Rare IBMFs

Mony Fahd

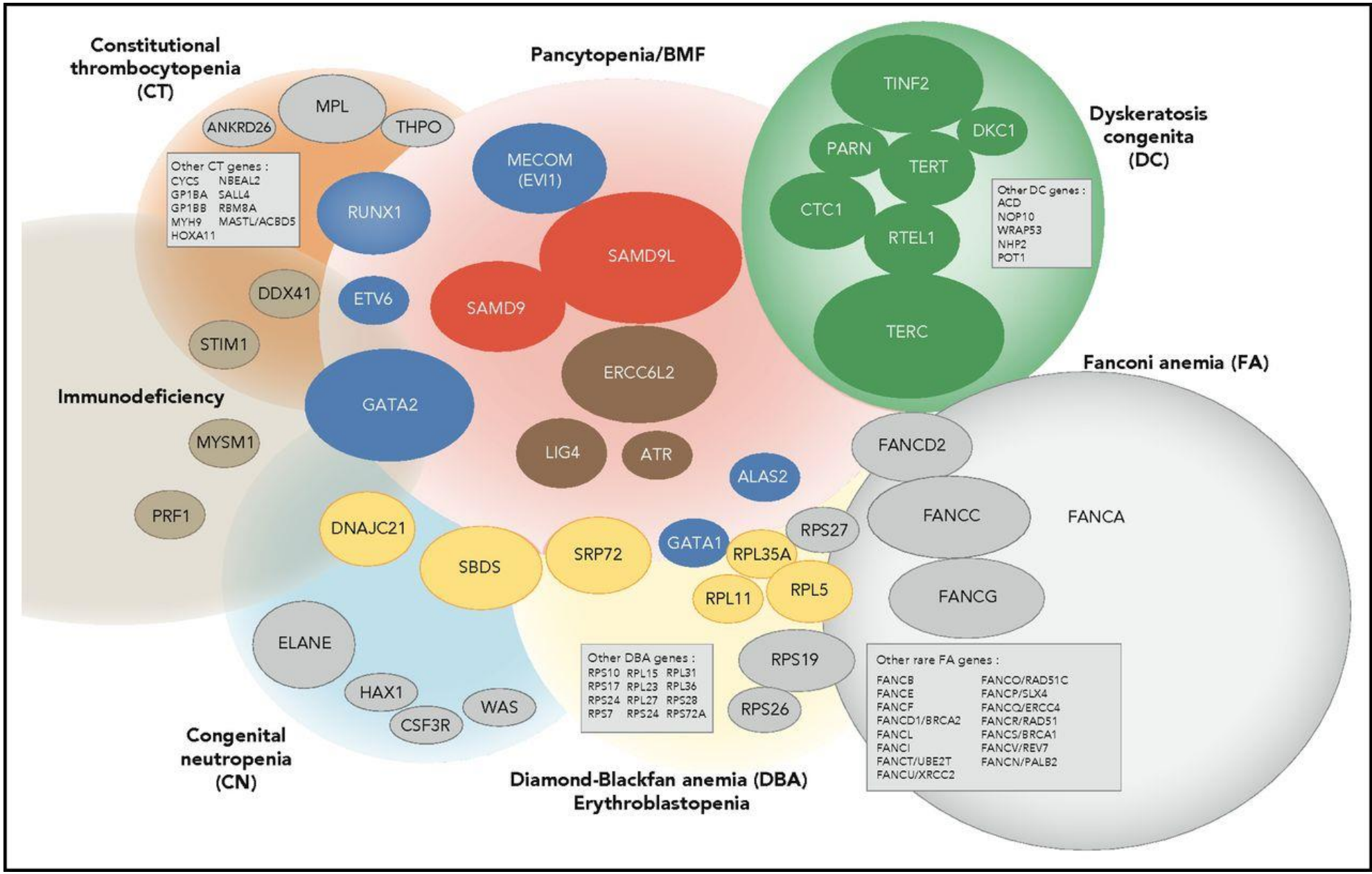
CRMR Aplasie

04/10/2024

IBMFs

Group of rare diseases dominated by Fanconi's disease, BDA, SBDS, telomeroptahy

Progress in genetics: more and more entities reported



A landscape of germ line mutations in a cohort of inherited bone marrow failure patients

Olivier Bluteau, Blood, 2018

IBMFs: presentation in paediatrics

- Presentation
  - Haematological disease may initially present as isolated cytopenia
  - Increased risk of MDS/LA(M)

- With or without associated abnormalities
  - IUGR/PSR ± microcephaly
  - Malformations (thumbs & hands, kidneys, etc.) & organ damage: pancreas, cerebellum, lungs, liver, skin & appendages…

- Therapeutic treatment: HSCT

A landscape of germline mutations in a cohort of inherited BMF patients

Systematic studies in patients with constitutional aplastic anemia likely to be constitutional
NB: FA was systematically excluded as were patients with identified classic IBMF like telomeropathies or other

N = 179 pts
Median age at evaluation: 11 years
DNA extracted from fibroblastes +++
Whole exome sequencing

Age at skin biopsy, no. (%), y	
≤2	37 (20.7)
>2 and <18	76 (42.5)
≥18	66 (36.9)

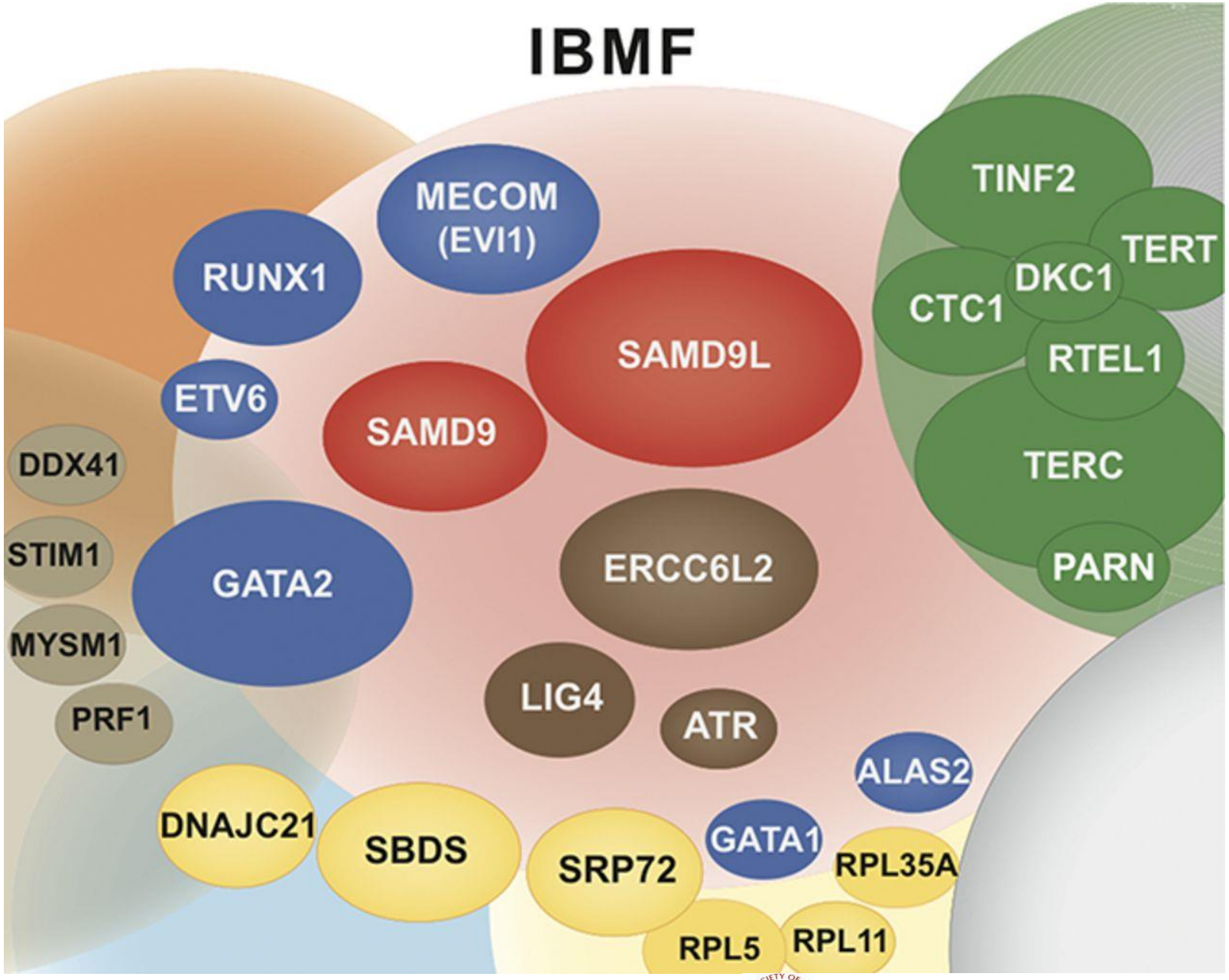
Group 1: germinal variant identified : 86 pts (48%)
Group 2: mutations VUS
Group 3: no variant

☞ **10 pts with *SAMD9L***

☞ **6 pts with *SAMD9* mutations**

Bluteau & al, Blood 2018

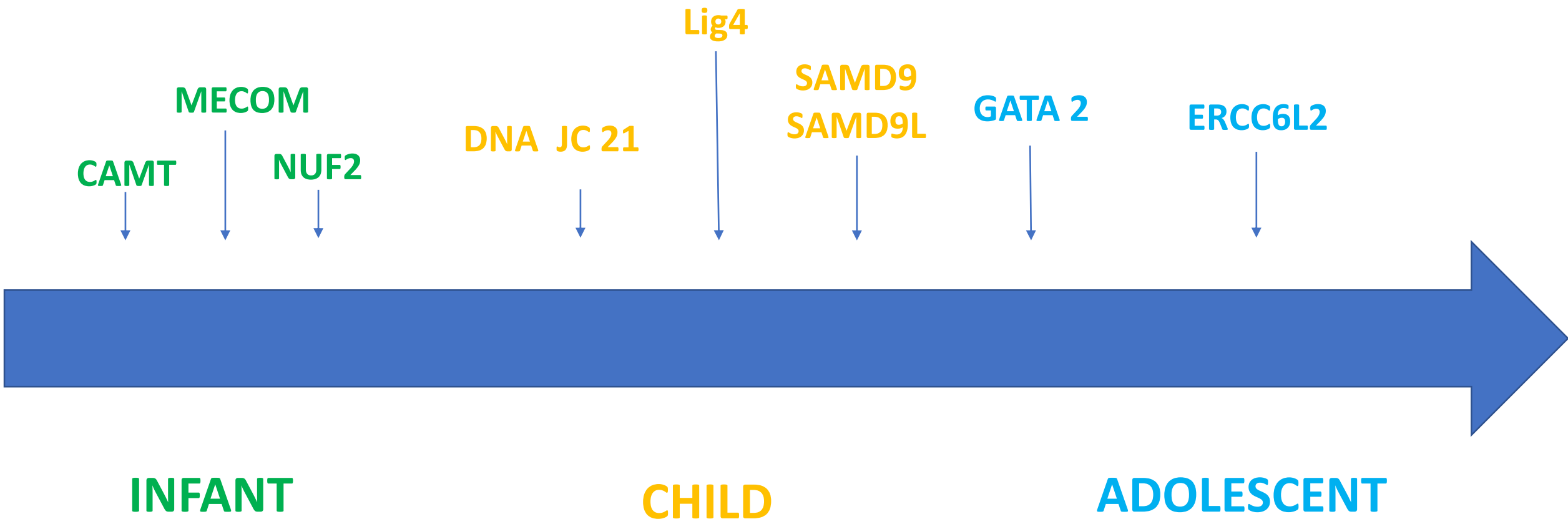
Rare IBMFs



Olivier Bluteau, Blood, 2018

A landscape of germ line mutations in a cohort of inherited bone marrow failure patients

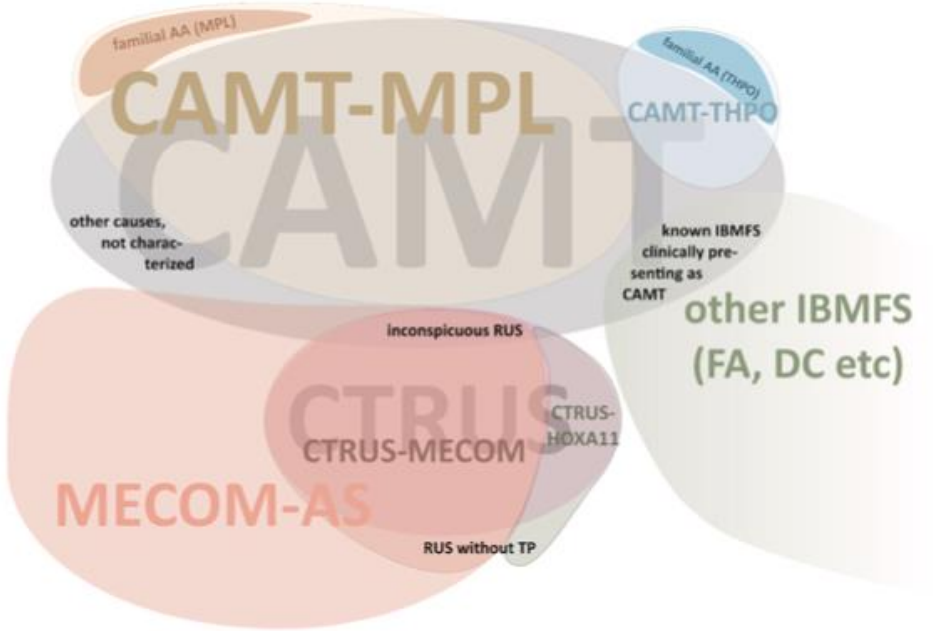
Rare IBMFs


CAMT
MECOM
NUF2
DNA JC 21
Lig4
SAMD9
SAMD9L
GATA 2
ERCC6L2
INFANT
CHILD
ADOLESCENT

Rare IBMFs

CAMT: Congenital Amegakaryocytic thrombocytopenia

- Often severe thrombocytopenia (<50,000 at birth)
- Normal platelet size
- BM: reduction or absence of megakaryocytes in the bone marrow
- Elevated TPO assay (X10/X50) (no clinical correlation with disease severity)
- No phenotypic abnormalities
- Mutation of the thrombopoietin receptor gene, c-Mpl (identified in 2/3 of cases, genetic heterogeneity)



Designations, delineations, and overlap between disease groups related to CAMT.

M. Germeshausen and M. Ballmaier Best Practice & Research Clinical Haematology 34 (2021)

CAMT: Congenital Amegakaryocytic thrombocytopenia

- Progression to bone marrow failure in the first 10 years of life
- Low risk of transformation compared with other IBMFS
  - One patient with ALL *(Steinberg, J Pediatr Hematol Oncol, 2007)*
  - 3 patients with cytogenetic abnormalities (trisomy 8 or monosomy 7)
- Without treatment, 50% died at 6 years *(Alter, Hematology of Infancy and Childhood, 1993)*

CAMT: Congenital Amegakaryocytic thrombocytopenia

Outcomes of patients undergoing allogeneic haematopoietic stem cell transplantation for congenital amegakaryocytic thrombocytopenia; a study on behalf of the PDWP of the EBMT

Clémence Aldebert[1✉], Mony Fahd[1], Jacques-Emmanuel Galimard[2], Ibrahim A. Ghemlas[3], Marco Zecca[4], Juliana Silva[5], Alexander Mohseny[6], Alphan Kupesiz[7], Rose-Marie Hamladji[8], Nuno Miranda[9], Tayfun Güngör[10], Robert F. Wynn[11], Pietro Merli[12], Mikael Sundin[13], Maura Faraci[14], Cristina Diaz-de-Heredia[15], Birgit Burkhardt[16], Victoria Bordon[17], Marie Angoso[18], Peter Bader[19], Marianne Ifversen[20], Concepcion Herrera Arroyo[21], Natalia Maximova[22], Susana Riesco[23], Jerry Stein[24], Arnaud Dalissier[25], Franco Locatelli[26], Krzysztof Kalwak[27], Jean-Hugues Dalle[1] and Selim Corbacioglu[28]

Congenital amegakaryocytic thrombocytopenia is a rare, inherited bone marrow failure syndrome. Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is currently the only curative treatment. In this retrospective study, we analysed 66 patients with allo-HSCT, reported in the European Society for Blood and Marrow Transplantation (EBMT) registry. Bone marrow (BM) was the most widely used stem cell source ($n = 40$; 61%) followed by peripheral blood (PB) ($n = 18$; 27%), and unrelated umbilical cord blood (UCB) ($n = 8$; 12%). Most frequently was a HLA-matched graft from related ($n = 26$; 39%) and unrelated ($n = 15$; 23%) donors after a myeloablative busulfan-based conditioning regimen. GvHD prophylaxis was mostly cyclosporine and methotrexate (53%). The 6-year cumulative incidence of graft-failure and second transplant were 25% and 17%, respectively. The 6-year disease-free survival (DFS) and overall survival (OS) were 66.9% and 85.6%, respectively. The 6-year transplant-related mortality (TRM) was 8.0%. In conclusion, most patients with CAMT benefit from allo-HSCT, but with many graft failures.

Bone Marrow Transplantation; https://doi.org/10.1038/s41409-024-02416-x

Retrospective multicentre study by the EBMT's Pediatric Disease Working Party (PDWP)

66 patients
25 centers

Received a first allogeneic HSC transplant for CAMT

Age<18 years

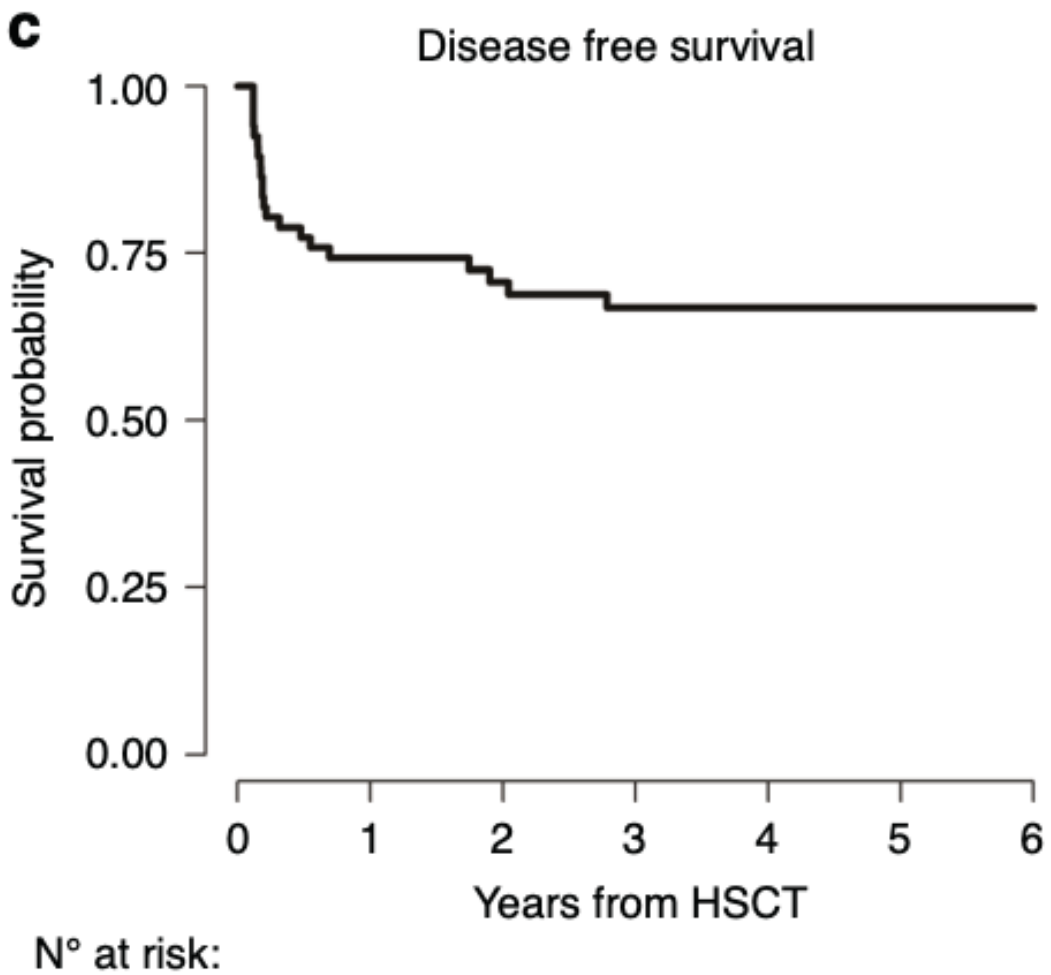
Between 1998 and 2020

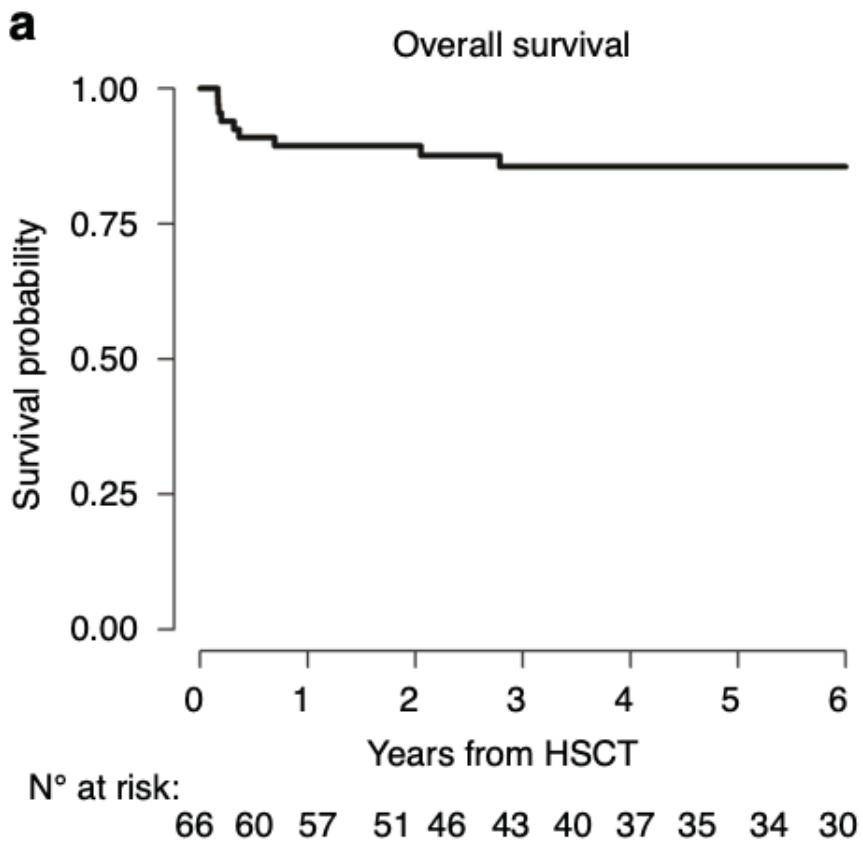
BMT 2024

CAMT: Congenital Amegakaryocytic thrombocytopenia

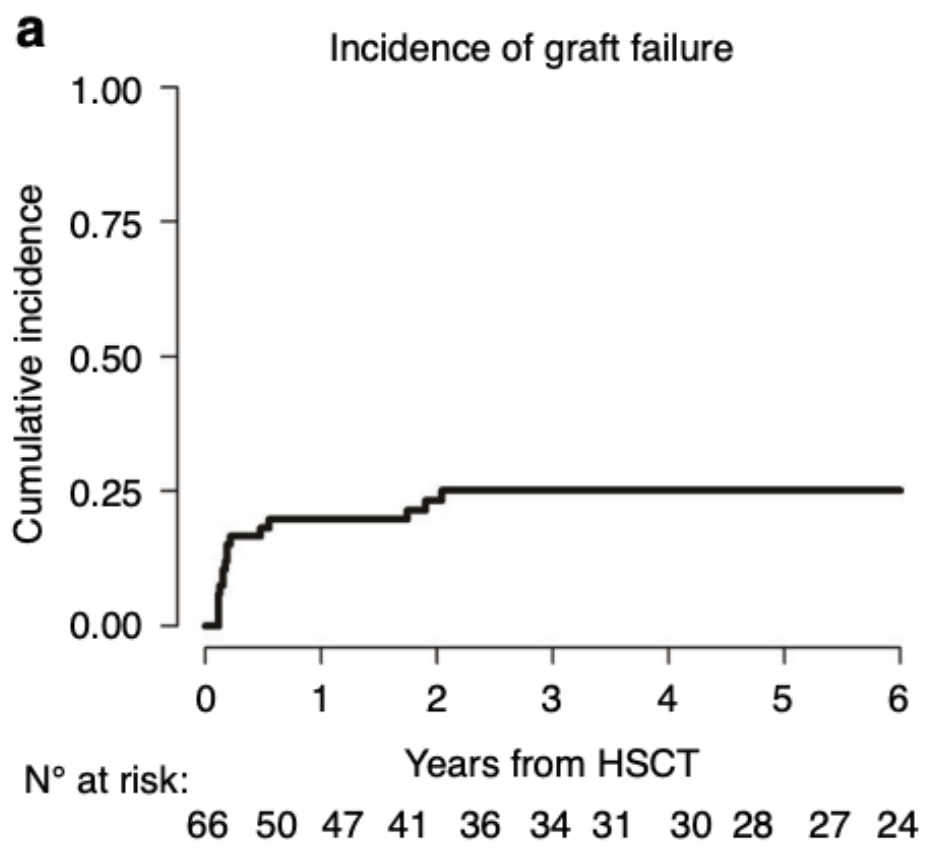
- Median age at diagnosis: 1.3 years
- Mutation identified in 18 patients
  absent in 7 patients
  No data for 40 patients
- Median platelet count at diagnosis 16,000
- Median age at transplant: 3.2 years
- BM 59% PB (27%) CB(12%)
- MSD 34.8% MUD 22.7%,
- MAC 86%
- RIC 16%

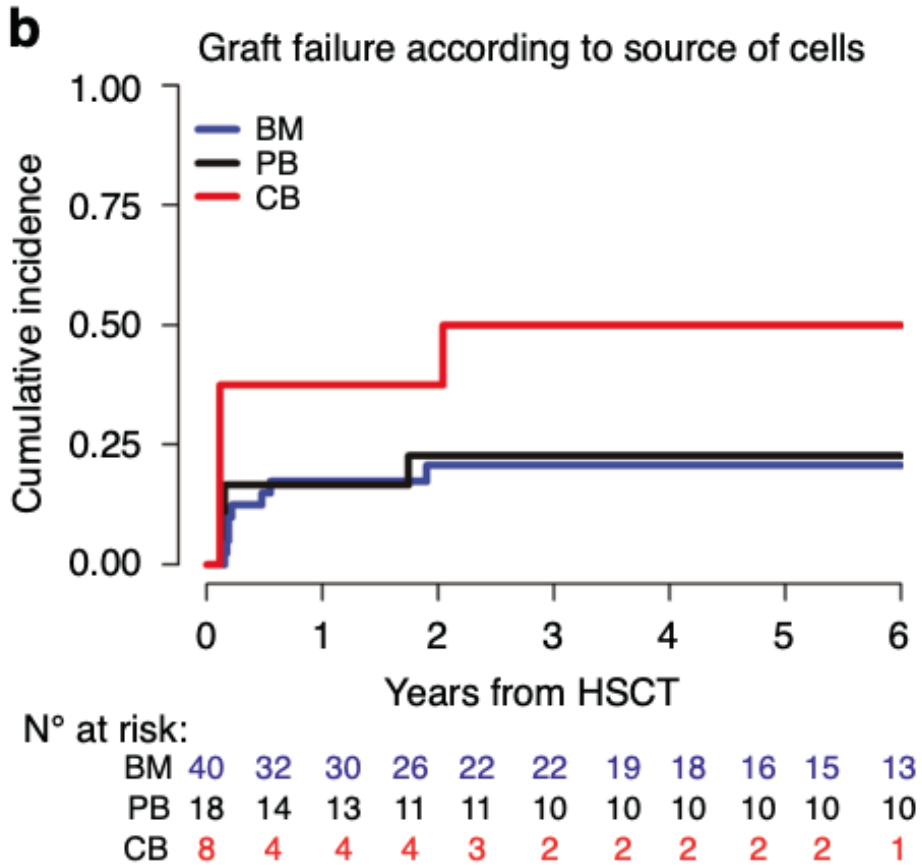
CAMT: Congenital Amegakaryocytic thrombocytopenia





CAMT: Congenital Amegakaryocytic thrombocytopenia





Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article

Pediatric

Outcomes in Hematopoietic Stem Cell Transplantation for Congenital Amegakaryocytic Thrombocytopenia

Maria Cancio[1,*], Kyle Hebert[2], Soyoung Kim[3], Mahmoud Aljurf[4], Timothy Olson[5], Eric Anderson[6], Lauri Burroughs[7], Anant Vatsayan[8], Kasiani Myers[9], Hasan Hashem[10], Rabi Hanna[11], Biljana Horn[12], Tim Prestidge[13], Jaap-Jan Boelens[1], Farid Boulad[1], Mary Eapen[2]

CIBMTR

86 patients

A B S T R A C T

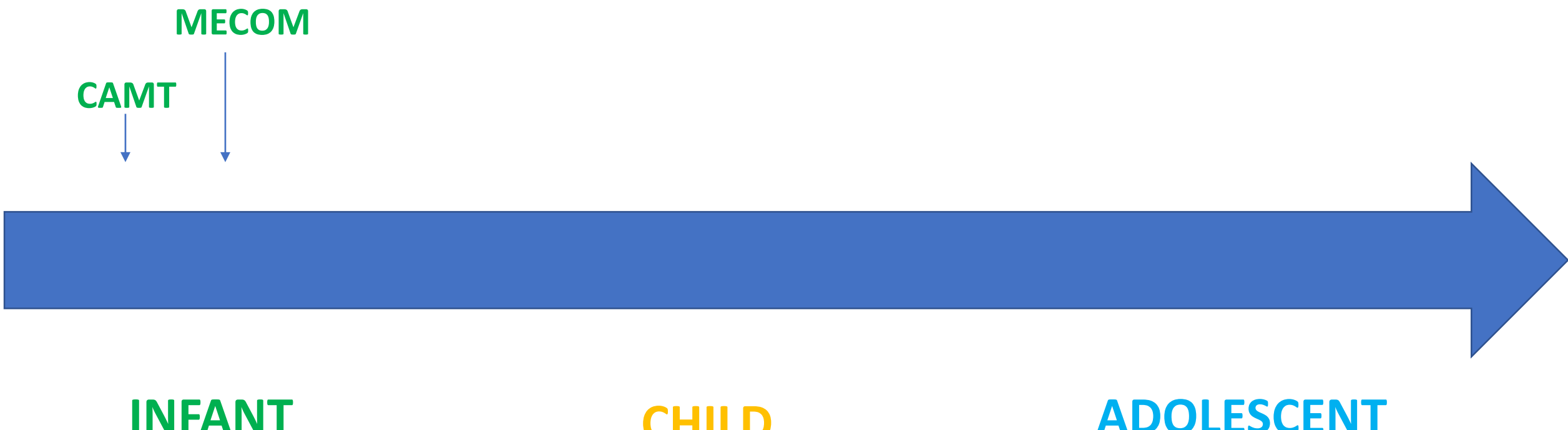
Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare, inherited bone marrow failure syndrome. Hematopoietic stem cell transplantation (HSCT) is considered a curative treatment option, but existing descriptions of patient and transplant characteristics and outcomes after related and unrelated donor HSCT are sparse. We describe outcomes after HSCT for congenital amegakaryocytic thrombocytopenia (CAMT; n = 86) from 2000 to 2018. We conducted an analysis of data collected by the Center for International Blood and Marrow Transplant Research on patients with CAMT receiving therapeutic allogeneic HSCT. The predominant donor type was HLA-matched or mismatched unrelated donors (n = 58, 67%). The remaining included HLA-matched sibling (n = 23, 27%) and HLA-mismatched relative (n = 5, 6%). The predominant graft types were bone marrow (n = 53, 62%) and cord blood (n = 25, 29%). The median age at transplantation was 3 years, with 82 of 86 patients being transplanted aged ≤10 years. The 5-year graft failure-free and overall survival were 83% (95% confidence interval [CI], 74-90) and 86% (95% CI, 78-93), respectively. An examination for risk factors confirmed mortality was higher after HLA-mismatched relative and mismatched unrelated donor HSCT compared to HLA-matched sibling and matched unrelated donor HSCT (hazard ratio 3.52, $P = .04$; 75% versus 93%). The 1-year incidence of graft failure was 19% after HLA-mismatched HSCT (n = 32) compared to 7% after HLA-matched HSCT (n = 54, $P = .15$). Day-100 grade II-IV acute graft-versus-host disease was 13%, 26%, and 30% after HLA-matched sibling, HLA-matched and mismatched unrelated donor HSCT. The 5-year incidence of chronic graft-versus-host disease was 33% with 24 of 28 patients having received grafts from HLA-matched (n = 13) and mismatched unrelated (n = 11) donors. Although HLA-matched donors are preferred, HLA-mismatched donors also extend survival for CAMT.

CAMT: TAKE HOME MESSAGE

- Diagnostic difficulties
- BM>CB
- High risk of Graft failure
- HSCT MAC

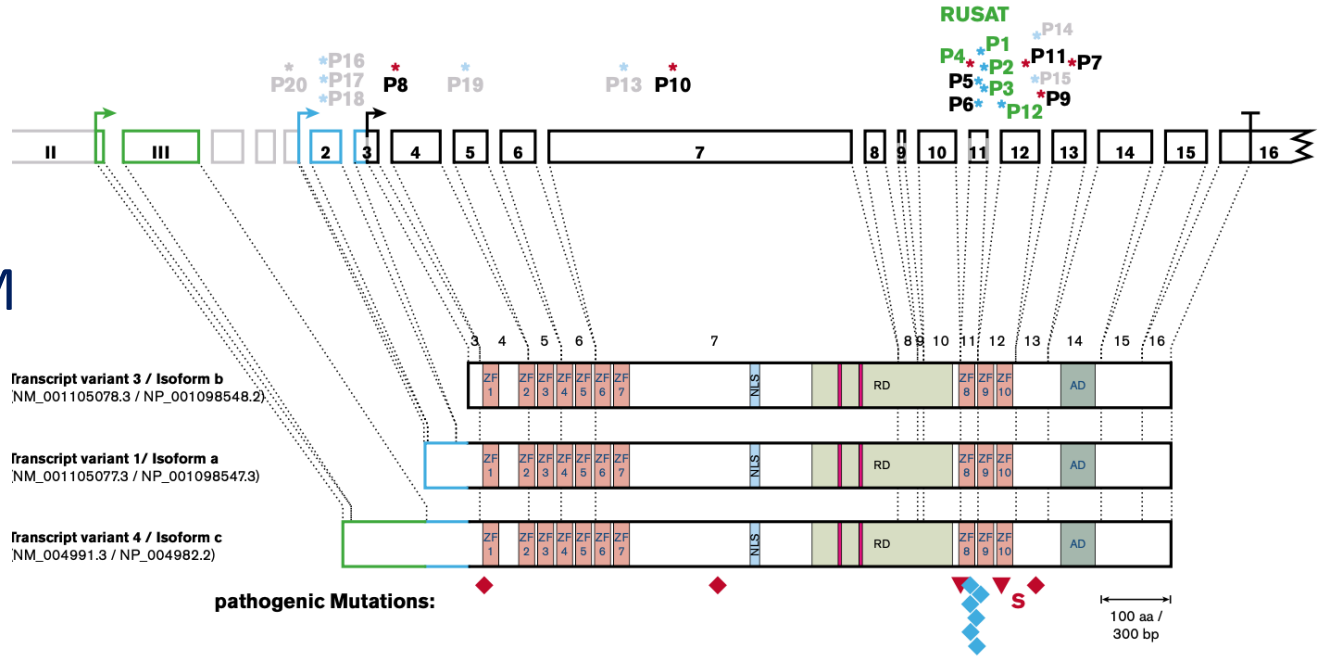
- Haploidentical transplants?

Rare IBMFs

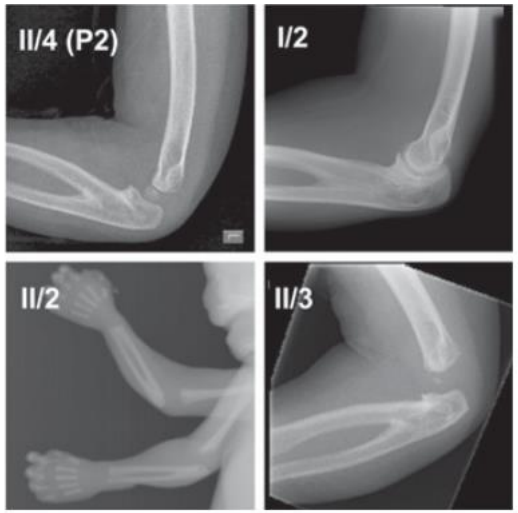


MECOM

- Heterozygous mutations in MECOM
- Affected different functional domains of the EVI1 protein
- Familial and sporadic cases



- Clinical presentation
  - Radioulnar synostosis
  - Bone marrow failure



RUSART

- +/-clinodactyly, cardiac and renal malformations, B-cell deficiency, and presenile hearing loss.

MECOM Phenotype and Treatment

MECOM-associated syndrome: a heterogeneous inherited bone marrow failure syndrome with amegakaryocytic thrombocytopenia

Manuela Germeshausen,[1] Phil Ancliff,[2] Jaime Estrada,[3] Markus Metzler,[4] Eva Ponstingl,[5] Horst Rütschle,[5] Dirk Schwabe,[6] Richard H. Scott,[7] Sule Unal,[8] Angela Wawer,[9] Bernward Zeller,[10] and Matthias Ballmaier[1]

[1]Central Research Facility Cell Sorting, Hannover Medical School, Hannover, Germany; [2]Haematology and Oncology Department, Great Ormond Street Hospital for Children, London, United Kingdom; [3]Pediatric Specialists of Texas, Methodist Healthcare System, San Antonio, TX; [4]Pediatric Oncology and Hematology, University Hospital Erlangen, Erlangen, Germany; [5]Pediatric Practice Horst Rütschle, Mutterstadt, Germany; [6]Pediatric Oncology, Hematology and Hemostaseology, University Hospital Frankfurt, Frankfurt, Germany; [7]Clinical Genetics Department, Great Ormond Street Hospital for Children, London, United Kingdom; [8]Center for Fanconi Anemia and Inherited Bone Marrow Failure Syndromes, Hacettepe University, Ankara, Turkey; [9]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Technische Universität München, Munich, Germany; and [10]Department of Pediatric and Adolescent Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway

Blood Advances, 2018 (Germeshausen and al)

1st series of 12 pts

- 10/12 pts allografted with MUD
- Familial and sporadic patients
- With germline mutation in the *MECOM*,
- Clinical spectrum ranged from isolated RUS with or without mild hematological abnormalities to severe IBMFS without evident skeletal abnormalities

N = 6 pts

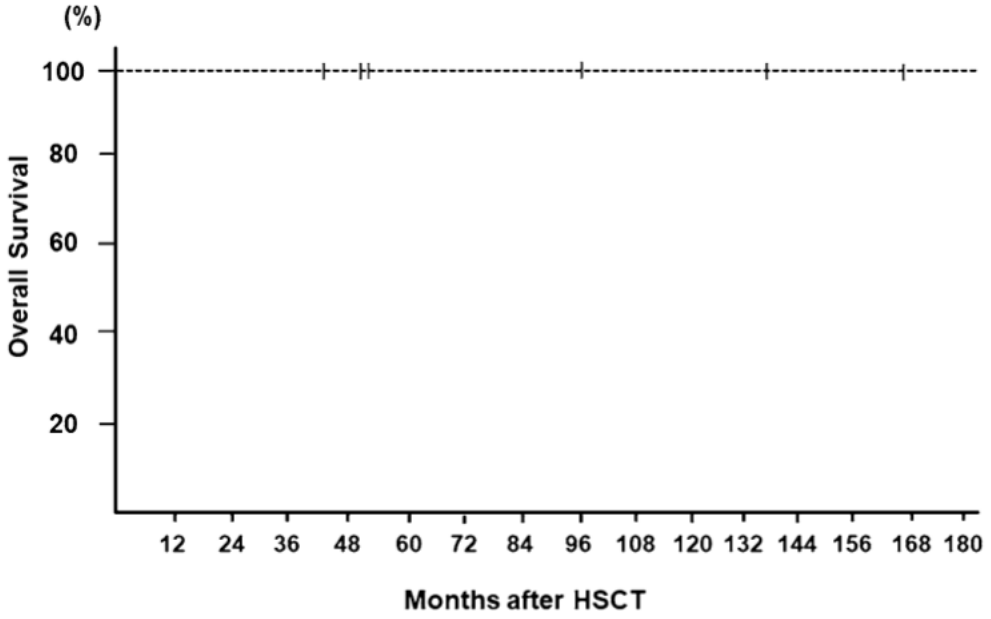
	UB004	UB036	UB093	UB100	UB104	UB153
Nucleic acid change	c.C2248T	c.G2334T	c.G1930T	c.1302_1306del	c.2900_2903del	c.2208-1G>A
Amino acid change	p.R750W	p.R778S	p.E644X	p.K434fs	p.D967fs	—
Sex	M	F	M	F	F	F
Age	18 mo	6 mo	3 mo	Neonatal	9 mo	9 mo
Family history	Simplex	Simplex	Simplex	Simplex	Simplex	Simplex
Hb, g/dL	5.7	6.0	6.0	9.2	5.5	8.0
Platelets, × 10⁹/L	1	10	10	62	36	10
ANC, × 10⁹/L	0.35	0.06	0	0	0.4	0
BM	Hypocellular	Hypocellular	Hypocellular	Hypocellular	Hypocellular	Hypocellular
BM karyotype	46,XY	46,XX	46,XY	46,XX	Trisomy 8	46,XX
Skeletal abnormality	Radioulnar synostosis	Thumb abnormalities	Clubfoot	No	No	Thumb abnormalities
Cardiac abnormality	Tetralogy of Fallot	Myocardial atrophy	Pulmonary stenosis	No	No	No
Other	—	—	Facial dysmorphia	—	—	Renal hypoplasia
Age at HSCT	3 y	6 mo	15 mo	9 mo	18 mo	3 y
Outcome	Died 3 mo after HSCT from a cardiac complication during severe infection	Died at 14 y from a cardiac complication during influenza infection	No major complication 9 y after HSCT (10-y old)	No major complication 1 y after HSCT (2-y old)	No major complication 8 mo after HSCT (2-y old)	No major complication 3 y after a second HSCT (6-y old)

Bluteau & al, Blood 2018

MECOM HSCT with RIC?

Reduced-intensity conditioning is effective for allogeneic hematopoietic stem cell transplantation in infants with *MECOM*-associated syndrome

Masahiro Irie[1] · Tetsuya Niihori[2] · Tomohiro Nakano[1] · Tasuku Suzuki[1] · Saori Katayama[1] · Kunihiko Mori
Hidetaka Niizuma[1] · Nobu Suzuki[3] · Yuka Saito-Nanjo[3] · Masaei Onuma[3] · Takeshi Rikiishi[3] · Atsushi Sato
Mayumi Hangai[4] · Mitsuteru Hiwatari[4,5] · Junji Ikeda[6] · Reo Tanoshima[6] · Norio Shiba[6] · Yuki Yuza[7] ·
Nobuyuki Yamamoto[8] · Yoshiko Hashii[9,10] · Motohiro Kato[4,11] · Junko Takita[12] · Miho Maeda[13] · Yoko Aok
Masue Imaizumi[3] · Yoji Sasahara[1]



6 pts MECOM+

Age at HSCT 5-18 months

RIC regimen comprised:

- -FLU
- -alkylating
- -low-dose rATG

3 pts aGVHD>II

No cGVH

No low-dose irradiation (if the patient is not at high risk of rejection) to prevent the risks of short stature and secondary malignancy.

International Journal of Hematology (2023)

MECOM : take home messages

- Variable hematological phenotype: from isolated thrombocytopenia to severe hematological failure
- Variable extra-hematological phenotype: radio-ulnar synostosis to multiple squeltic malformations or other organs.
- Severe forms
- CDT and donor?

Rare IBMFs

Severe microcephaly
Congenital bone marrow failure
Growth retardation
Renal hypoplasia

MECOM
CAMT
NUF2

Alterations in the mitose

De novo *NUF2* variant in a novel inherited bone marrow failure syndrome including microcephaly and renal hypoplasia

Yoann Vial[1,2] | Elodie Lainey[3,4] | Thierry Leblanc[5] | Véronique Baudouin[6] | Marie Emilie Dourthe[5] | Pierre Gressens[2] | Alain Verloes[1,2] | Hélène Cavé[1,4] | Séverine Drunat[1,2]

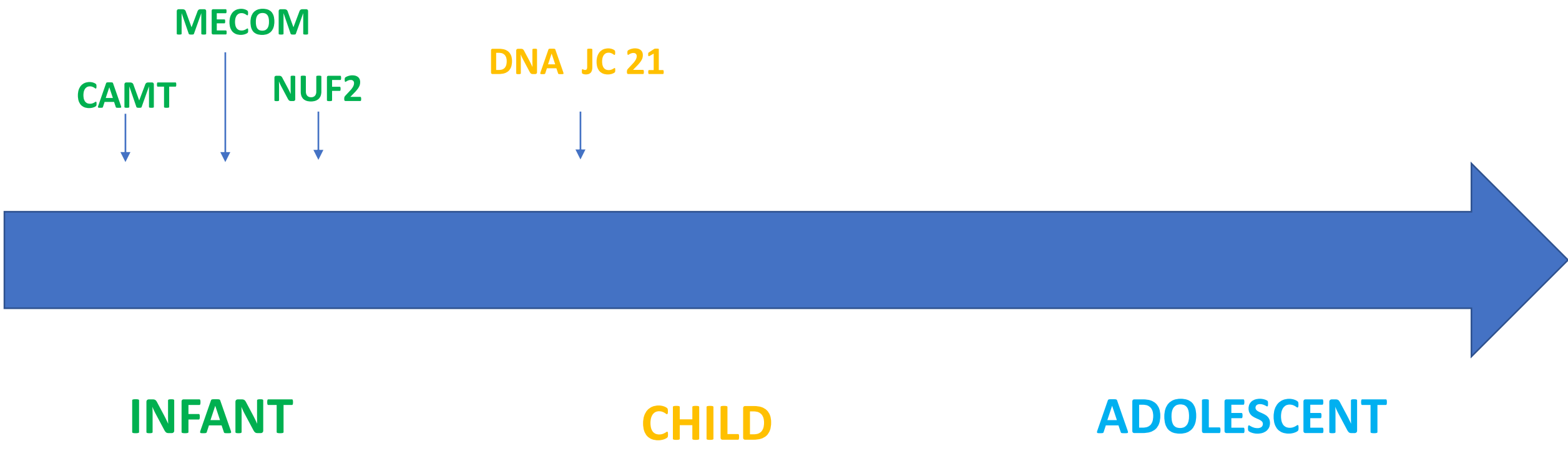
BJH,2022

INFANT

CHILD

ADOLESCENT

Rare IBMFs



DNA JC 21

Shwachman-Diamond syndrome-like disorder with telomeropathy aspects

- Average age of onset for BMF is two years (0 to 15 years, n=19)
- Phenotype:

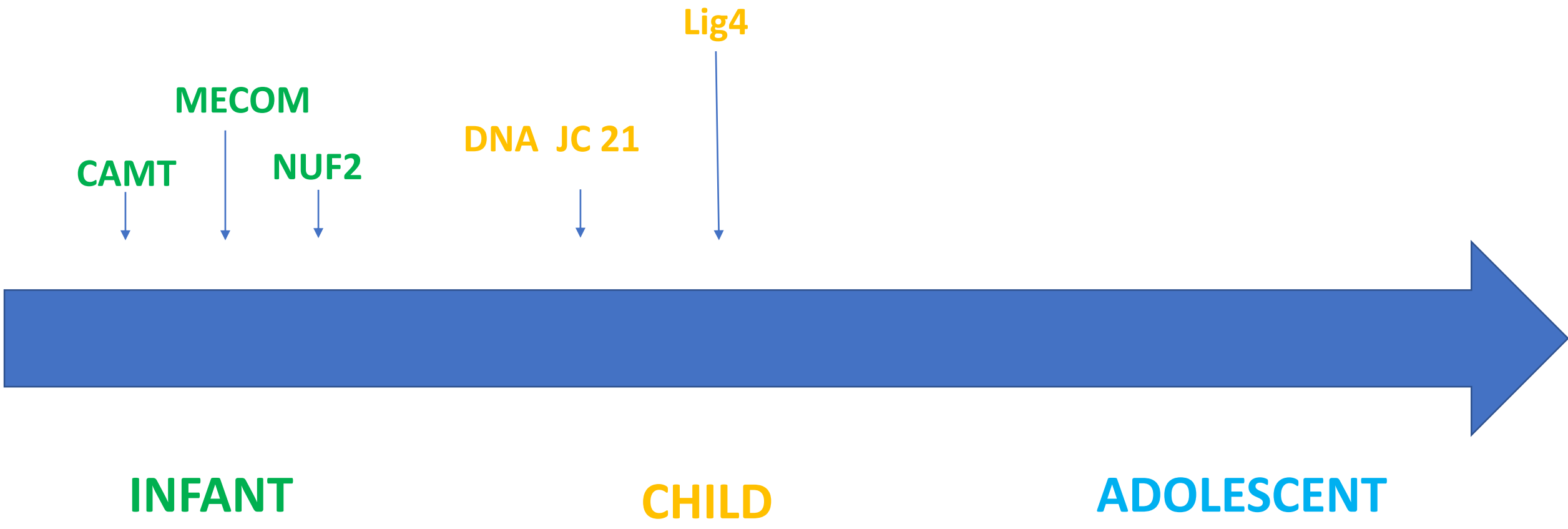
-Skin hypopigmentation
-Dental and retinal abnormalities
-Growth delay and/or short stature
-Developmental delay and/or neurological abnormalitie
-Exocrine pancreatic dysfunction

- AML developed in two patients

- CDT and donor?

Frontiers in Oncology, 2023

Rare IBMFs



DNA ligase 4

- Role in the repair of DNA double- strand breaks
- Autosomal recessive disorder

- 86 cases have been reported with heterogenous phenotypes (Staines et al)
  - Microcephaly
  - Delayed growth and development,
  - Skin abnormalities including photosensitivity and psoriaform lesions
  - Pancytopenia.
  - Immune deficiency.
  - Malignant disease

DNA ligase 4: Description

Failing to Make Ends Meet: The Broad Clinical Spectrum of DNA Ligase IV Deficiency. Case Series and Review of the Literature

Aidé Tamara Staines Boone [1], Ivan K Chinn [2 3], Carmen Alaez-Versón [4], Marco A Yamazaki-Nakashimada [5], Karol Carrillo-Sánchez [4], María de la Luz Hortensia García-Cruz [6], M Cecilia Poli [2 7], M Edith González Serrano [8], Edgar A Medina Torres [8], David Muzquiz Zermeño [1], Lisa R Forbes [2 9], Francisco J Espinosa-Rosales [8 10], Sara E Espinosa-Padilla [8], Jordan S Orange [2 9], Saul Oswaldo Lugo Reyes [8]

Front Pediatr. 2018

10/41 malignant disease or solids cancers

DNA ligase 4: HSCT

Allogeneic hematopoietic stem cell transplantation corrects ligase IV deficiency

Jing He [1], Xin Tian [1], Tong Luo, Runying Zou, Zexi Yin, Keke Chen, Chengguang Zhu, Xiangling He [*]

Department of Hematology and Oncology, Children's Medical Center, Hunan Provincial People's Hospital/The First Affiliated Hospital of Hunan Normal University, Changsha, China

Transplant Immunology (2023)

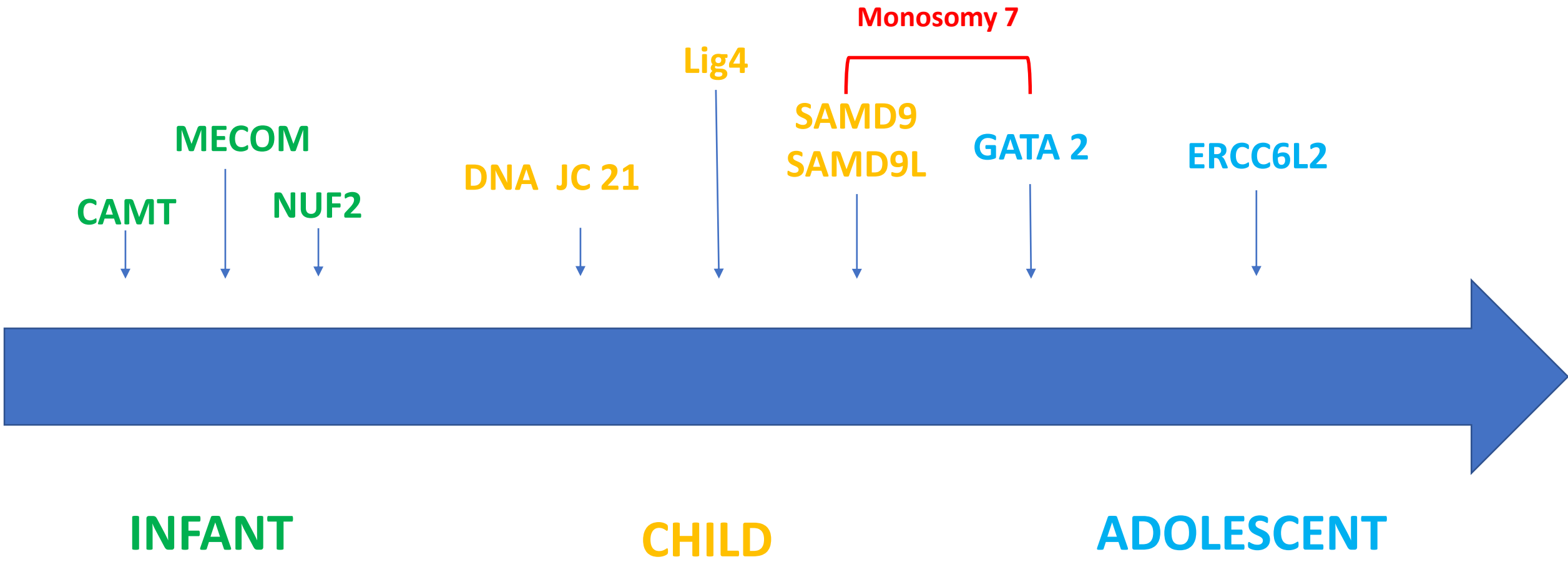
15 reported cases of LIG4 syndrome that underwent HSCT

- seven cases survived
- causes of death
  - 3 patients : fungal infections
  - 1 patient: Epstein-Barr virus-related lymphoproliferative syndrome
  - 1 patient: viral infection
  - 1 patient: MAT

DNA ligase 4: Take home messages

- Heterogenous phenoytpe
- Radiosensitivity
- Hematologic complications: malignant disease
- Infectious complications
- Treatment: RIC HSCT

Rare IBMFs


Monosomy 7
Lig4
SAMD9
SAMD9L
GATA 2
MECOM
DNA JC 21
ERCC6L2
CAMT
NUF2
INFANT
CHILD
ADOLESCENT

ERCC6L2

- ERCC6L2 encodes a DNA repair protein

- Phenotype:
  - Mild and fluctuating cytopenias with bone marrow hypoplasia.
  - Patients develop clonal hematopoiesis with somatic mutations in *TP53*,
  - +/- developmental delay and microcephaly

- Median age 18 years (range 6-65 years old)

N = 7

	UB657	UB008	UB075	UB196	UB083	UB134	UB168
Nucleic acid change	c.2187delG c.3708-2A>T	c.2187delG c.3708-2A>T	c.C1504T c.C3796T	c.C1504T c.C3796T	c.C1963T c.C1963T	c.G847A c.G847A	c.C1963T c.C1963T
Amino acid change	p.E729fs —	p.E729fs —	p.Q502X p.R1266X	p.Q502X p.R1266X	p.R655X p.R655X	p.D283N p.D283N	p.R655X p.R655X
Other causal mutation	—	—	—	—	—	*TERC*	—
Sex	M	F	F	F	M	F	M
Age, y	7	13	22	18	2	22	13
Family history	Brother of UB008	Sister of UB657	Sister of UB196	Sister of UB075	N/A	Simplex	Consanguinity, brother with intellectual disability
Hb, g/dL	11.4	<12	11.9	12.9	10.9	10.7	9.0
Platelets, × 10^9/L	64	<150	107	101	48	38	4
ANC, × 10^9/L	<1.5	<1.5	0.4	1.6	1.0	0.1	0.7
BM	Hypocellular	Hypocellular	Dysplasia	N/A	Hypocellular	Hypocellular dysplasia	Hypocellular
BM karyotype	46,XX	46,XX	Monosomy 7	N/A	46,XY	46,XX	46,XY
Microcephaly	No	No	No	No	No	No	Yes
Neurological defect	No	No	No	No	No	No	Learning difficulties, intellectual disability, vascular abnormalities in the right frontal lobe (MRI)
Other	—	—	—	—	Facial dysmorphia	—	Bilateral pyeloureteral junction abnormalities
Age at HSCT, y	14	13	22	—	—	—	—
Outcome	No significant complication after HSCT (15-y old)	No significant complication after HSCT (27-y old)	Died at 24 y, of EBV lymphoma post-HSCT	Thrombo-cytopenia and neutropenia (26-y old)	Mild thrombo-cytopenia (15-y old)	Died at 43 y, after AML with −7, hypomethylating agent failure	Stable, macrocytosis without anemia, no neurological signs (21-y old)

Only 1 pt/7 with microcephalia

HSCT: only 3/7 (AYA pts)

1/7 AML (age 43)

Bluteau & al, Blood 2018

ERCC6L2: take-home messages

- BMF with microcephaly + developmental delay ± ataxia
- Neurological phenotype may be absent
- Leukemia predisposing syndrome
- Treatment HSCT before clonal evolution

Conclusion Rare IBMFs

- Difficulty diagnostic
- Difficulty therapeutic

- Only curatif treatment: HCST

- Modality? Cdt? Donor selection?
  - Indications and modality of treatment should be discussed at an expert meeting. (RCP national)

- Gene therapy?

MERCI