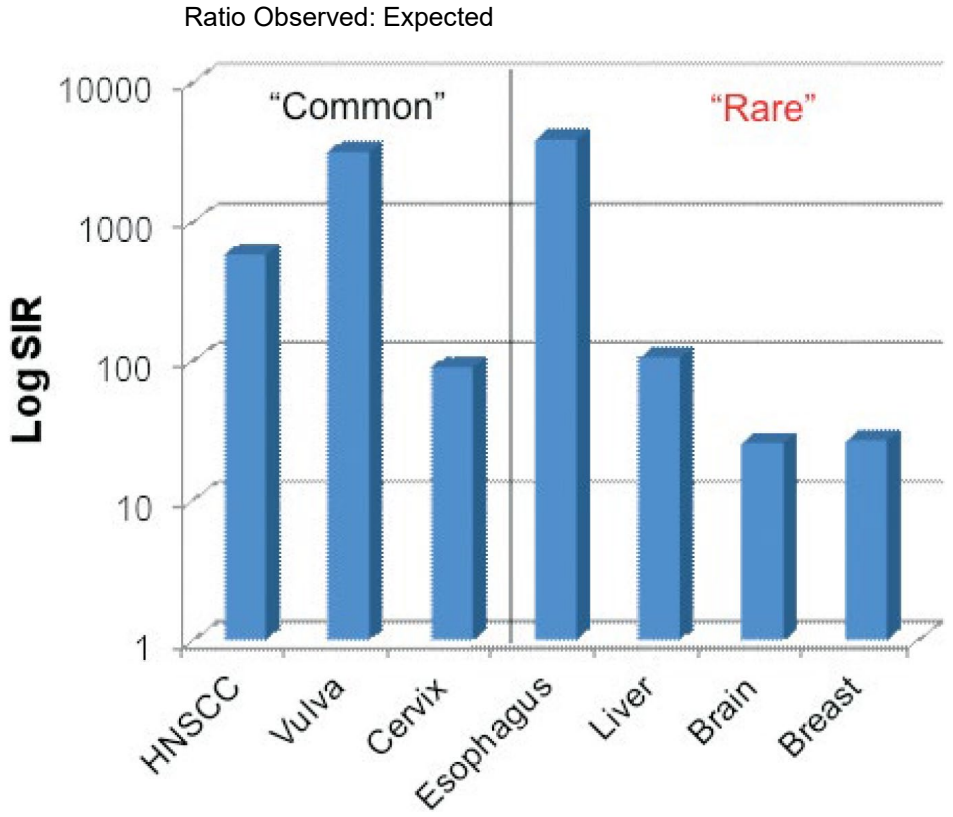
~80% develop BMF by age of 20 years
~40% develop MDS/AML by middle age
~30% develop solid tumors by 48 years



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

HNSCC and Gyn cancers are most common





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 therapies: gene therapy, antioxidants.
  - Multidisciplinary care:
    - Endocrinology, ENT, GU, orthopedics/plastics, genetics.
  - Aggressive cancer surveillance:
    - ENT, gynecological, bone marrow surveillance.

Patient Case 2

HPI: 55 yo M with decades-long thrombocytopenia, referred for evaluation of BMF.
Physical exam: Fit middle-aged male with unremarkable physical exam.
Labs: 2.9>10.6<29; with 58.9% granulocytes, 6.2% monocytes, and 34.9% lymphocytes. MCV 121.
Family history: brother with thrombocytopenia.
Pathology: Bone marrow 15% cellular hypocellular without dysplastic changes.

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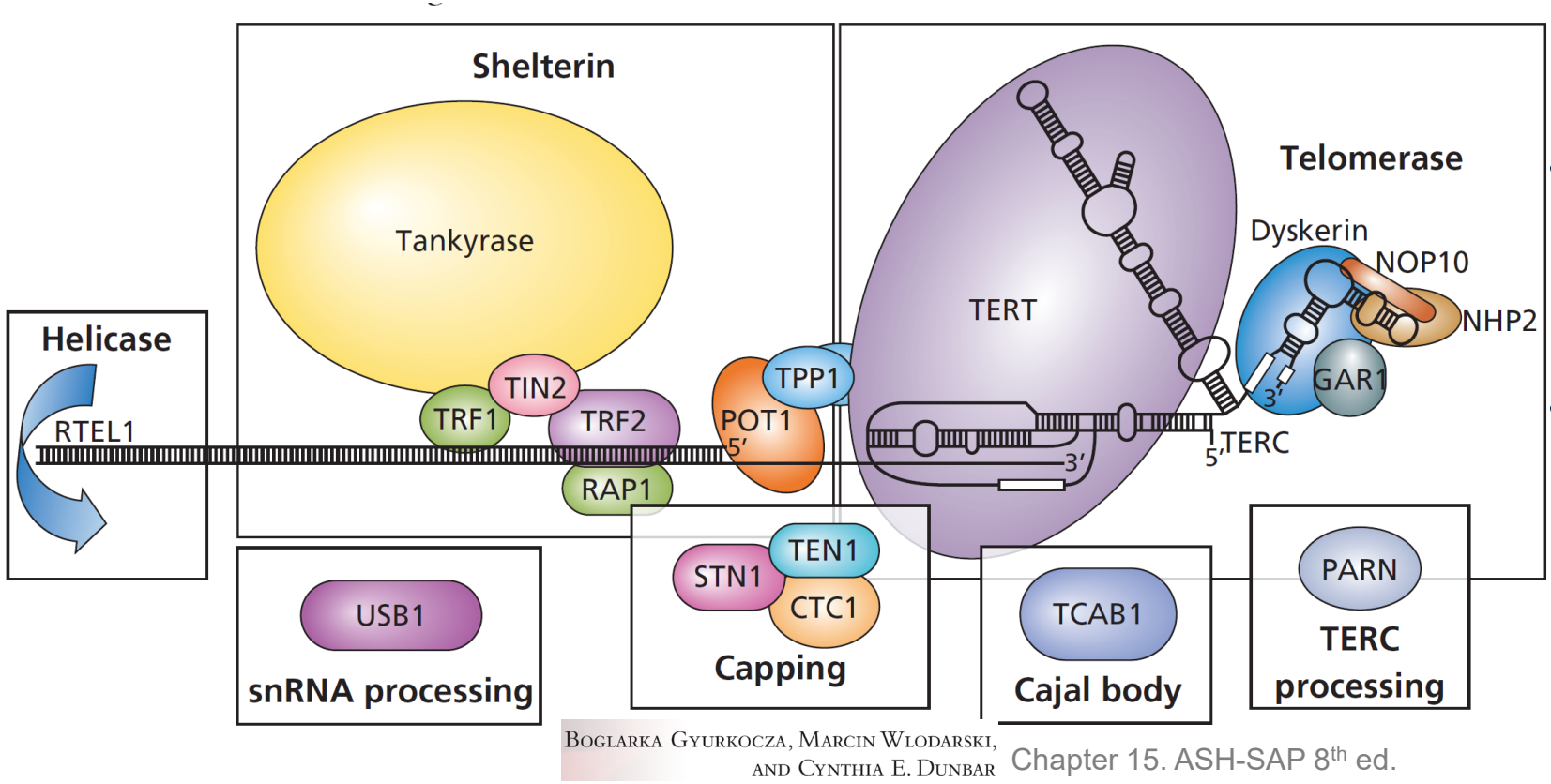
Family history: brother with thrombocytopenia.
Pathology: Bone marrow 15% cellular hypocellular without dysplastic changes, normal karyotype, and no acquired mutations.

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).

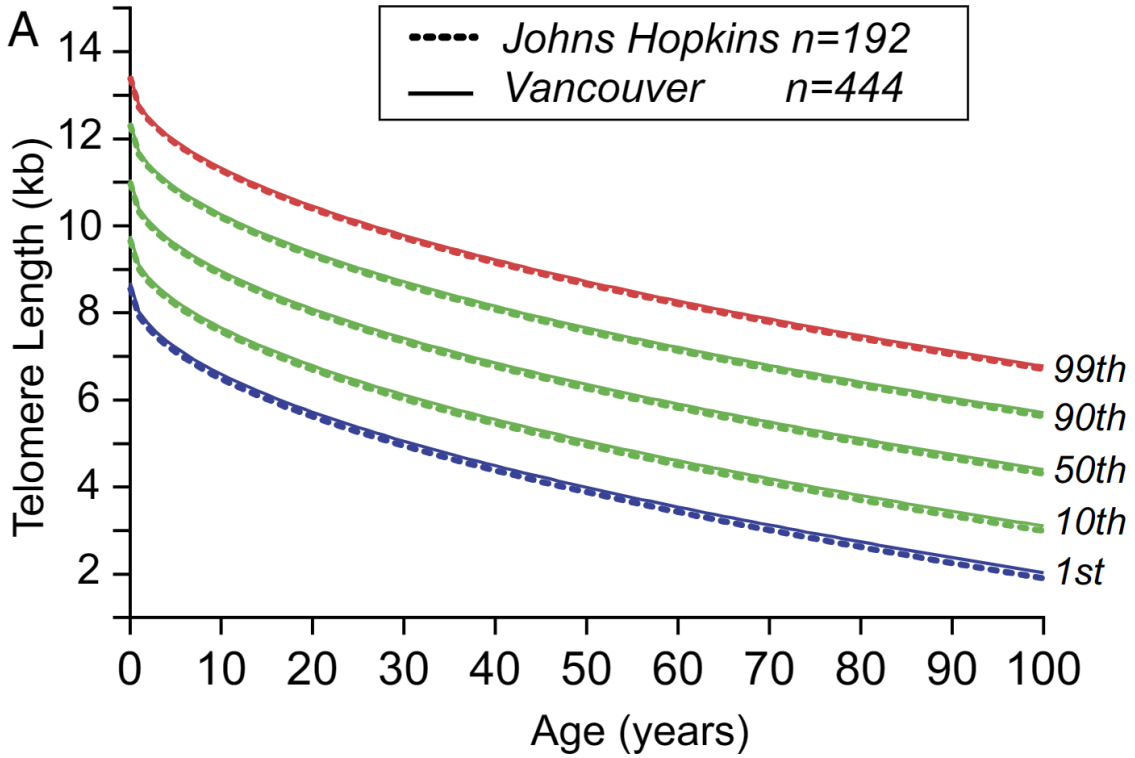
Pathogenesis of Short Telomere Syndromes



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

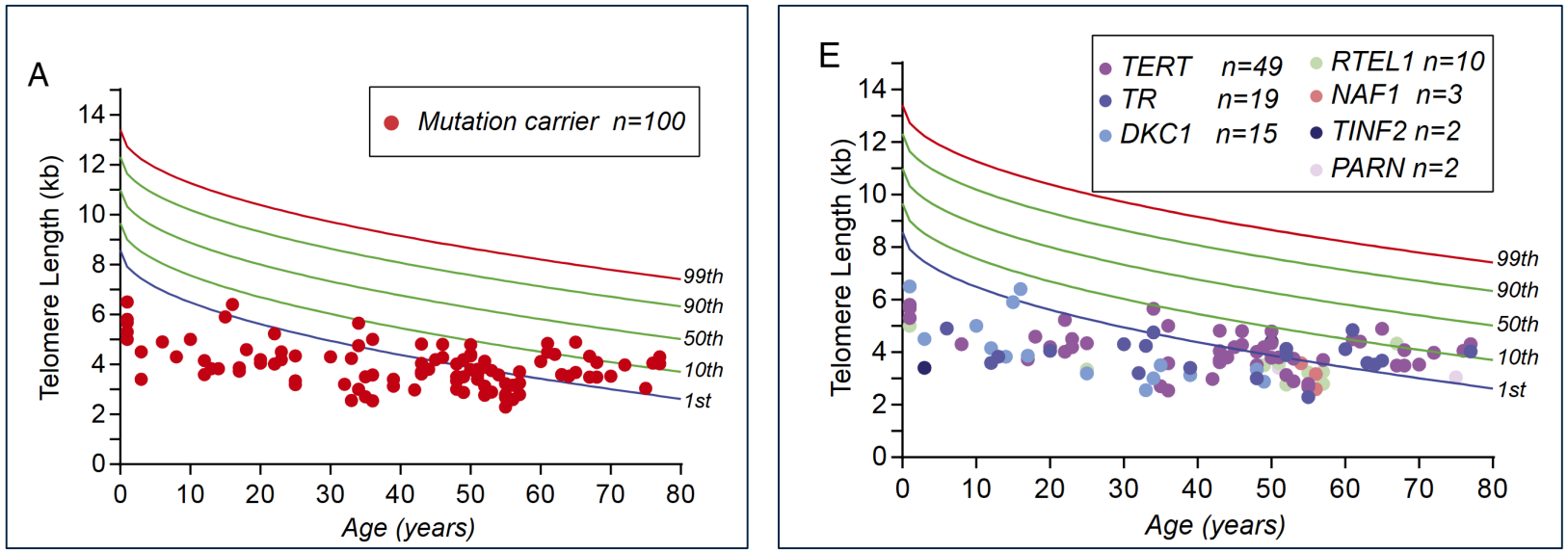
Diagnostic test: Telomere Length Measurement (flow-FISH)



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

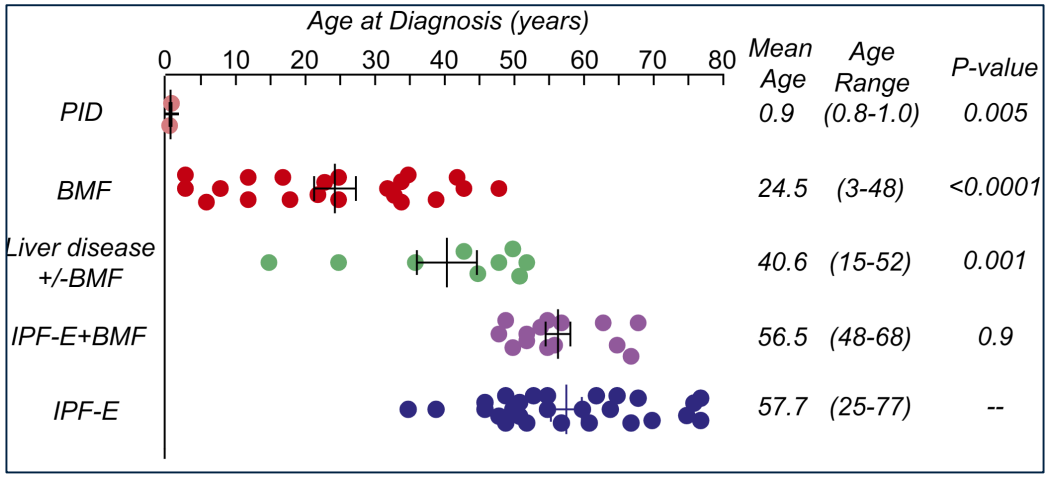
- TL by flow FISH is highly reproducible
- Standardized, age-dependent diagnostic thresholds.
- Low TL test should be followed by genetic testing to establish genetic diagnosis

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



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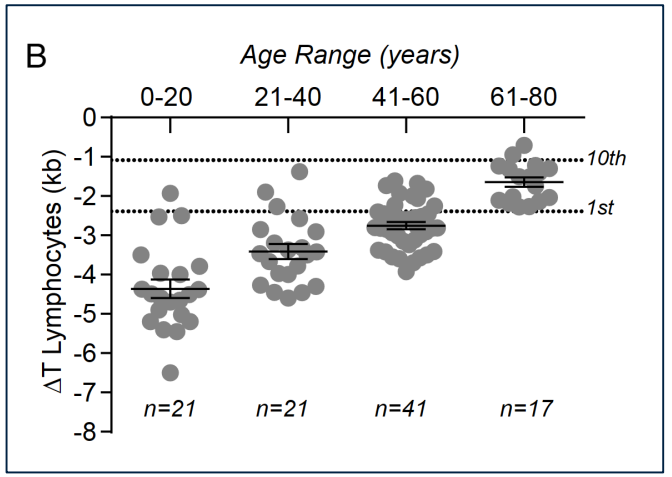
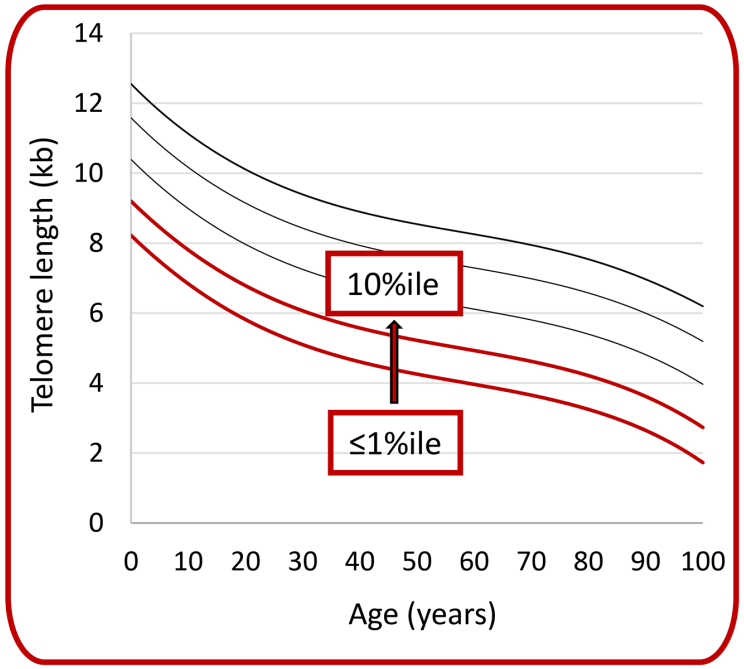
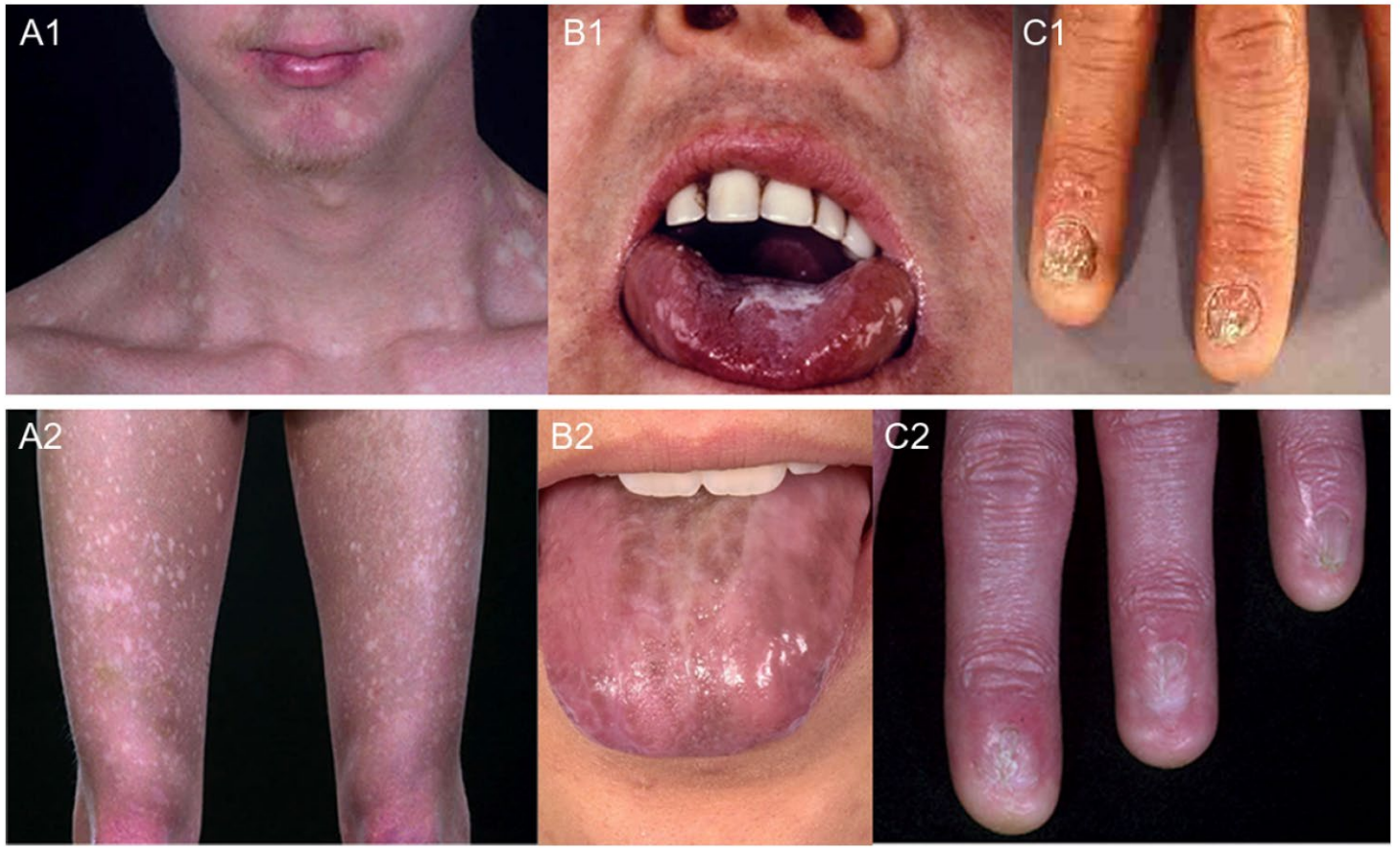


Telomere length measurement



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

TABLE 11.1 Multisystem Clinical Features of Classic DC

Clinical Feature/Abnormality	% of Patients[a]
A. Major Features	
Abnormal skin pigmentation	89.0
Nail dystrophy	88.0
Bone marrow failure	85.5
Leukoplakia	78.0
B. Other Recognized Clinical Features	
Epiphora	30.5
Learning difficulties/developmental delay/mental retardation	25.4
Pulmonary disease	20.3
Short stature	19.5
Extensive dental caries/loss	16.9
Esophageal stricture	16.9
Premature hair loss/graying/sparse eyelashes	16.1
Hyperhidrosis	15.3
Malignancy	9.8
Intrauterine growth retardation	7.6
Liver disease/peptic ulceration/enteropathy	7.3
Ataxia/cerebellar hypoplasia	6.8
Hypogonadism/undescended testes	5.9
Microcephaly	5.9
Urethral stricture/phimosis	5.1
Osteoporosis/aseptic necrosis/scoliosis	5.1
Deafness	0.8

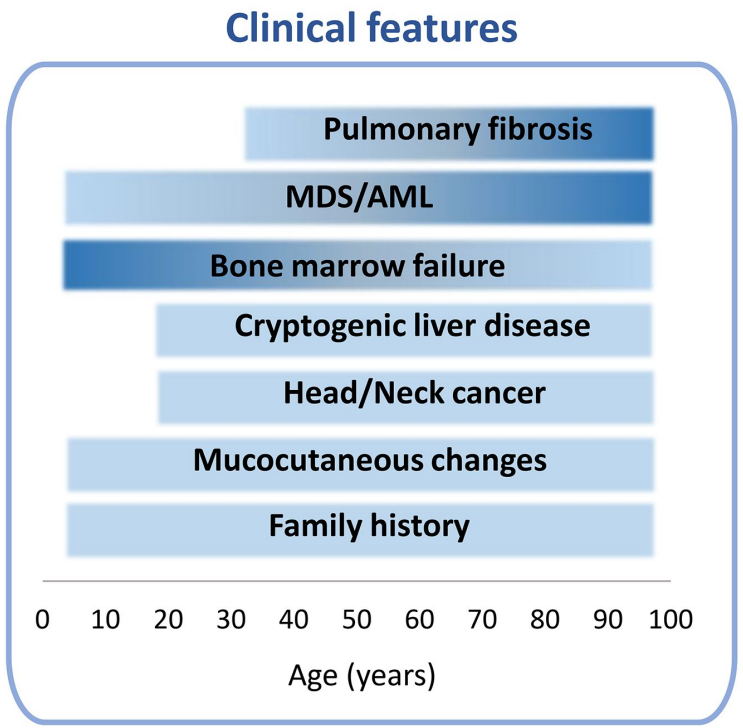
[a]*These percentages refer to the first 118 patients recruited to the Dyskeratosis Congenita Registry (DCR) in London before the identification of any DC genes.*

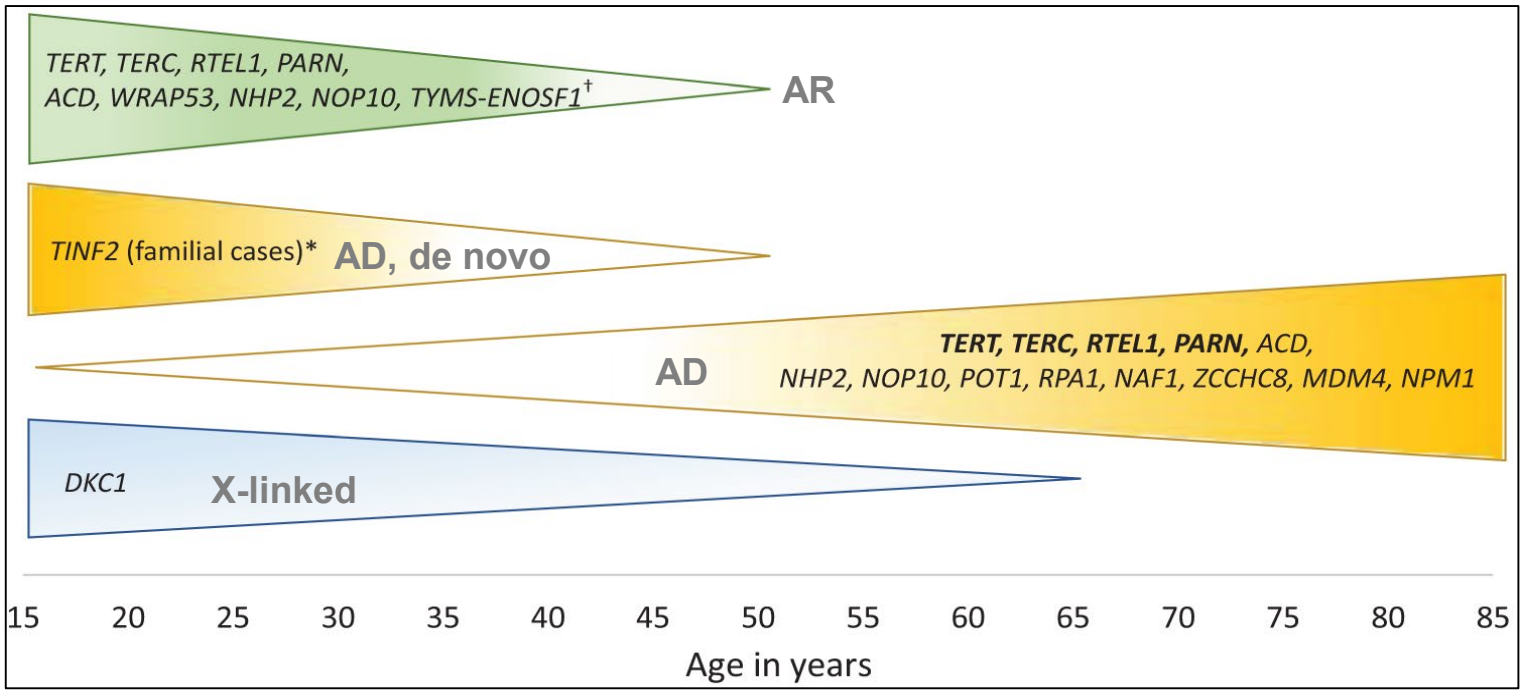
Dokal, Dyskeratosis Congenita, 2014

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

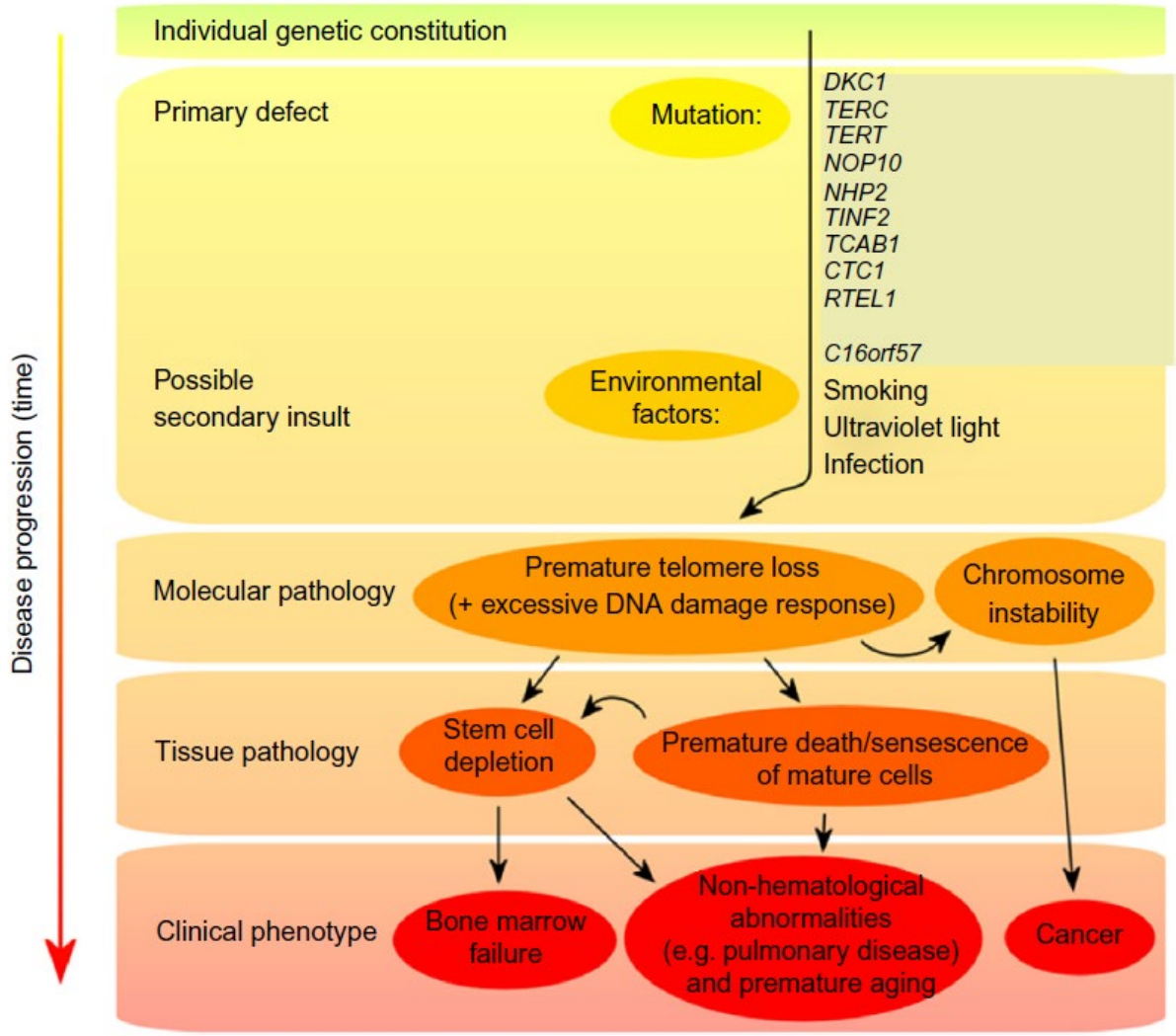
Genes and patterns of inheritance in adult TBD patients





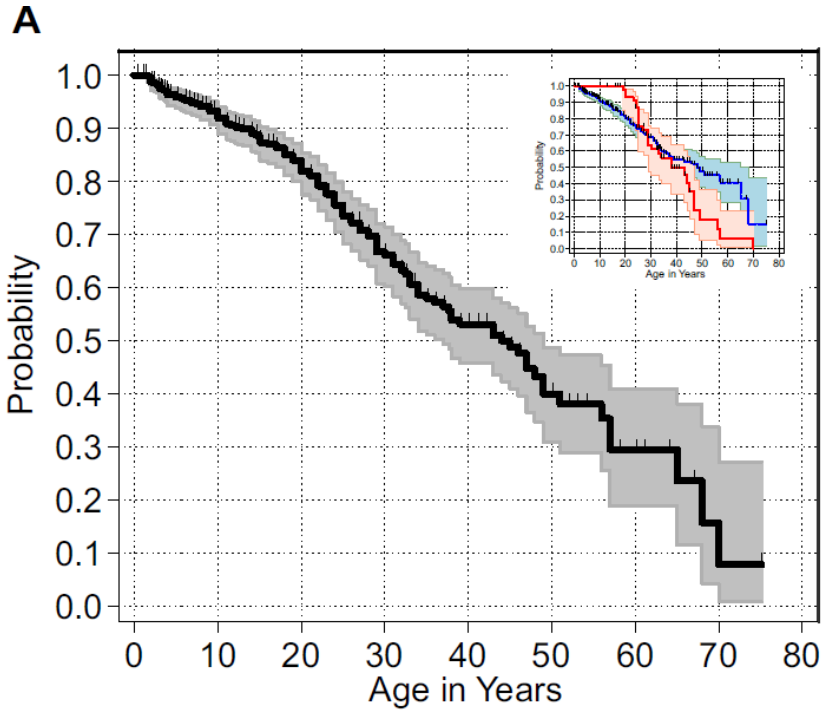
Niewisch, et al. Hematology, 2023

Pathophysiology of BMF in TBD



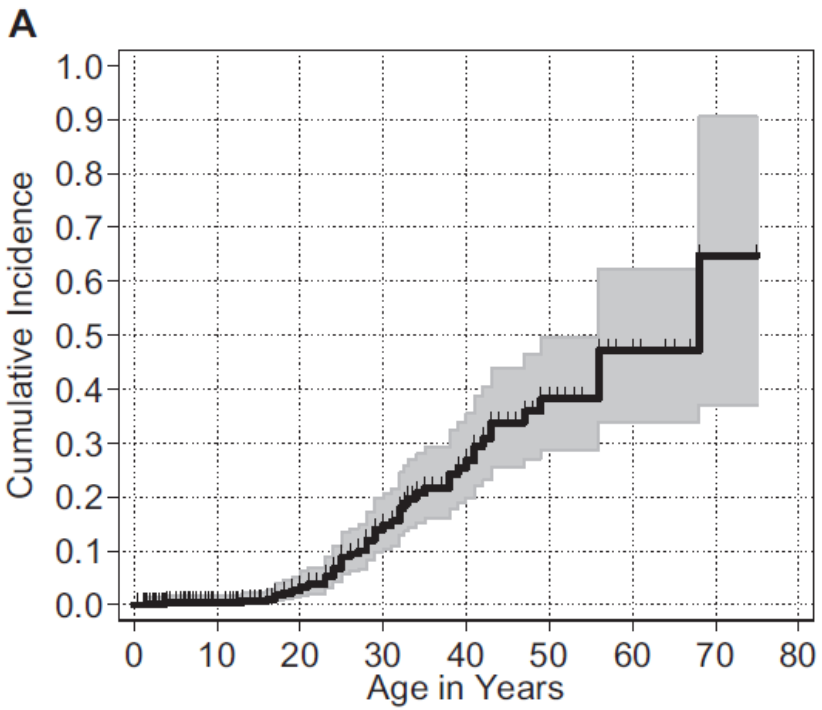
Dokal, Dyskeratosis Congenita, 2014

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

- 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.

Patient Case 3

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).

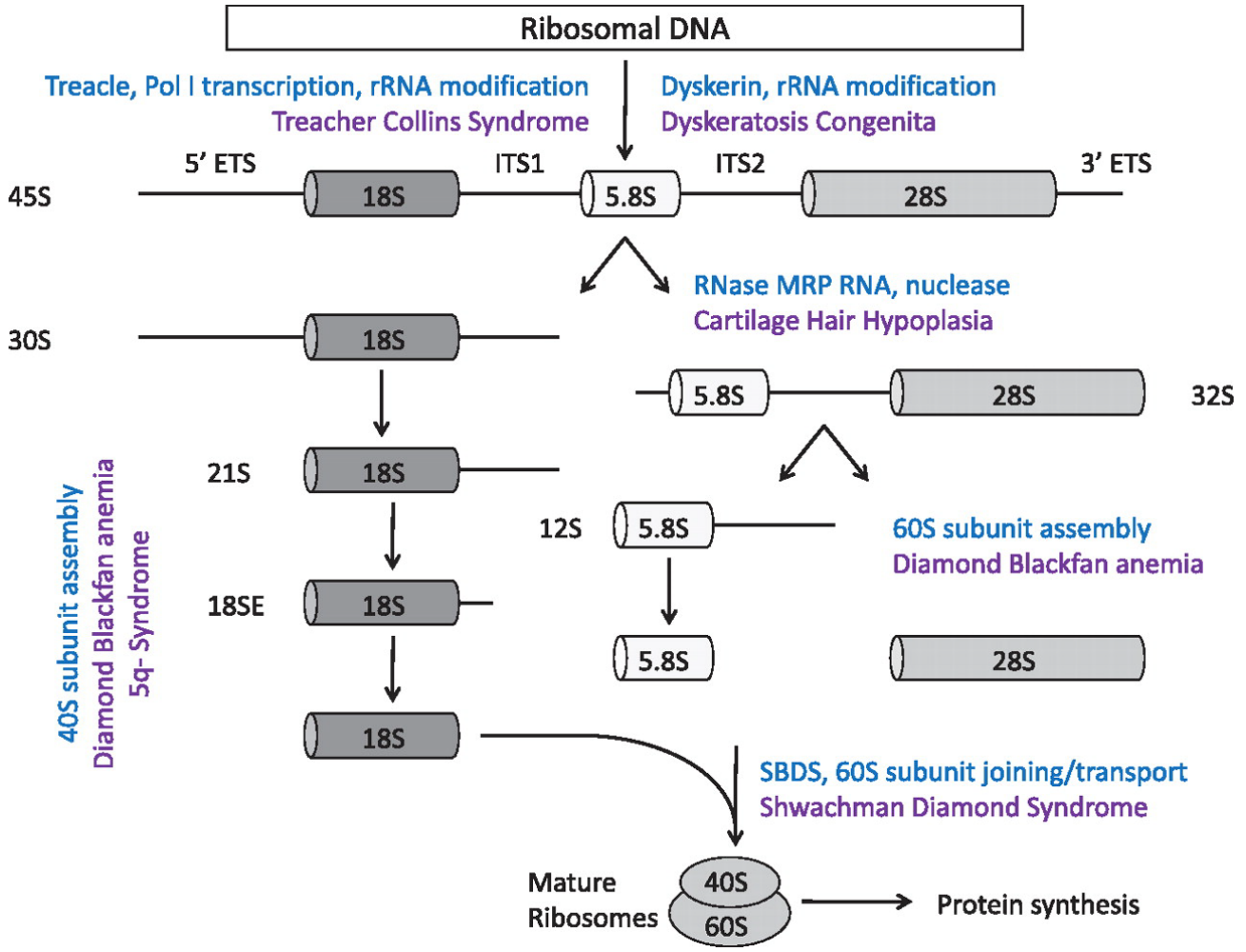
Physical exam: Small for age. Pallor, otherwise no apparent abnormality. Holosystolic murmur.

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?

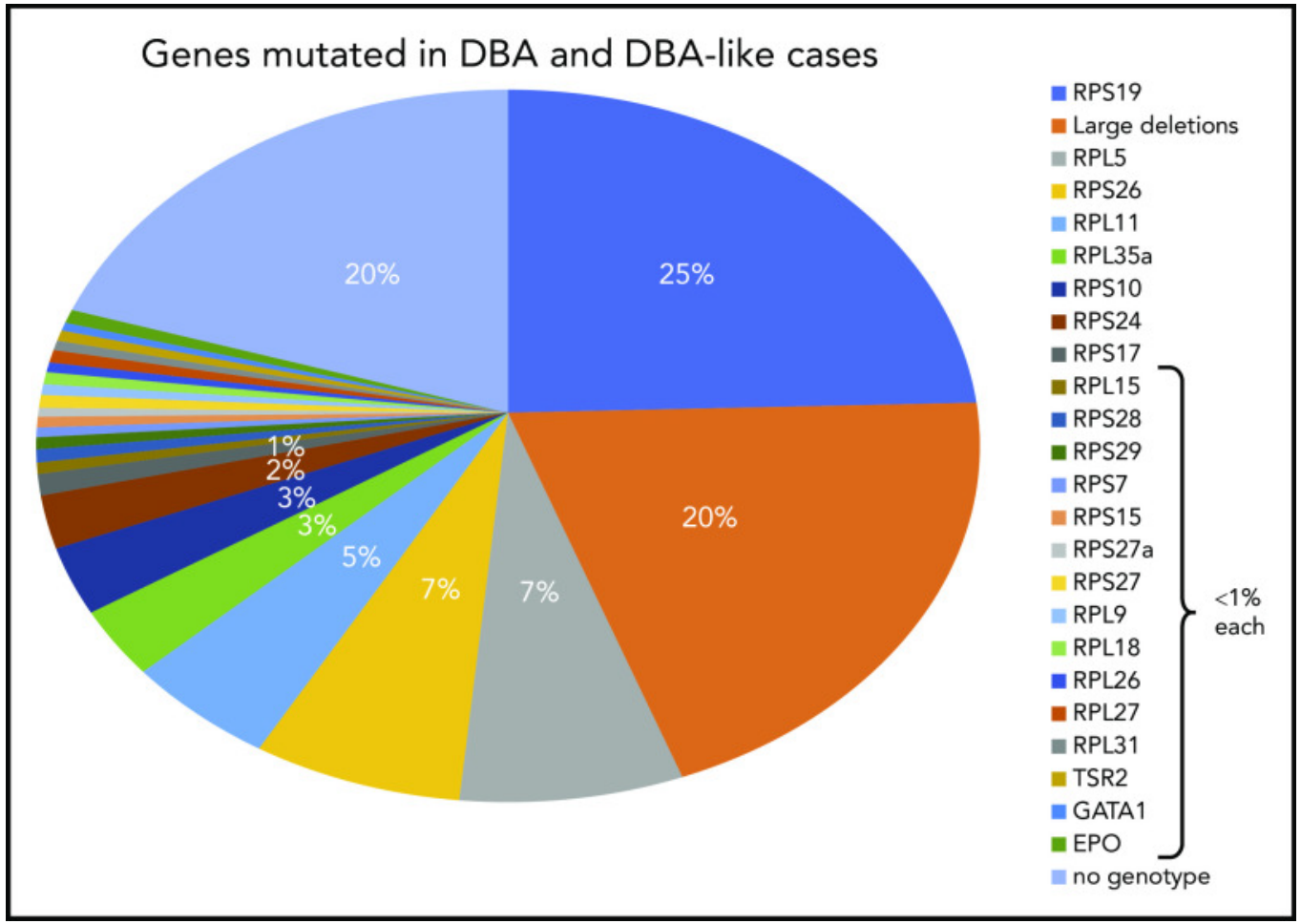
Pathogenesis of Diamond Blackfan Anemia (DBA)



- 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.

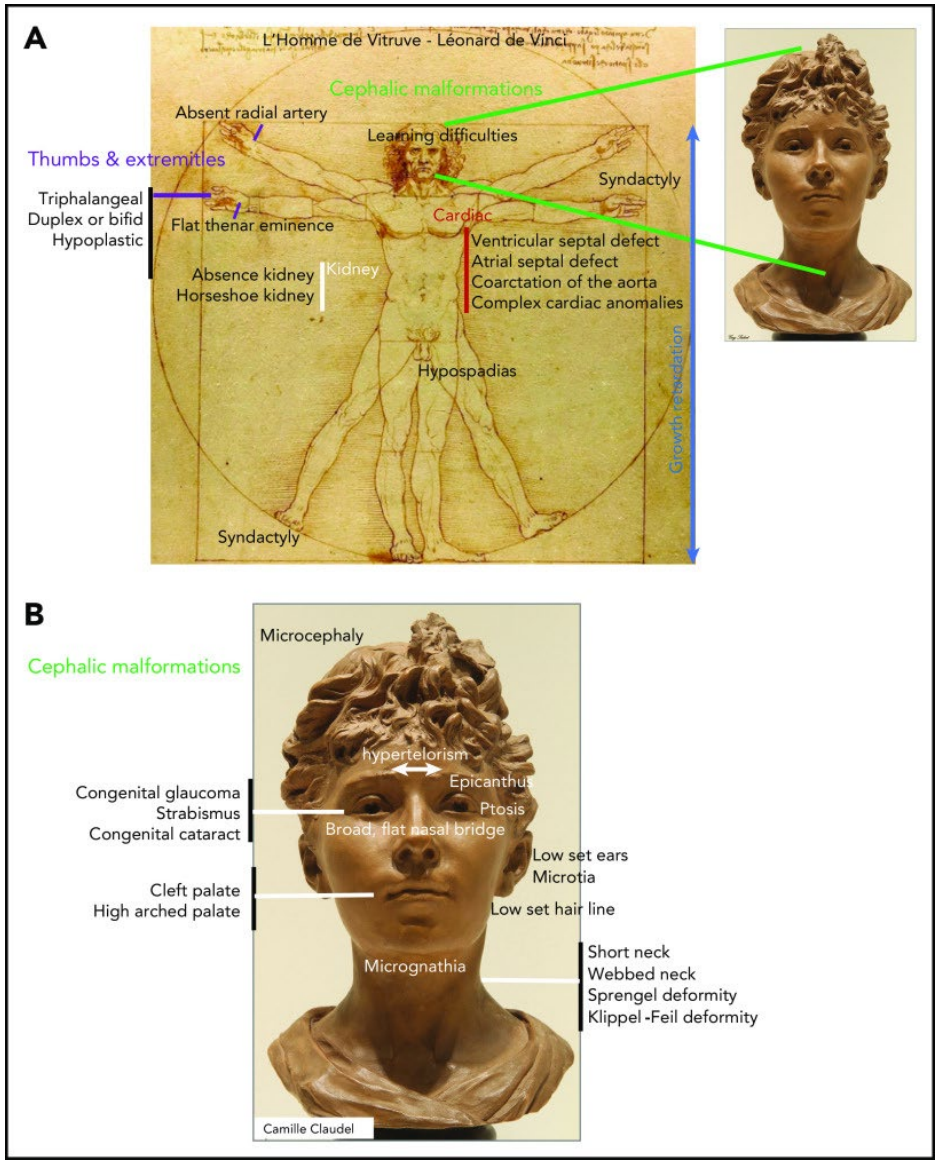
- AD, haploinsufficiency in RP
  - Most common: RPS19, RPL5, RPL11
- X-linked: GATA1, TSR2
- AR: EPO

- Mutations and large deletions

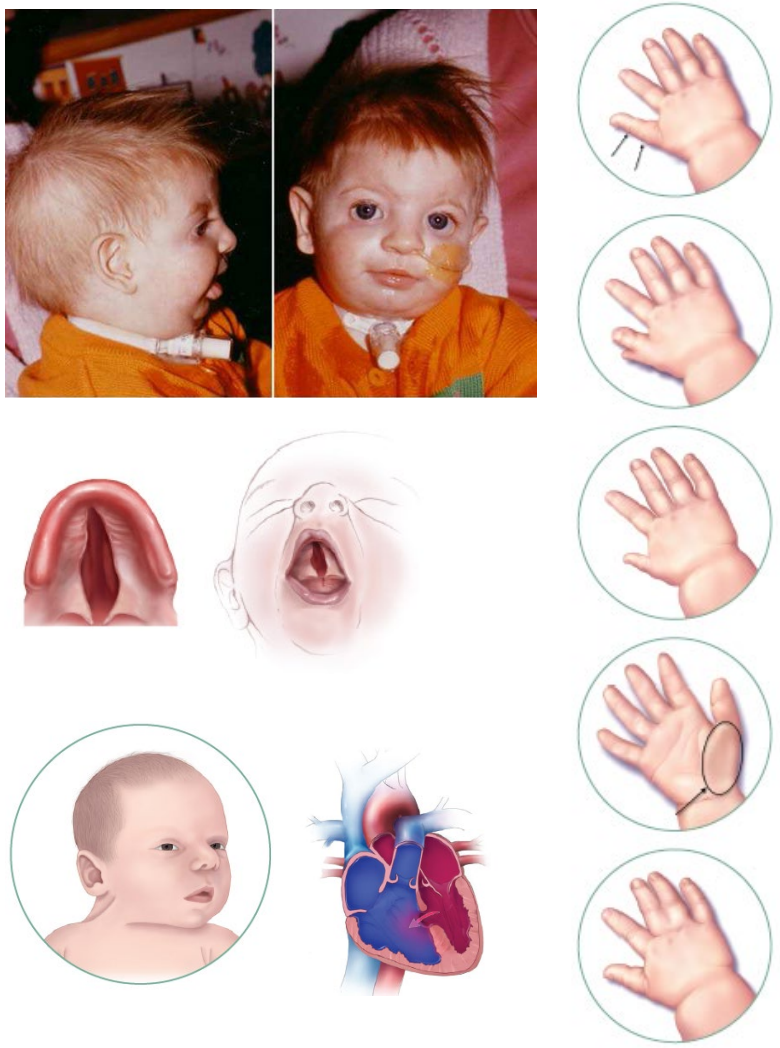
- Diagnosis is established by:
  - Genetic testing
  - Elevated erythrocyte ADA

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.



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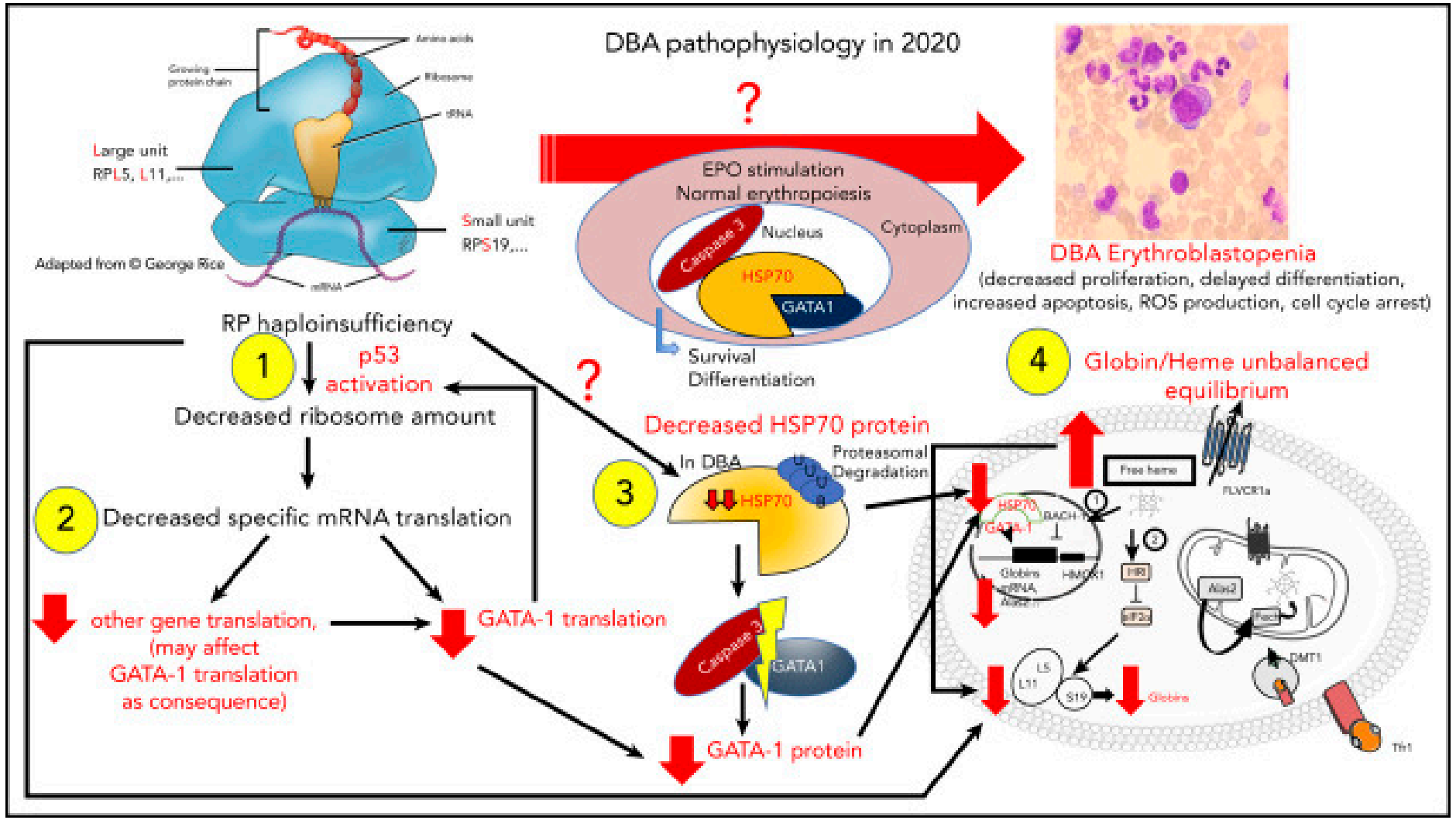
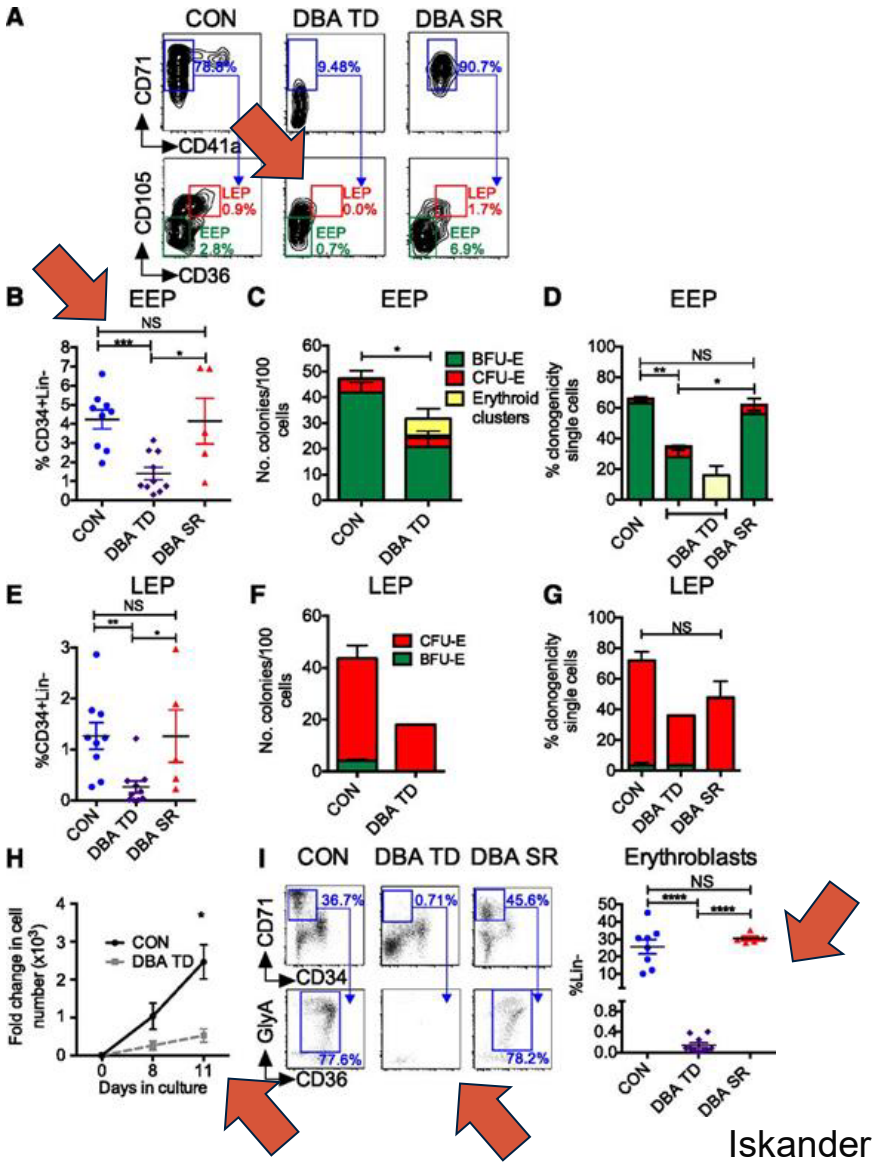
Hematol Oncol Clin North Am. 2009 April; 23(2): 261–282.

DBA Pathogenesis



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

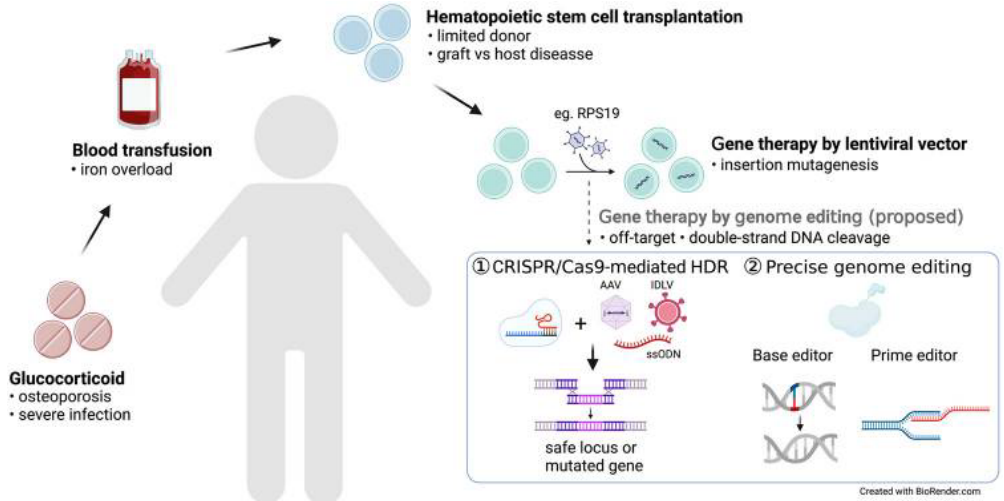
Erythroid Maturation Defect



Iskander et al. Blood (2015) 125 (16): 2553–2557.

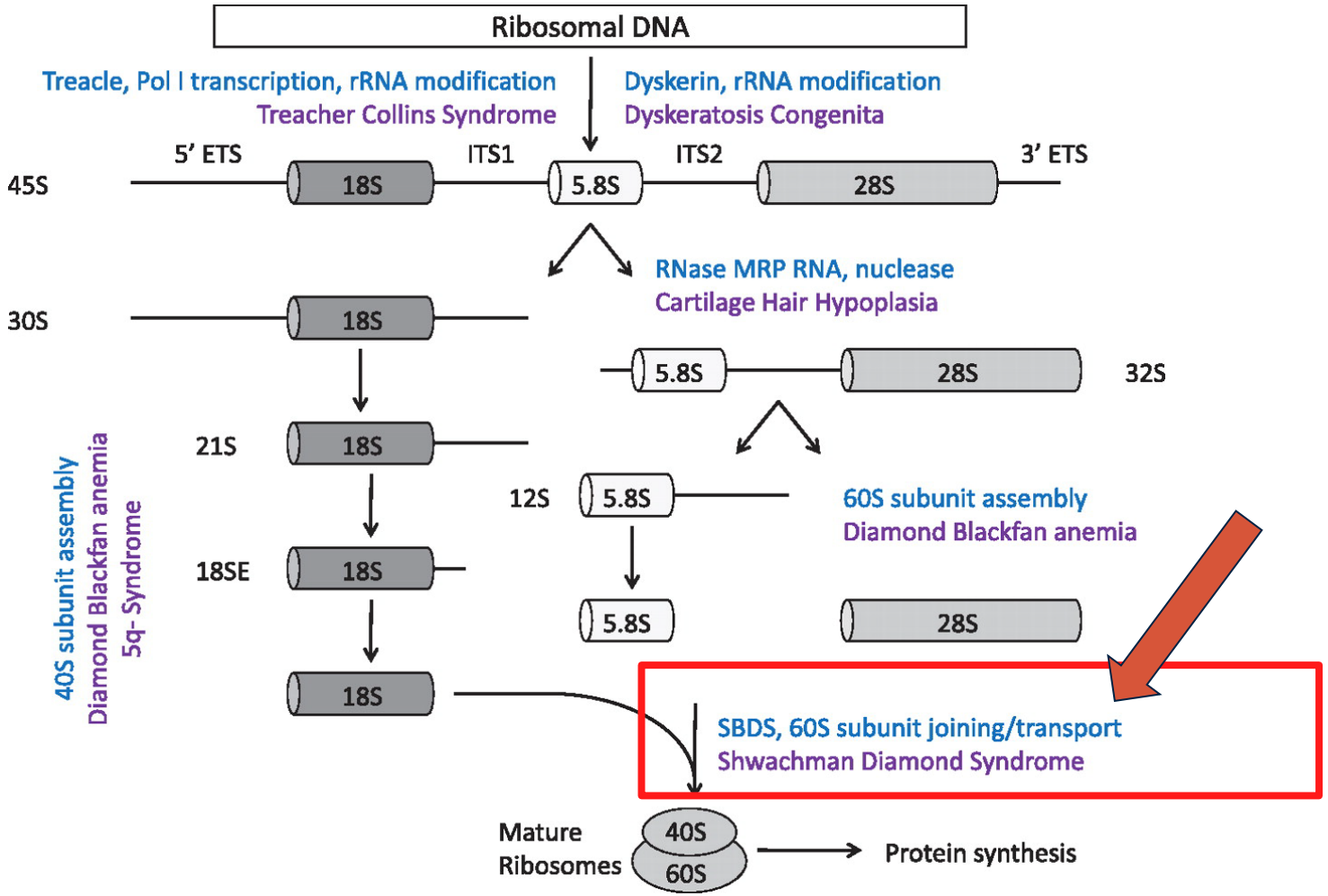
Clinical Management

- 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.

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
- Up to 30% rate of transformation to MDS/AML (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

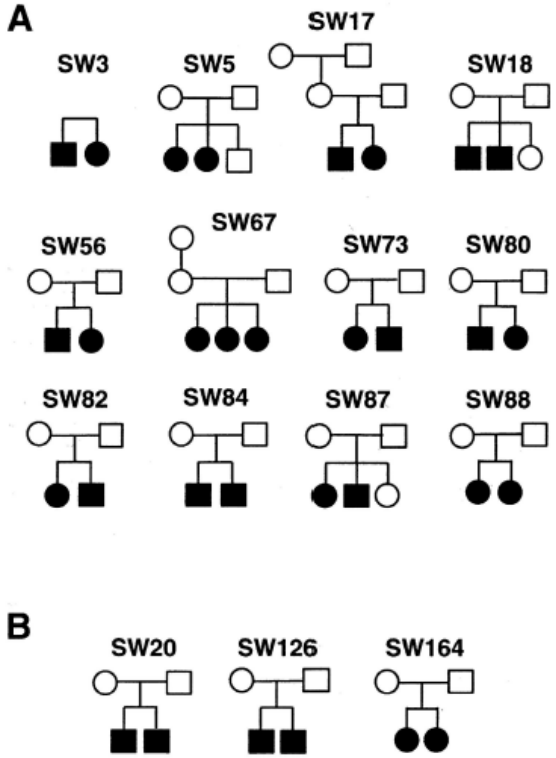
Diagnosis

- 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
  - Bone marrow surveillance for adverse clonal evolution
  - HSCT for transfusion-dependent BMF or adverse clonal evolution
- Endocrinology and orthopedics evaluation
- Pancreatic insufficiency responds to pancreatic enzymes
- Genetic counseling

GATA2 Deficiency

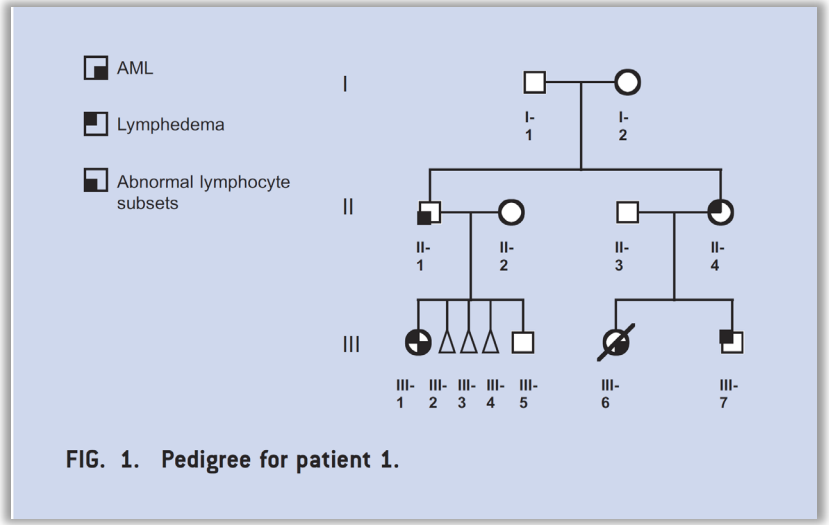
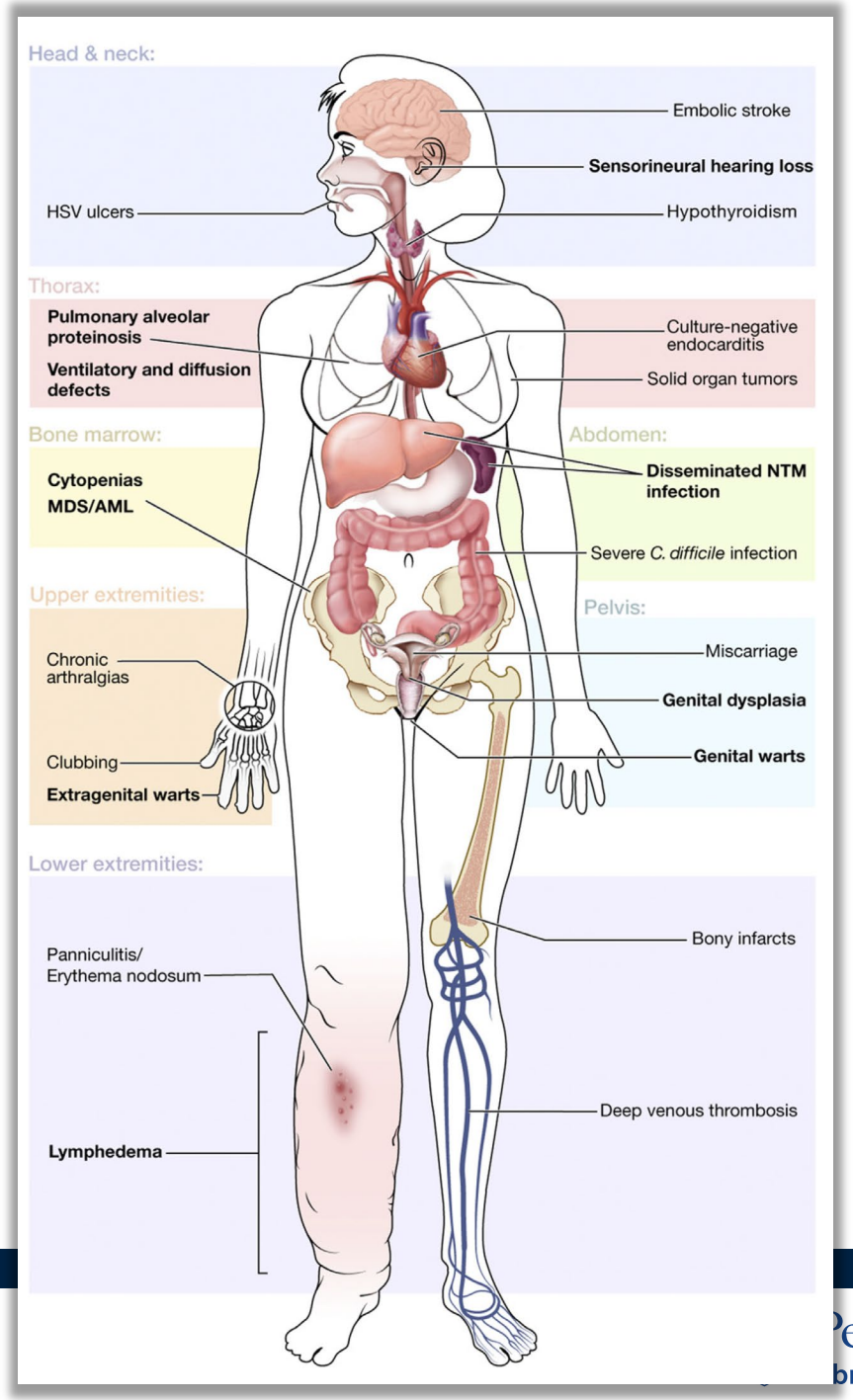


FIG. 1. Pedigree for patient 1.

- Immunodeficiency
- Lymphedema
- MDS predisposition



Defining a new human disease

- 1972, 1976, 1979, 1985:
  - case reports of individual families with familial segregation of MDS/AML and lymphedema

2010

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics

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

Sahar Mansour,[1]* Fiona Connell,[1] Colin Steward,[2] Pia Ostergaard,[1] Glen Brice,[1] Sarah Smithson,[3] Peter Lunt,[3] Steve Jeffery,[1] Inderjeet Dokal,[4] Tom Vulliamy,[4] Brenda Gibson,[5] Shirley Hodgson,[1] Sally Cottrell,[1] Louise Kiely,[1] Lorna Tinworth,[1] Kamini Kalidas,[1] Ghulam Mufti,[6] Jackie Cornish,[2] Russell Keenan,[7] Peter Mortimer,[8] Victoria Murday,[9] and Lymphoedema Research Consortium

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[2]Bone Marrow Transplant Unit, Royal Hospital for Children, Bristol, UK

[3]Department of Clinical Genetics, St Michael's Hospital, St Michael's Hill, Bristol, UK

[4]Centre for Paediatrics, Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, London, UK

[5]Department of Haematology, Yorkhill Hospital, Glasgow, UK

[6]Department of Haematology, School of Medicine, King's College Hospital, London, UK

[7]Department of Paediatric Haematology, Alderhey Children's Hospital, Liverpool, UK

[8]Department of Cardiac and Vascular Sciences, St. George's, University of London, London, UK

[9]Department of Clinical Genetics, Yorkhill Hospital, Glasgow, UK

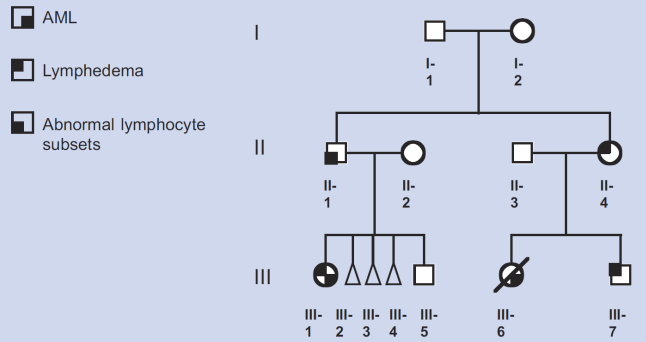


FIG. 1. Pedigree for patient 1.

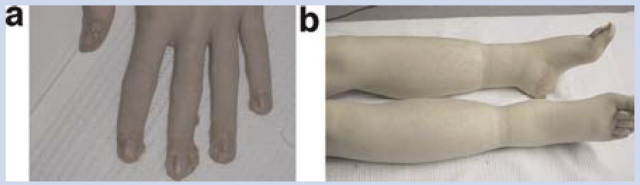
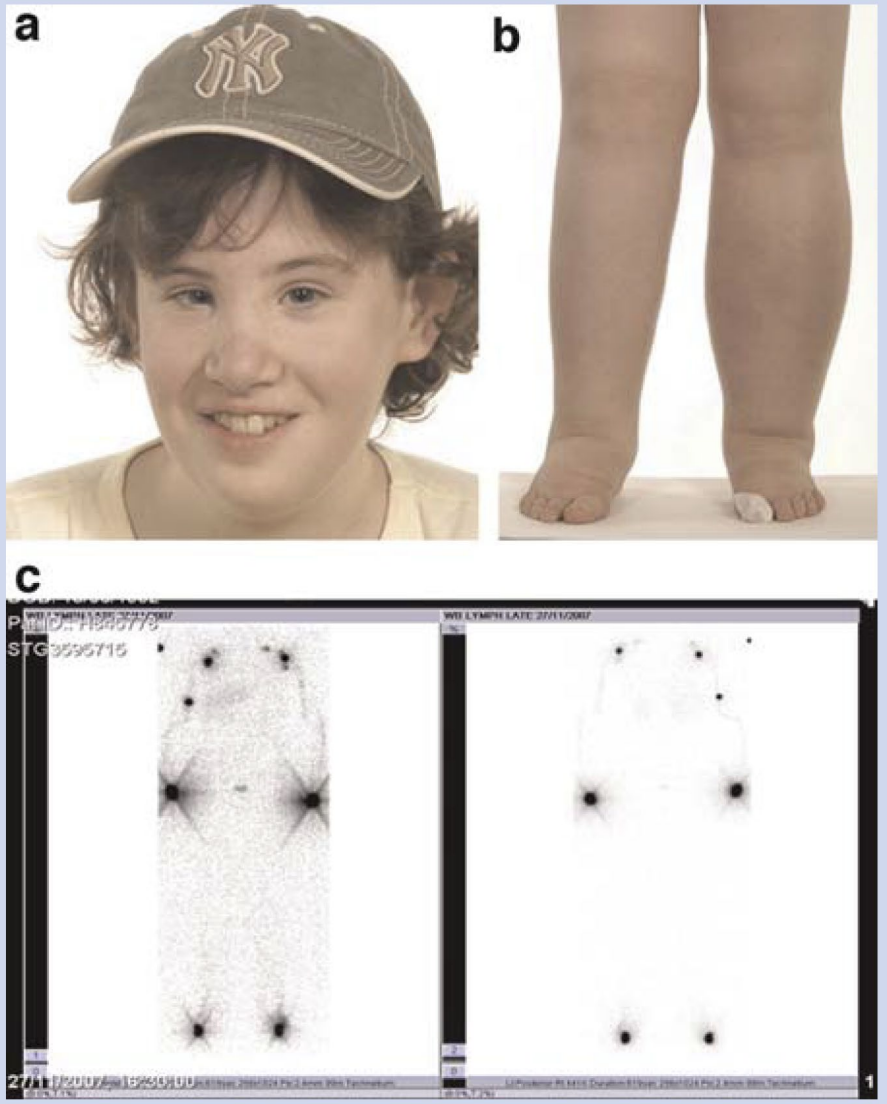


FIG. 3. a: Patient 2, multiple and persistent warts. b: Patient 2, bilateral lower limb lymphoedema.



Emberger Syndrome

- Autosomal-dominant inheritance
- Associated with:
  - Lymphedema
  - Predisposition to MDS/AML
  - Warts
  - Sensorineural deafness
- Genetic cause unknown

Meanwhile at NIAID…

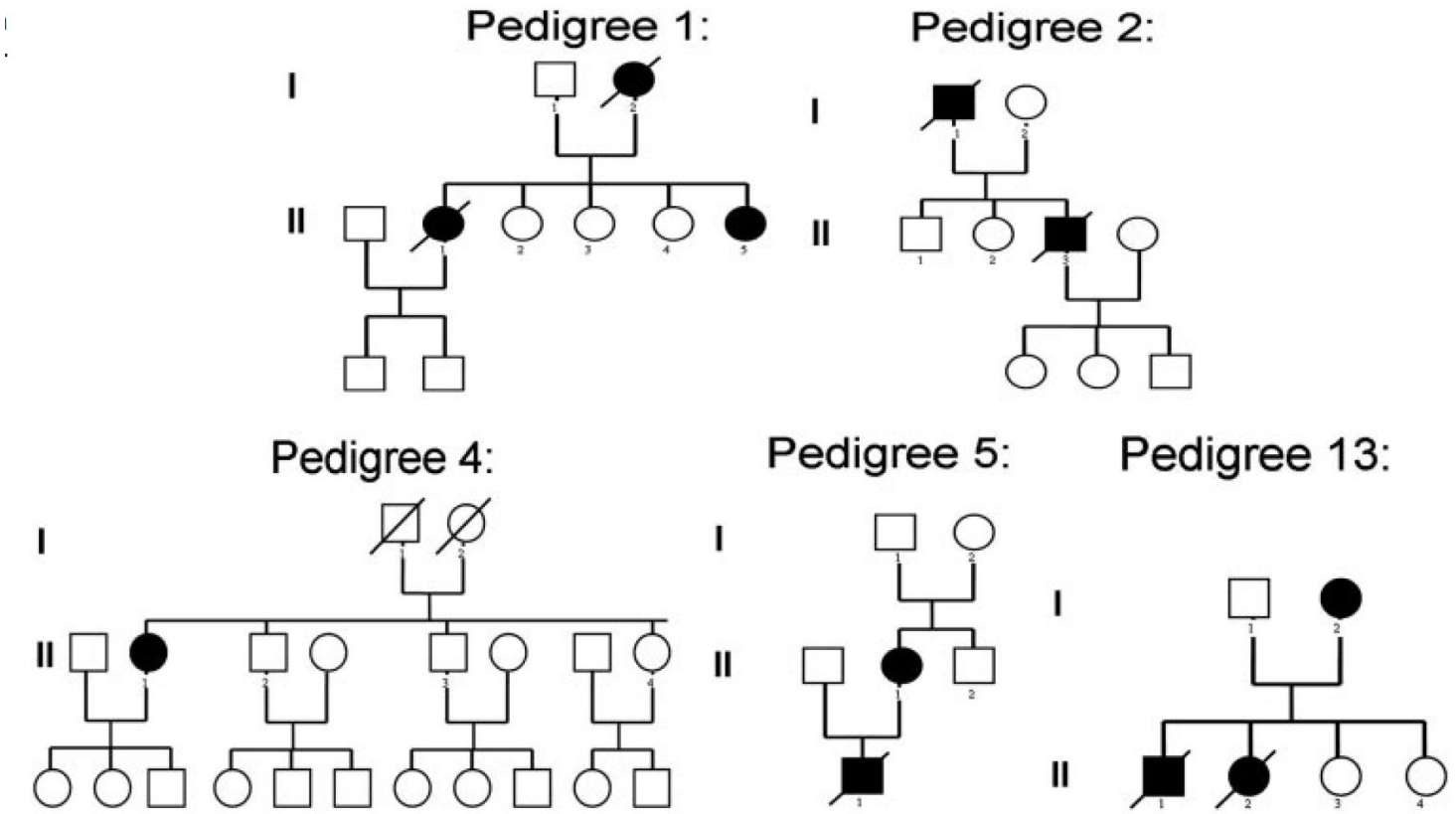
BLOOD, 25 FEBRUARY 2010 • VOLUME 115, NUMBER 8

Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia

*Donald C. Vinh,[1] *Smita Y. Patel,[1] Gulbu Uzel,[1] Victoria L. Anderson,[1] Alexandra F. Freeman,[1,2] Kenneth N. Olivier,[1] Christine Spalding,[1] Stephen Hughes,[3] Stefania Pittaluga,[4] Mark Raffeld,[4] Lynn R. Sorbara,[5] Houda Z. Elloumi,[1] Douglas B. Kuhns,[6] Maria L. Turner,[7] Edward W. Cowen,[7] Danielle Fink,[6] Debra Long-Priel,[6] Amy P. Hsu,[1] Li Ding,[1] Michelle L. Paulson,[1] Adeline R. Whitney,[8] Elizabeth P. Sampaio,[1] David M. Frucht,[9] Frank R. DeLeo,[8] and Steven M. Holland[1]

[1]Immunopathogenesis Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD; [2]Intramural Clinical Management and Operations Branch, SAIC, Frederick, MD; [3]Paediatric Immunology Unit, Newcastle General Hospital, Newcastle, United Kingdom; [4]National Cancer Institute (NCI) Laboratory of Pathology, NIH, Bethesda, MD; [5]NCI Cancer Biomarkers Research Group, Bethesda, MD; [6]SAIC, Frederick, MD; [7]Dermatology Branch, NCI, NIH, Bethesda, MD; [8]Laboratory of Human Bacterial Pathogenesis, Rocky Mountain Laboratories, NIAID, NIH, Hamilton, MT; and [9]Laboratory of Cell Biology, Office of Biotechnology Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Bethesda, MD

- Ongoing study of mycobacterial infections
- Identified 5 kindreds where NTB mycobacterial infections co-occurred with other infections and familial hematologic malignancies



Monocytopenia, and B, NK, and T cell deficiencies

Table 1. Peripheral blood immunophenotyping of the index cases of all kindreds

	Affected cell lineage (reference range, cells/μL)						
	CD14/monocytes (210-660)	Total lymphocytes (1320-3570)	CD20/B cells (49-424)	$CD3^{-}$ $CD16^{+}$ NK cells (87-505)	CD3/T cells (650-2108)	$CD4^{+}$ T cells (362-1275)	$CD8^{+}$ T cells (344-911)
Autosomal dominant cases							
1.II.1	0	402	2	4	396	124	234
1.II.5	20	646	8	69	569	260	273
2.II.3	4	179	0	0	179	84	81
4.II.1	10	759	4	3	752	246	494
5.II.1	25	633	4	5	624	396	205
13.I.2	19	1493	21	22	1450	301	1140
13.II.1	0	112	1	2	109	37	64
Sporadic cases							
3.I.1	20	442	13	2	427	198	210
6.I.1	22	828	16	6	796	408	329
7.I.1	13	700	3	55	642	261	364
8.I.1	16	807	4	10	793	438	396
9.III.1	27	1987	30	24	1933	1021	864
10.I.1	21	520	4	1	515	233	246
11.II.1	4	1300	51	39	1210	538	613
12.I.1	0	280	1	0	279	193	80
14.II.1	29	1797	2	22	1773	808	964
15.II.1	9	999	5	24	970	489	432
16.II.1	0	747	0	0	747	345	330

Pulmonary alveolar proteinosis (PAP)

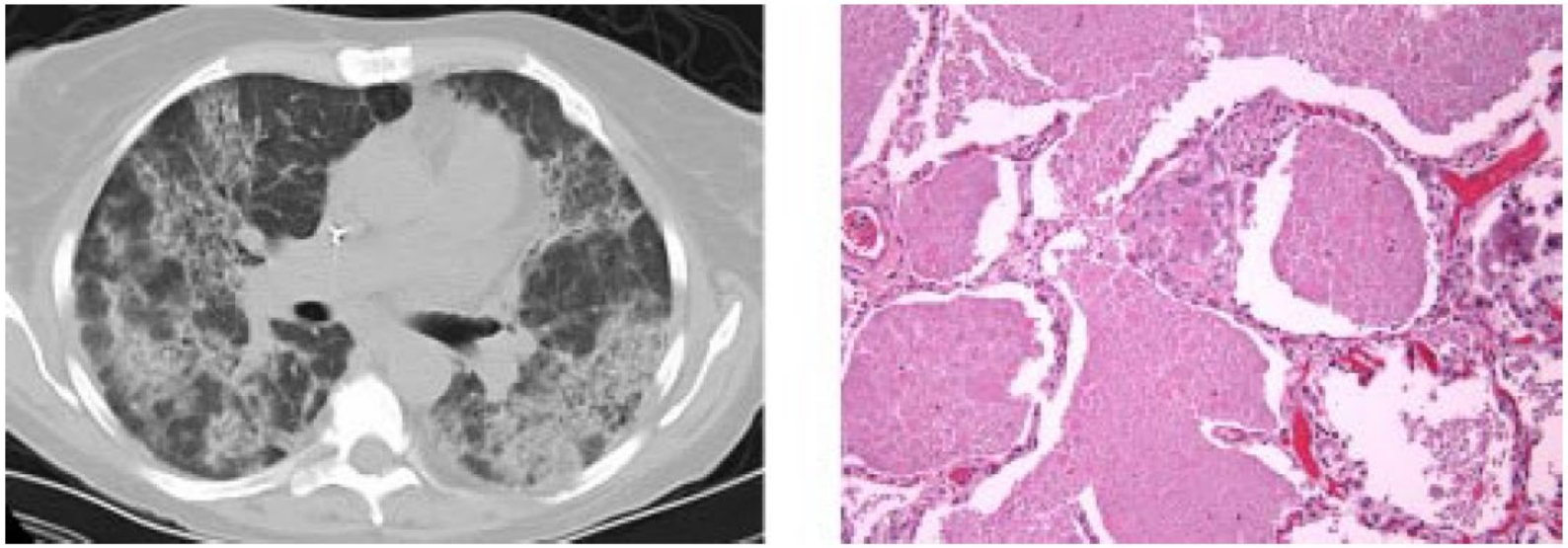


Figure 2. PAP in patient 3.I.1. Computed tomography (left) demonstrates significant bilateral airspace disease. Histopathology (right) demonstrates excessive accumulation of amorphous proteinaceous material in the alveolar spaces. Images were taken using an Olympus Bx41 microscope, objectives UPlanFI 40×/0.75 ∞/0.17, and UPlanFI 20×/05.0 ∞/0.17, with an adaptor U-TV0.5×C using a digital camera Q-imaging Micropublisher 5.0RTV. The images were captured using Q-Capture Version 3.1 and imported into Adobe Photoshop 7.0.

Defining “Monocytopenia + MAC infection+ risk of progression to MDS/AML” = “MonoMAC syndrome”

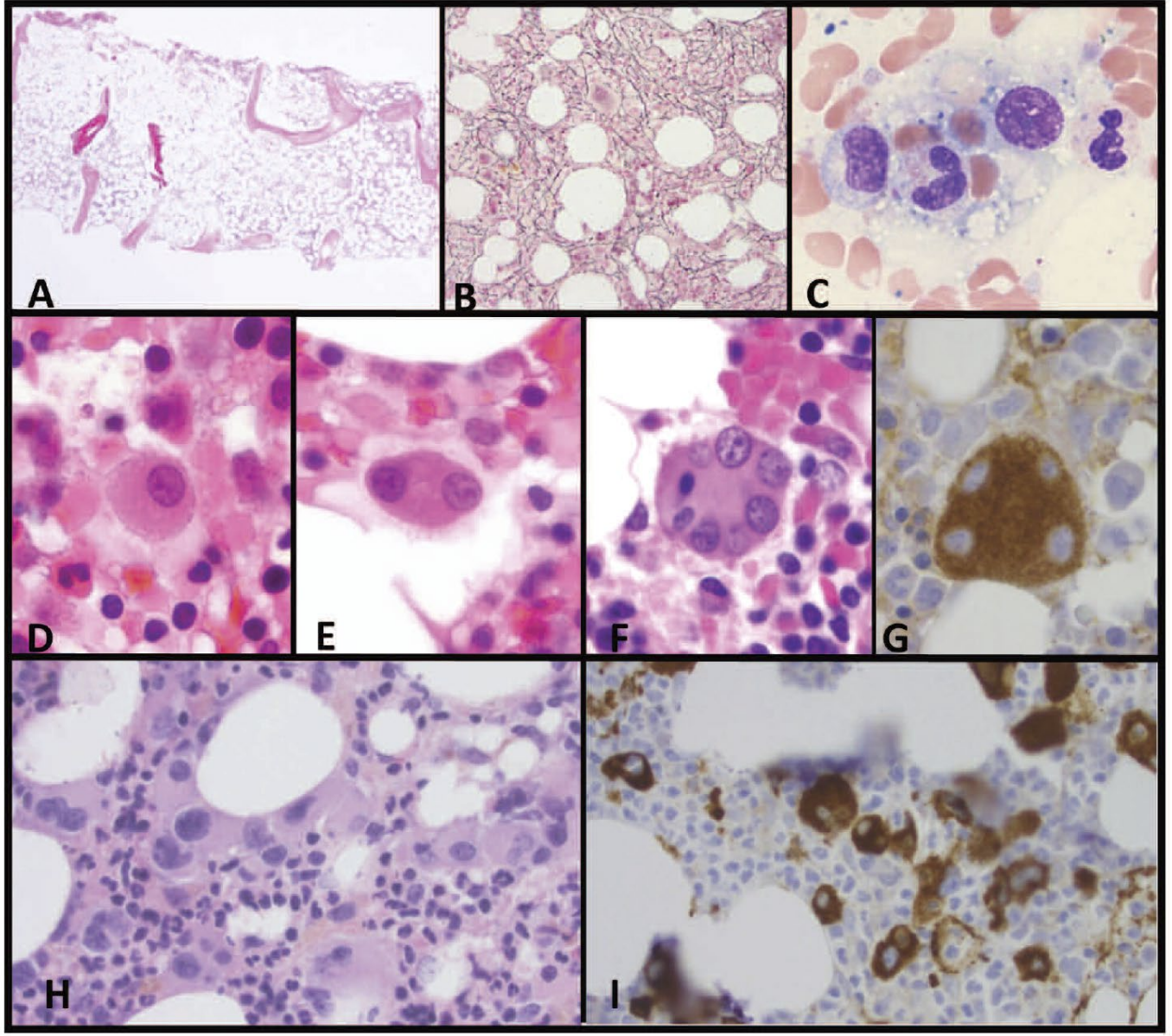
Table 2. Clinical features and salient complications of the syndrome

Clinical feature	Frequency overall, percentage (n = 18), no. (%)	Autosomal dominant patients, percentage (n = 7), no. (%)	Sporadic patients, percentage (n = 11), no. (%)
Infection			
Mycobacteria	14/18 (78)	6/7 (86)	8/11 (73)
HPV	14/18 (78)	6/7 (86)	8/11 (73)
Fungi	5/18 (28)	3/7 (43)	2/11 (18)
Complication			
PAP	6/18 (33)	2/7 (29)	4/11 (36)
Panniculitis/erythema nodosum	6/18 (33)	2/7 (29)	4/11 (36)
Myelodysplasia/acute myeloid leukemia	9/18 (50)	5/7 (71)	4/11 (36)
Death during study	5/18 (28)	3/7 (43)	2/11 (18)

Bone Marrow Features

A. Hypocellular
B. Fibrosis
C. Hemophagocytic histiocytes

D-G. Abnormal megakaryocytes



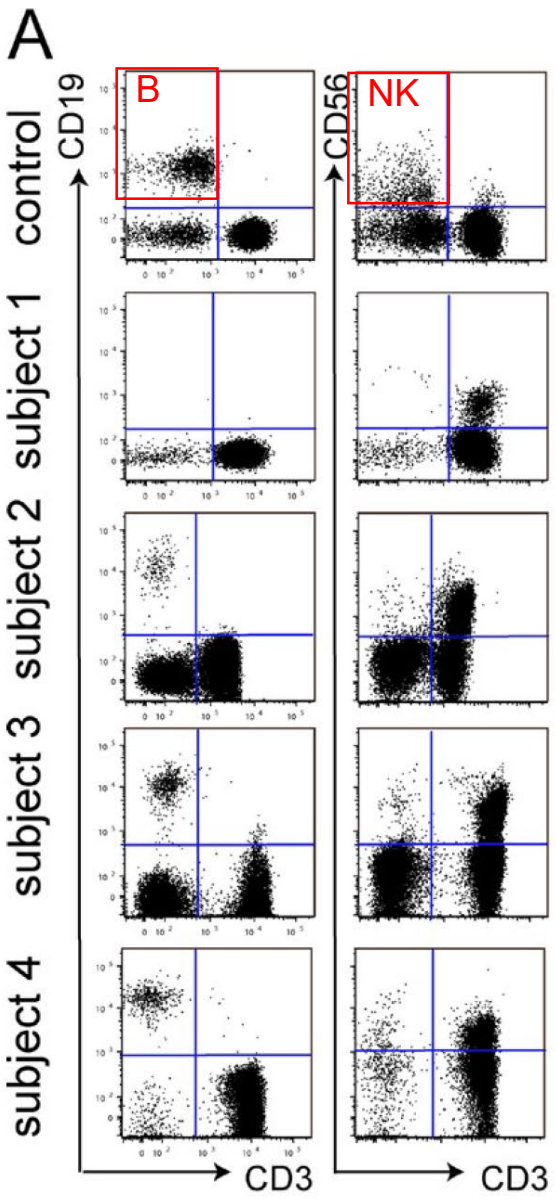
JEM VOL. 208, February 14, 2011

Meanwhile in Europe, a study of patients with DC deficiency

The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency

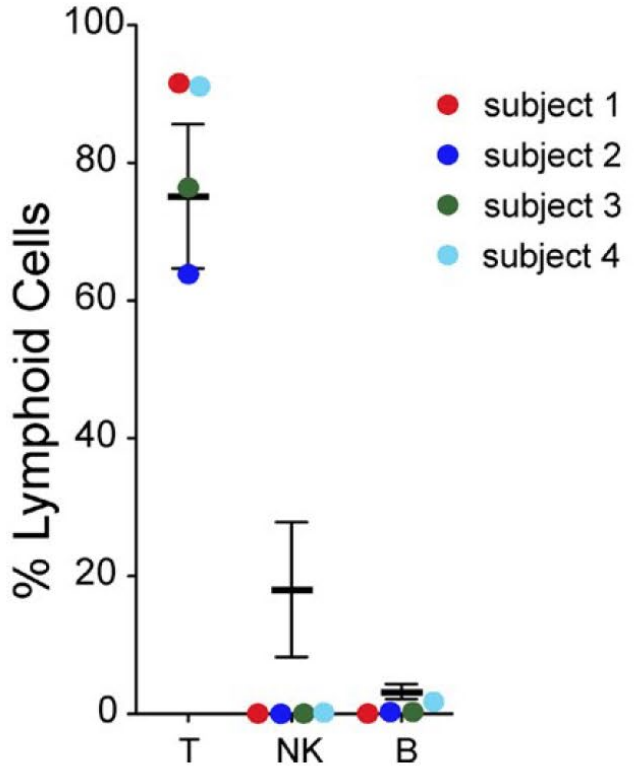
Venetia Bigley,[1] Muzlifah Haniffa,[1] Sergei Doulatov,[2] Xiao-Nong Wang,[1] Rachel Dickinson,[1] Naomi McGovern,[1] Laura Jardine,[1] Sarah Pagan,[1] Ian Dimmick,[1] Ignatius Chua,[3] Jonathan Wallis,[4] Jim Lordan,[4] Cliff Morgan,[5] Dinakantha S. Kumararatne,[6] Rainer Doffinger,[6] Mirjam van der Burg,[7] Jacques van Dongen,[7] Andrew Cant,[4] John E. Dick,[2] Sophie Hambleton,[1] and Matthew Collin[1]

[1]Institute of Cellular Medicine, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, England, UK
[2]Division of Cell and Molecular Biology, University Health Network and Department of Molecular Genetics, University of Toronto, Toronto, Ontario M5G 1L7, Canada
[3]University College London Centre for Immunodeficiency, Royal Free Hospital, NW3 2QG London, England, UK
[4]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne NE7 7DN, England, UK
[5]Royal Brompton Hospital Sydney Street, London SW3 6NP, England, UK
[6]Department of Clinical Biochemistry and Immunology, Addenbrookes Hospital, Cambridge CB2 2QQ, England, UK
[7]Department of Immunology, Erasmus MC University Medical Center Rotterdam, 3015 CE Rotterdam, Netherlands

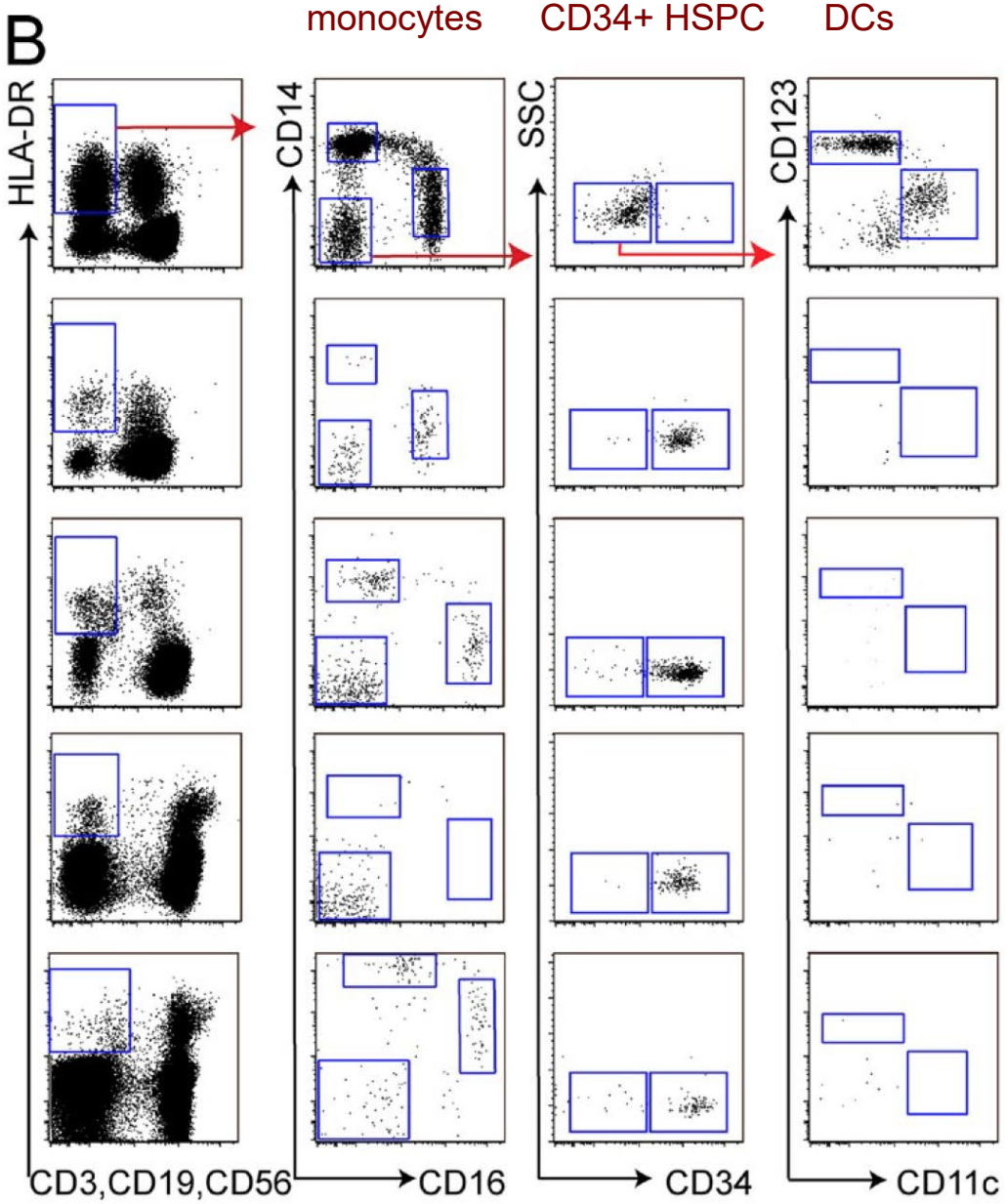


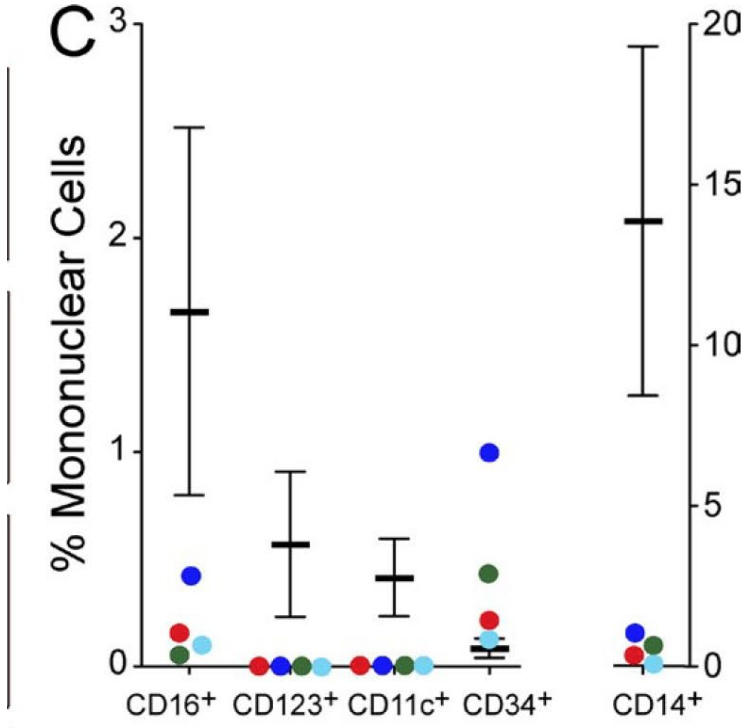
4 subjects with DC deficiency, also associated with monocyte, B, NK lymphocyte deficiency (and MONOMAC-like infections…)

CD19+ B and CD56+ NK cell deficiency



Abnormal monocyte and DC maturation





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]

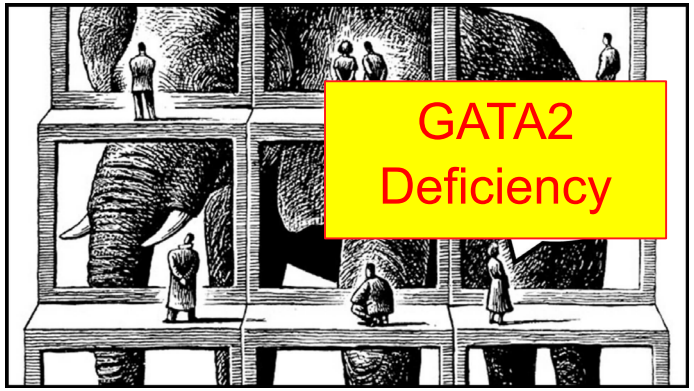
Mutations in *GATA2* cause human NK cell deficiency with specific loss of the CD56^{bright} subset

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]

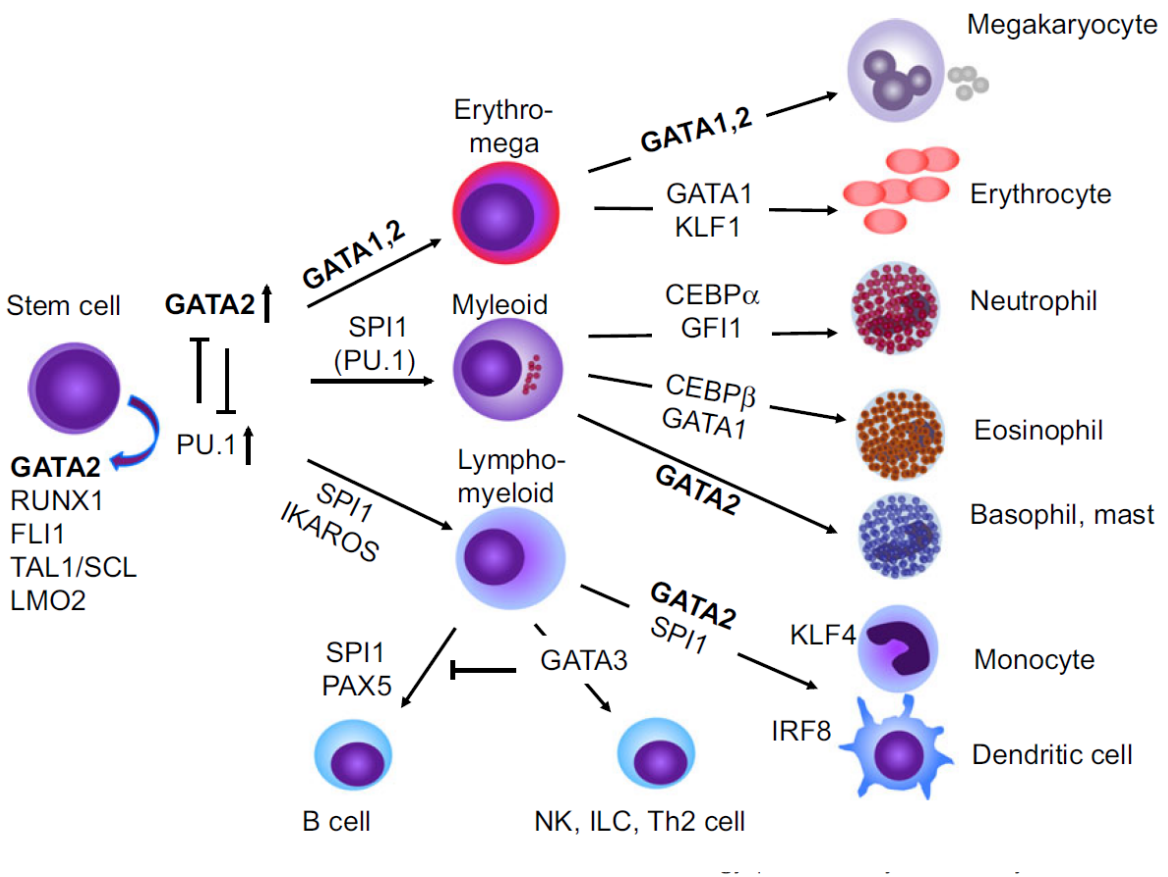
Mutations in *GATA2* cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome)

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

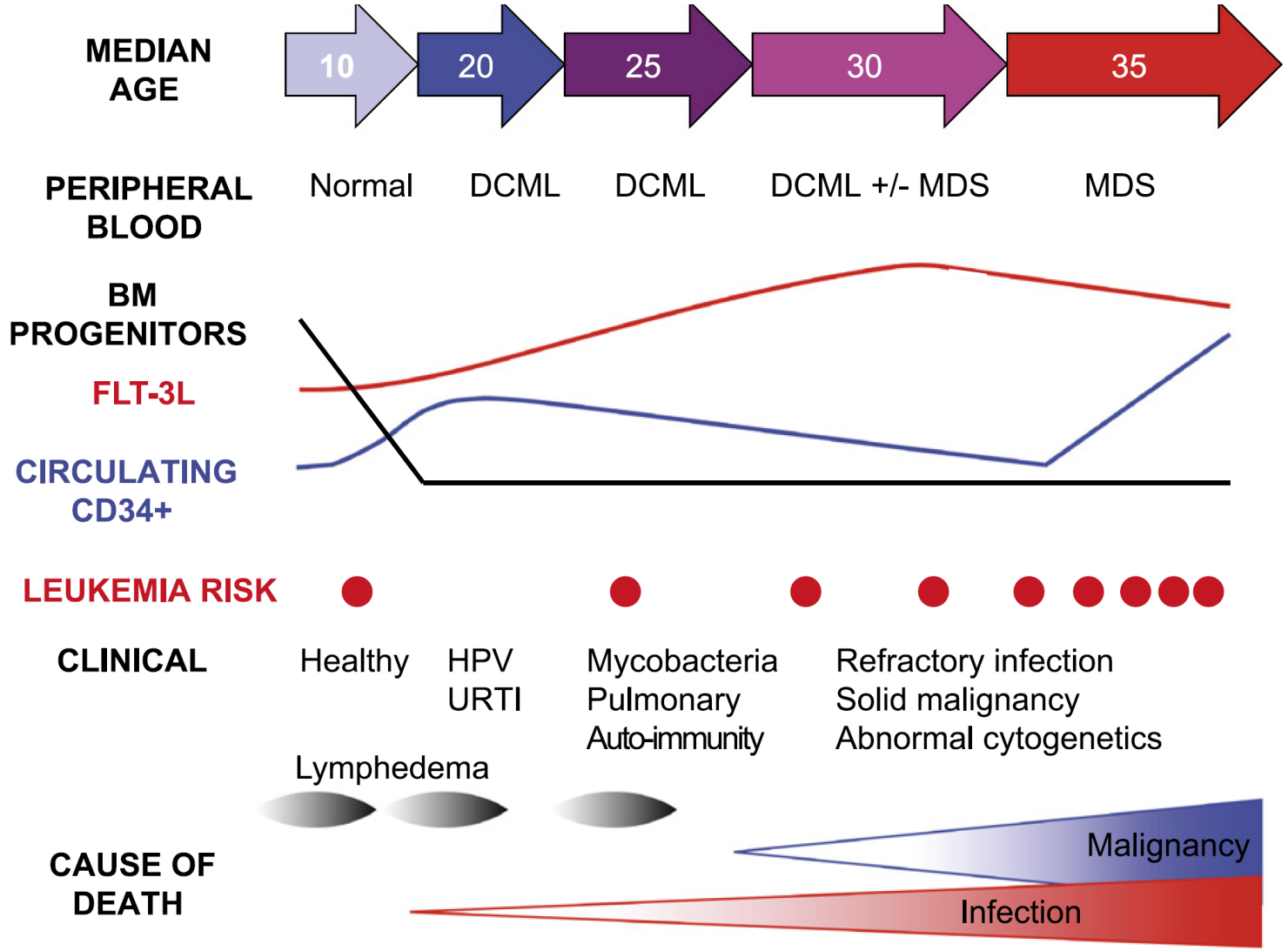


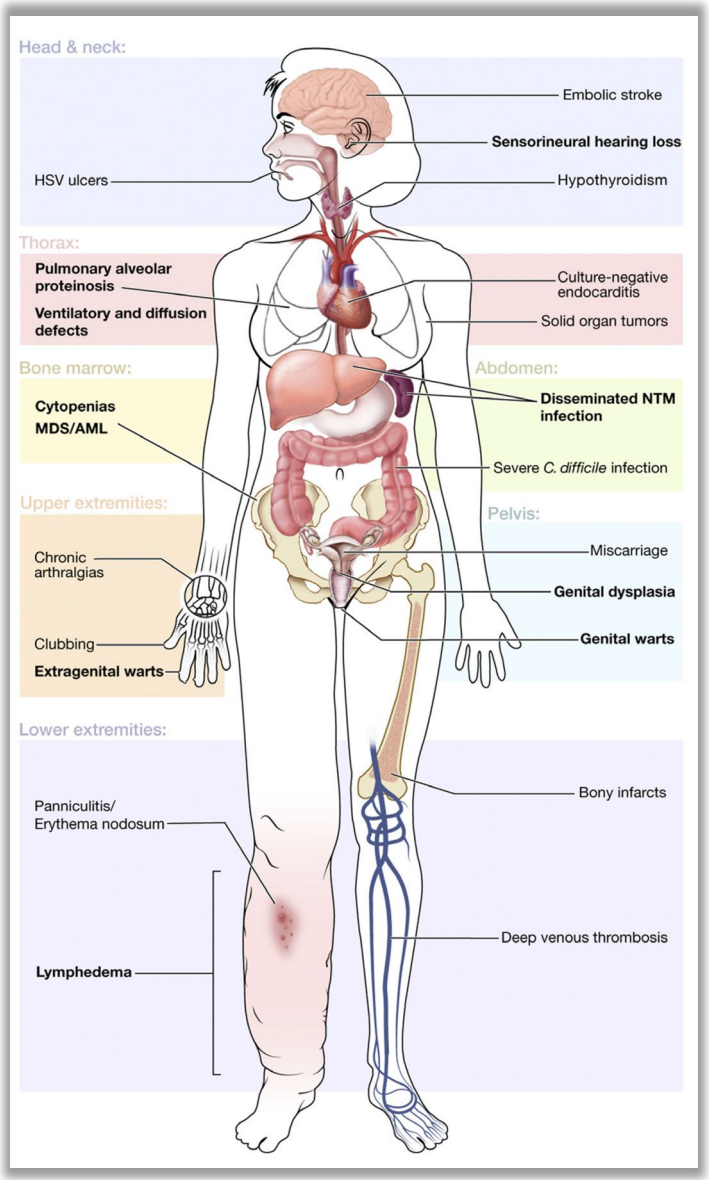
GATA2 is a key transcriptional regulator of hematopoiesis



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





BLOOD, 6 FEBRUARY 2014 • VOLUME 123, NUMBER 6

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

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)
GATA2 deficiency	~20s	Unknown (~500 reported cases)	Haploinsufficiency of GATA2 transcription factor	AD	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)

When to Suspect an Inherited BMF Syndrome?

- **Age at diagnosis** (younger>older)
- **Duration of cytopenias** (life-long cytopenias)
- **Associated conditions and congenital malformations:**
  - pulmonary fibrosis (e.g., in TBD)
  - genitourinary malformation (e.g., in FA, DBA)
  - liver cirrhosis (e.g., in TBD)
  - avascular necrosis (e.g., in TBD)
  - recurrent pre-eclampsia/pregnancy loss (e.g., in TBD, GATA2 deficiency)
  - congenital heart defect (e.g., in DBA)
  - vascular malformation (e.g., in TBD)
  - lymphedema (e.g., in GATA2 deficiency)
  - warts, NTM, EN (e.g., in GATA2 deficiency)
  - thumb and upper limb abnormalities (e.g., in FA, DBA, TAR)
  - café au lait (e.g., in FA)
  - nail abnormalities, early graying (e.g., in TBD)
  - skeletal abnormalities (e.g. hip dysplasia, very short stature) (e.g., in SDS, FA)
- **Personal history of cancers (particularly, at young age)**
- **Sensitivity to chemotherapy/radiotherapy**
- **Classical somatic abnormalities, including**
  - isochromosome 7q (e.g., in SDS)
  - gain 1q (e.g., in FA, TBD)
- **Family history**
  - consanguinity (autosomal recessive conditions)
  - blood disorders
  - associated conditions and congenital malformations
  - cancers
  - death at an early age