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The new inherited Bone Marrow Failure syndromes

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ERN-EuroBloodNet

Paris, France

March 1st, 2022

Université de Paris
URP 3518

Executive

Hôpital Robert Debré

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Co-funded by the Health Programme of the European Union

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Filière de santé Maladies Rares Immuno-Hématologiques

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Conflicts of interest

I have no actual or potential conflict of interest in relation to this presentation

Learning objectives of the webinar

1. Learn about *SAMD9* and *SAMD9L* syndromes and on the management of a child with monosomy 7 in this context
2. Learn about *MECOM* syndrome
3. Learn about *ERCC6L2* syndrome

ARTICLE

Ataxia-Pancytopenia Syndrome Is Caused by Missense Mutations in *SAMD9L*

Dong-Hui Chen,[1] Jennifer E. Below,[2,10] Akiko Shimamura,[3,4,5,6,11] Sioban B. Keel,[4] Mark Matsushita,[7] John Wolff,[7] Youngmee Sul,[7] Emily Bonkowski,[1] Maria Castella,[6] Toshiyasu Taniguchi,[6] Deborah Nickerson,[2] Thalia Papayannopoulou,[4] Thomas D. Bird,[1,7,8,*] and Wendy H. Raskind[7,8,9,*]

Ataxia-Pancytopenia syndrome

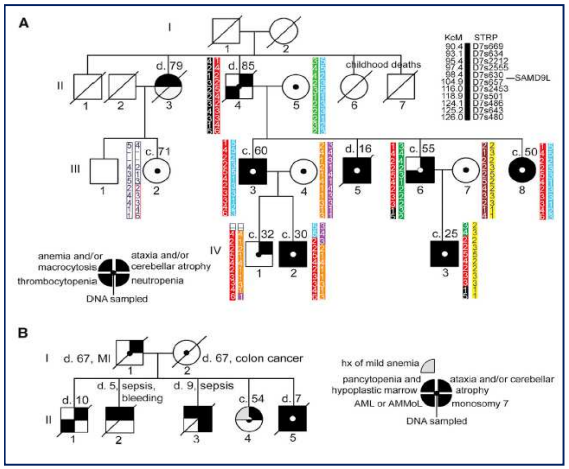
Ataxia (hypoplastic cerebelum)

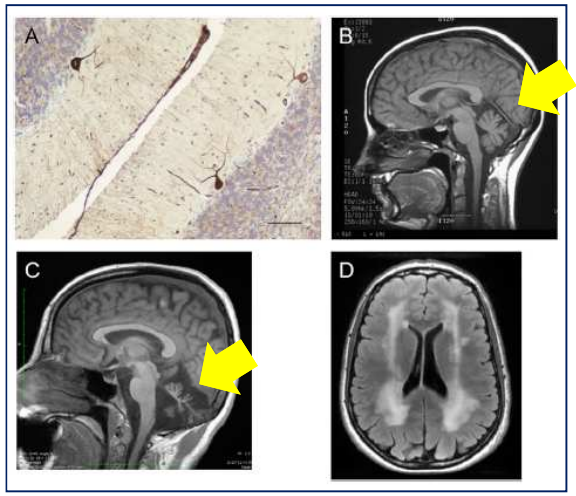
Cytopenias + predisposition to MDS/AML ± monosomy 7

1 large family: linkage analysis:

☞ mutation *SAMD9L*: c.2640C>A / p.His880Gln

Somatic mosaicism reported on peripheral blood samples





Chen & al, Am J Hum Genet, 2016

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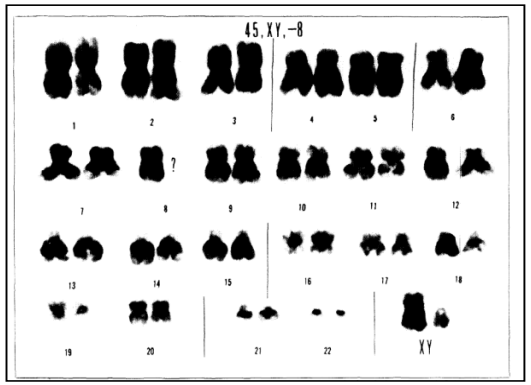
A Family with Acute Leukemia, Hypoplastic Anemia and Cerebellar Ataxia

Association with Bone Marrow C-Monosomy

At that time:

- **FA?**
- **DC?**
- **Bloom?**

Monosomy C



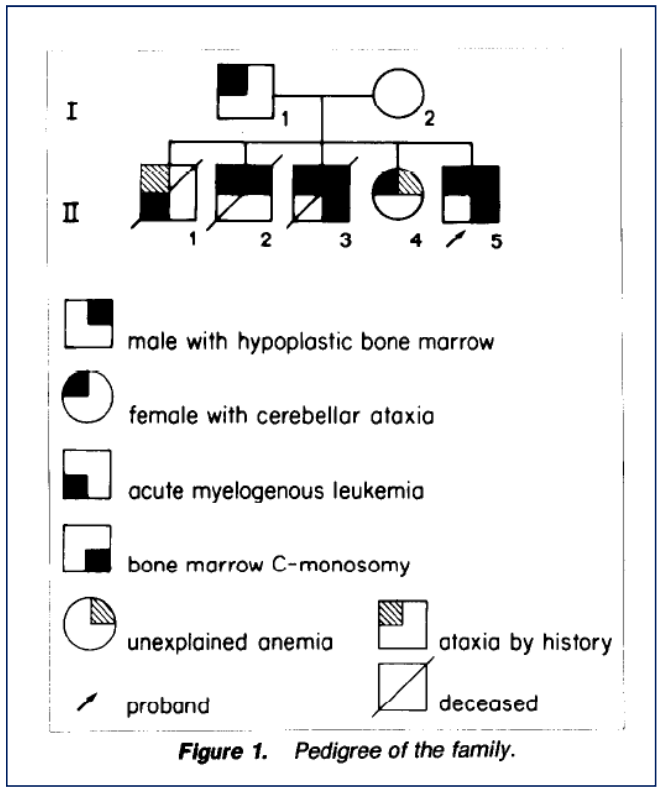


Figure 1. *Pedigree of the family.*

Frederick P. Li & al, Am J Med, 1978

Recent analysis of this very family:

***SAMD9L*: mutation c.3587G>C/ p.Cys1196Ser**

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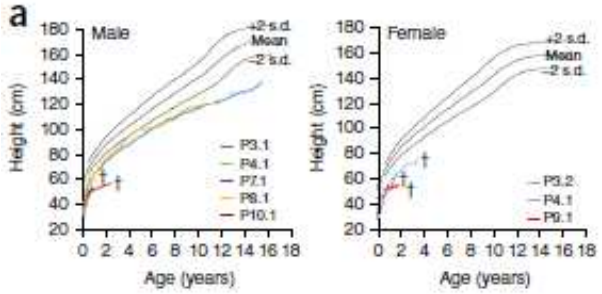
nature genetics

N = 11 patients

SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7

MIRAGE syndrome:



Myélodysplasia

Infections

Restriction of growth

Adrenal hypoplasia

Genital phenotype

Entheropathy

Syndromic adrenal hypoplasia

Monoallelic mutations

Very severe disease:

- **Died from disease: 8/11**
- **Died ≤ 2 years: 7/8**

Narumi & al, Nat Genet 2016

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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 : <u>86 pts (48%)</u>
mutations Group 2: VUS

Group 3: no variant

☞ **10** pts with ***SAMD9L*** ***(9 families)***

☞ **6** pts with ***SAMD9*** mutations

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Bluteau & al, Blood 2018

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SAMD9L patients

ID (UB)	Mutation	Sex/age	Family history	Hb, g/dL Plt, × 10⁹/L ANC, × 10⁹/L	BM	BM cytogenetic	Short TLM	GR	Immune deficiency	Neurological defect	Genitourinary abnormality	Other	Age at BMT	Outcome
195	*SAMD9L**	M/8 mo	Consanguinity	6.5 5 0.06	Hypocellular dysplasia	45,XY, −7[7/15]	No	No	No	No	No	—	24 mo	Alive, 2 months after HSCT, GVHD
609	*SAMD9L*	F/13 mo	Yes (see Figure 3E)	<6 <2 <1	N/A	ND	ND	No	No	Nystagmus	No	—	—	Mild thrombocytopenia (33-y old)
612	*SAMD9L*	M/13 mo	Yes (see Figure 3E)	6 10 0.25	Hypocellular	45,XY, −7[16/28]	No	No	Transient Ig deficiency (IgG < 3 g)	Nystagmus	No	—	—	BM FISH −7[8%] (2-y old) Mild cytopenias (5-y old)
194	*SAMD9L*	F/13 mo	Simplex	6 17 0.27	Hypocellular	45,XX, −7	No	No	No	No	No	—	25 mo	Spontaneous blood cell count improvement; relapse after vaccination; clonal progression with del6q; then HSCT
081	*SAMD9L*	M/13 mo	Uncle with Hodgkin disease	9.5 3 0.25	Hypocellular dysplasia	Normal, no −7 by FISH	ND	No	No	Hydrocephaly, arachnoid cyst on MRI	No	—	—	Complete regression of cytopenias (9-y old)
022	*SAMD9L* *TERC*	M/27 y	Father with transient thrombo-cytopenia. Grandfather died of AML	13 79 1.68	Hypocellular dysplasia	Del13q, then −7	Yes	No	Recurrent infection in infancy	No	No	Hepatitis, pulmonary fibrosis	33 y	RAEB1 with del13q and −7 (33-y old); CR after 1 cycle of azacytidine; HSCT; pulmonary fibrosis (37-y old)
049	*SAMD9L*	F/10 mo	Brother with cytopenias	11 <100 0.72	Hypocellular dysplasia	45,XX, −7[17/20]	No	No	No	No	No	—	24 mo	Alive 5 years after HSCT
085	*SAMD9L*	F/20 mo	Mother and uncle with mild intellectual disability	8.2 20 1.7	Dysplasia	Normal	No	Yes	Ig deficiency (IgG, 3 g)	Mild intellectual disability, hydrocephaly, bilateral white substance changes and arachnoid cyst on MRI	No	Asthma, coxa valga	27 mo	Neurological defects with unsteady gait (6-y old), cerebellar hypoplasia and abnormal white matter signal and arachnoid cyst on MRI. Growth defect and parenteral nutrition
260	*SAMD9L* *RTEL1*	M/46 y	—	10.9 19 <1	Dysplasia	46,XY, der(7)[6/ 46,XY,ish add(7)[14]	Yes	No	—	No	No	Tongue cancer, cirrhosis	—	Lost sight

ID (UB)	Mutation	Sex/age	Family history	Hb, g/dL Plt, × 10⁹/L ANC, × 10⁹/L	BM	BM cytogenetic	Short TLM	GR	Immune deficiency	Neurological defect	Genitourinary abnormality	Other	Age at BMT	Outcome
112	*SAMD9L*	F/19 mo	Simplex	8.1 5 0.12	N/A	Normal no −7 on FISH	No	Yes	N/A	No	No	—	19 mo	Died in intensive care unit during severe infection (21-mo old)
096	*SAMD9*	F/3 y	Simplex	11.9 240 0	Hypocellular dysplasia	45,XX, −7[12/20]	No	Yes	Severe infections	Abnormal white matter signal on MRI	No	Hyper-thyroidism	4 y	No GVHD, persistent hyperthyroidism (9-y old)
136	*SAMD9*	M/9 y	Simplex	12 15 0.5	Dysplasia	−7	ND	Yes	No	No	No	—	9 y	No major complication after HSCT (15-y old)
037	*SAMD9*	F/8 y	Simplex	10.2 14 0.94	Dysplasia	Normal	ND	Yes	Ig deficiency (IgM, IgG2, IgG4), recurrent infections	No	No	—	—	Thrombocytopenia with dysplasia in BM, normal karyotype, immunodeficiency (15-y old)
660	*SAMD9*	M/24 mo	Simplex	11.4 19 0.7	Dysplasia	45,XY, −7[14/20]	ND	Yes	No	Language delay	Hypospadias, testicular dysgenesis	Diarrhea	—	Complete regression of cytopenias and of −7, persists at 6-y old
062	*SAMD9* *RTEL1*	F/M/21 y	Simplex	12.1 88 0.5	Hypocellular dysplasia	45,XY, −7	No	No	Recurrent severe infections	No	Hypospadias, cryptorchidism, sexual ambiguity, renal hypoplasia	Diarrhea	21 y	HSCT, died (22-y old)
026	*SAMD9*	F/6 y	Simplex	11.5 102 1.0	Hypocellular	45,XX, −7	No	Yes	IgG deficiency, recurrent infections	No	No	—	13 y	No major complication after HSCT (20-y old)

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SAMD9 & SAMD9L genes

2 single exon genes with 60% homology (common ancestral gene)

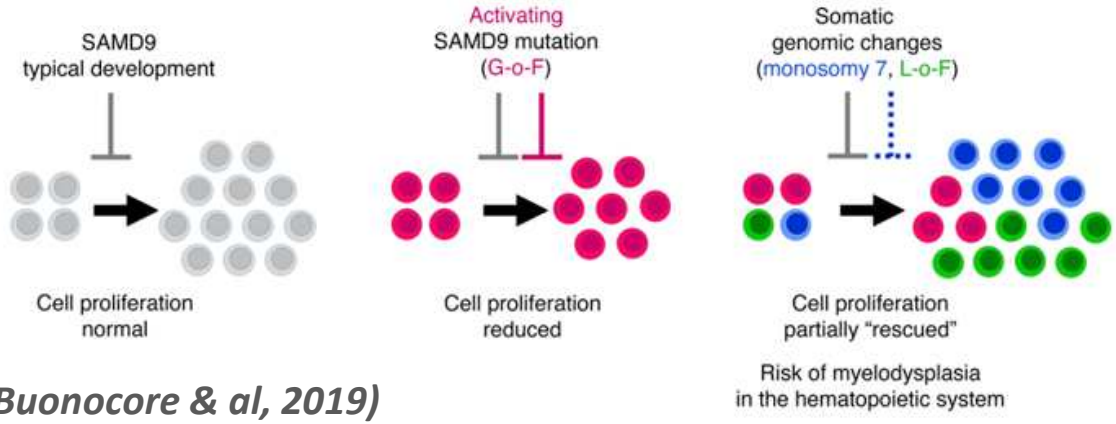
Encode cytoplasmic proteins

and response to

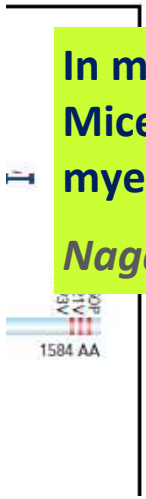
whereas DNA damage response genes such as *ERCC6L2*, *LIG4*, and *ATR* were mutated in 11 patients (12.8%), and immune

well known to be associated with IBMF and/or MDS/AML. These included *DC*, *DBA*, and *SDS*

blood® 15 FEBRUARY 2018 | VOLUME 131, NUMBER 7 725



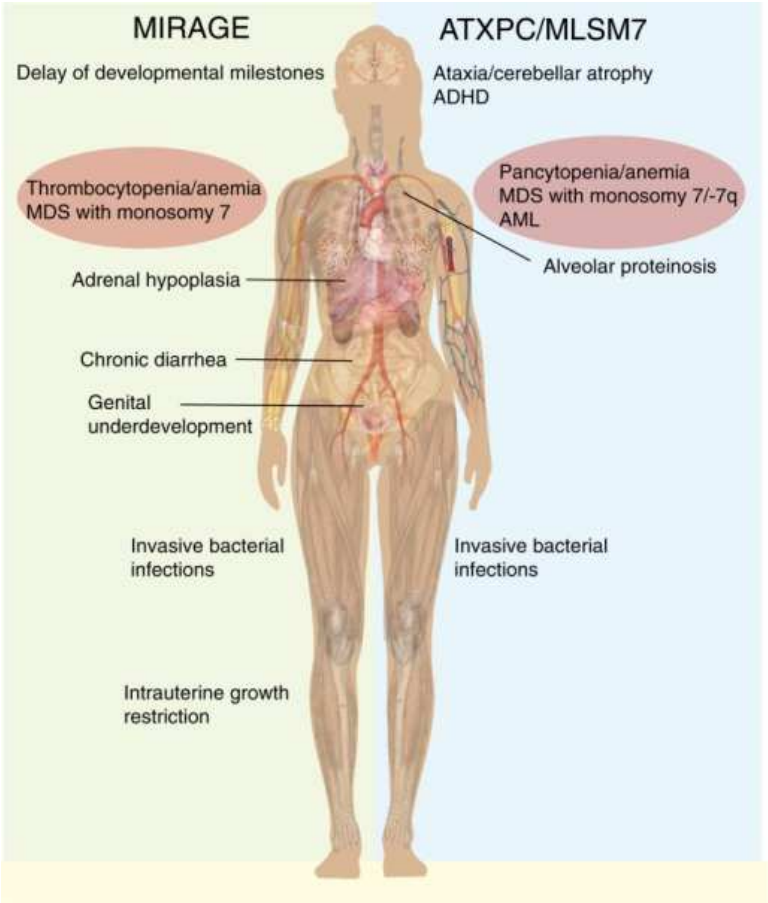
(Buonocore & al, 2019)



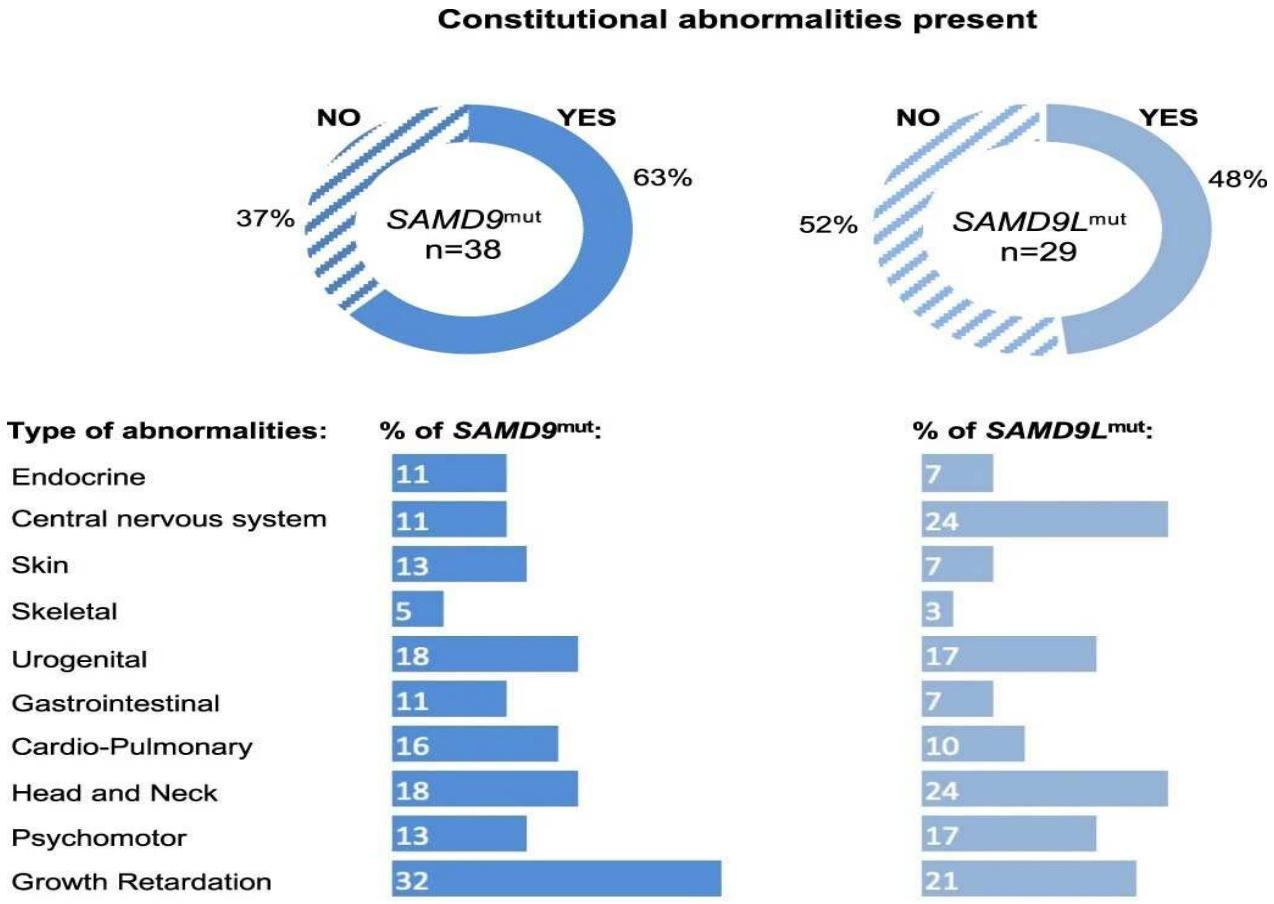
In mice: only *SAMD9L* is present
Mice *SAMD9L* $^{-/-}$ *and* $^{+/-}$ develop myeloid malignancies

Nagamachu & al, Cancer Cell 2013

SAMD9 and SAMD9L mutated patients extra hematological phenotype



Davidson & al, Leukemia 2018



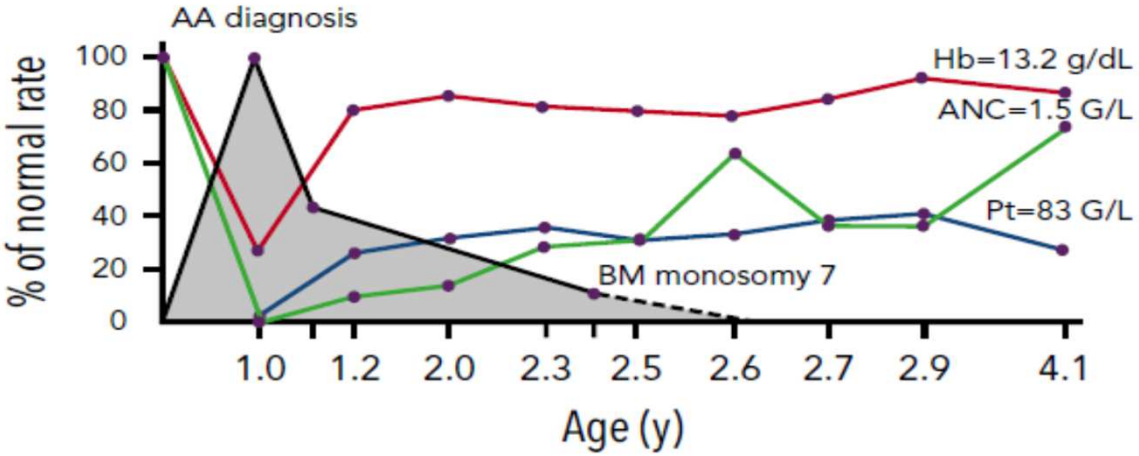
Sahoo & al, Nat Med 2021

SAMD9/SAMD9L syndrome

Spontaneous hematological improvement associated with somatic mosaicism

In the French cohort: 11/13 pts (85%) w/o up front HSCT experimented hematological improvement including 5 patients with monosomy 7 disappearance (md FU: 4 yrs)

Actually 5 planned HSCT were canceled



Wait and watch attitude?

Bluteau & al, Blood 2018

Many other studies did report on high incidence of monosomy 7 and of somatic genetic rescue in *SAMD9* & *9L* patients

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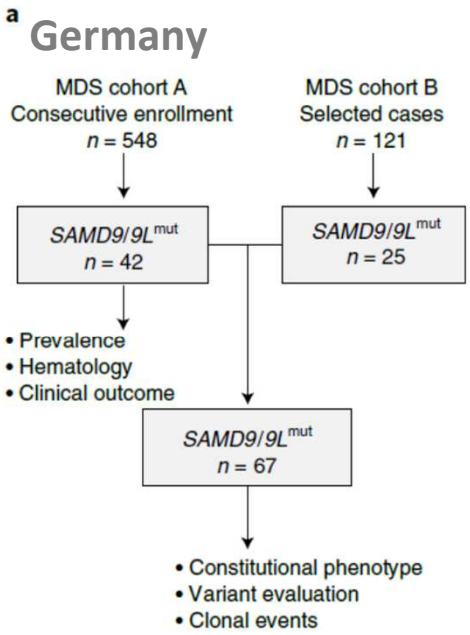
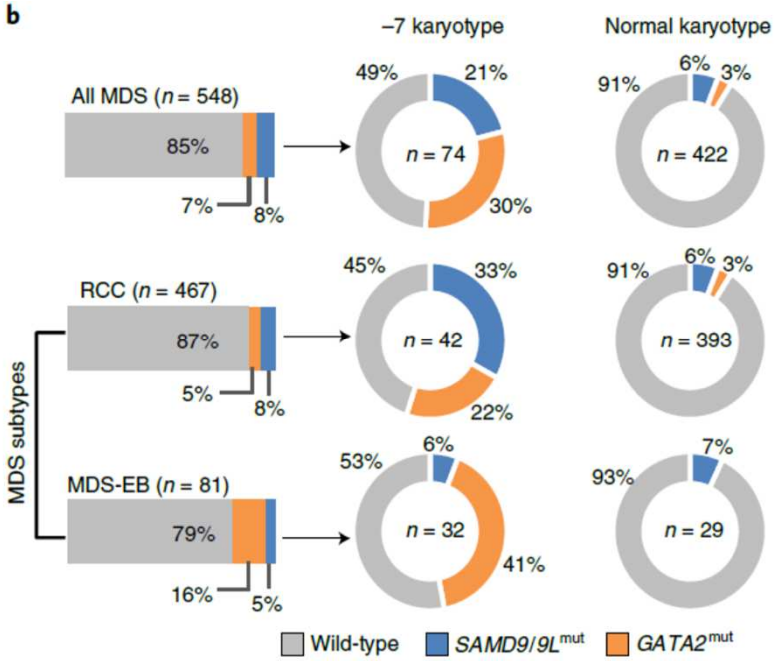
Number of cases in the litterature at publication: N = 64

SAMD9 & *SAMD9L* and childhood MDS





2 cohorts: 669 patients

***SAMD9/9L*: 8%: N = 67**

- Mostly private mutations
- Hot spot: AA 635 to 998 (P-loop/NTPase domains (middle region)

NB: high frequency (72%) of class 3 variants (VUS)

Functional studies: expression of mutant proteins in HEK293 cell line: 45/48 with growth suppressive effect

SAMD9/SAMD9L cases:

- **90% classified as RCC**
- **57% with constitutional abnormalities**
- **38% with monosomy 7 or del(7q)**

Sahoo & al, Nat Med 2021

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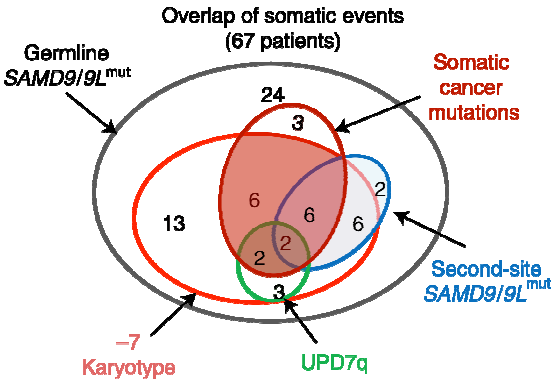
How to treat a patient with BMF & *SAMD9 & 9L* variant?

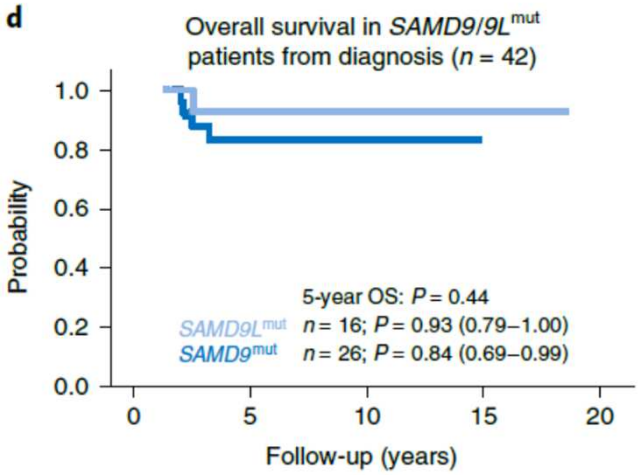
Main problem: HSCT indication. Especially if a monosomy 7 is present

In this study:

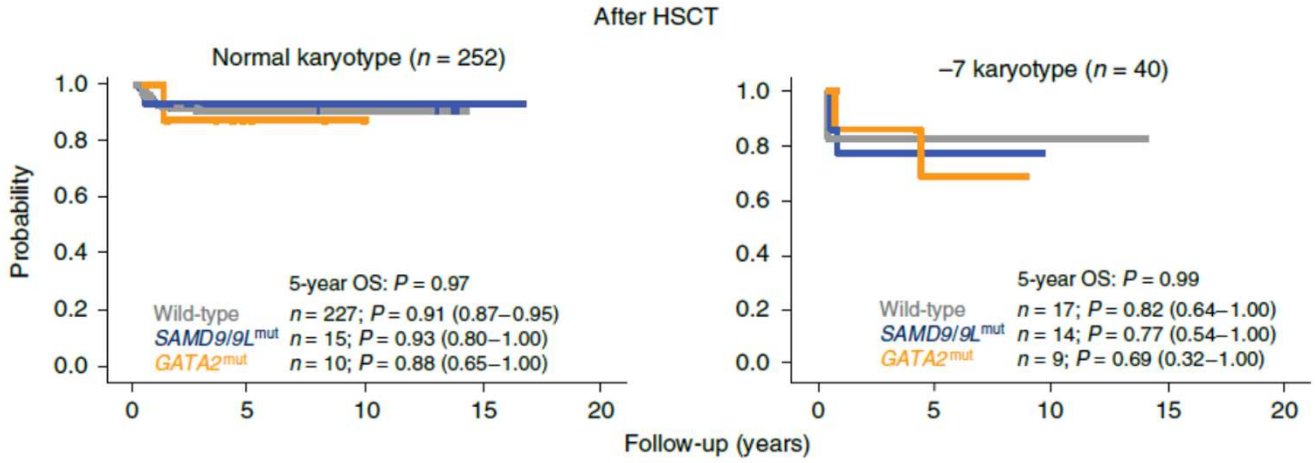
61% of pts with SG:

- **21/41: somatic^{mut} (mostly truncating) and UPD7q**
- **39/41: monosomy 7**





29 pts underwent HSCT (43%) with good results:



Suppl. Table 14:
To note: report on 15 pts w/o HSCT
All alive (age range: 1.5-23.1 years)

Sahoo & al, Nat Med 2021

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HSCT indication in children with SAMD9 & 9L variants (1)

Evident : **blasts excess, complex karyotype, additional somatic variants in myeloid genes with "significant" VAF:**

- present in 30% (19/64): *SEPTB11, ASXL1, RUNX1, EZH2, PTPN11, CBL, ETV6*
- associated with monosomy 7: 84% (16/19)

Sahoo & al, Nat Med 2021

Other cases : **is monosomy 7 an indication per se?**

: **do we have identified factors associated with clinical outcome & SGR?**

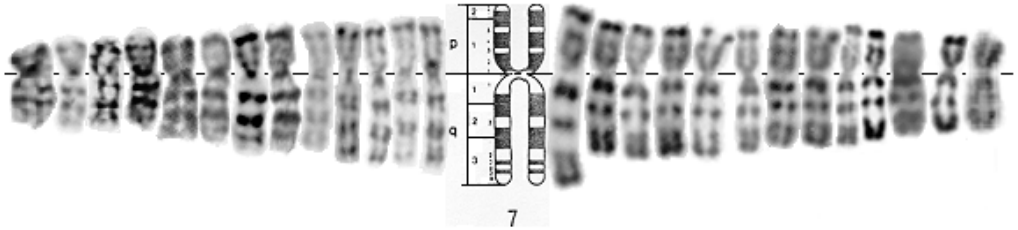
<u>Some facts from EWOG/Saint-Jude study</u>:

- **Younger age at diagnosis is associated with the «remission group» & «stable disease group» versus the HR/progression group**
- **UPD7q frequency correlates with young age at diagnosis**
- **Somatic mutations *in cis* correlate with germinal variant localized in the middle/C-ter region of both genes**

Sahoo & al, Nat Med 2021

What about familial history?

Monosomy 7 and myeloïd malignancies

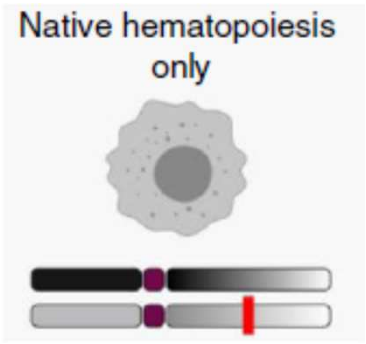


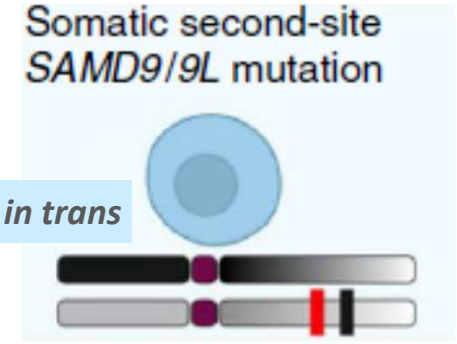
Germinal variants of *GATA2* and *SAMD9/SAMD9L* account for ± 40 to 50% of cases of monosomy 7 in children with myeloid malignancies

For *GATA2* patients: monosomy 7 usually indicates urgent transplant

What in *SAMD9/9L* patients?
Is monosomy 7 may be classified as « just one another clone » ?

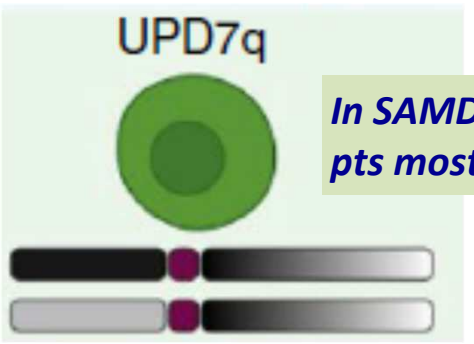
Somatic genetic rescue: a large spectrum of genetic events potentially associated in one patient





NB: or in trans

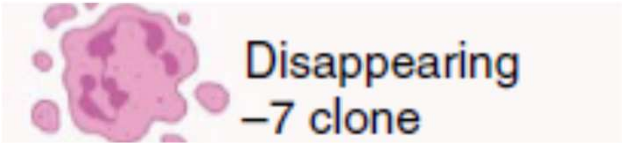
➔ **incomplete hematology recovery?**



In SAMD9L pts mostly

➔ **complete hematology recovery?**

➔ **progression towards leukemia**



➔ **hematological recovery (thanks to other clones)**

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Adapted from Sahoo & al, Nat Med 2021

HSCT indication in children with SAMD9 & 9L variants (1)

Current French recommendations:

"Children w/o obvious indication, especially for children lacking a good donor, should be followed like the milk on the stove…"

Regular:

- **Clinical evaluation**
- **Blood counts**
- **Bone marrow aspirations for:**
  - **cytology (expert required!)**
  - **karyotype: additional anomalies? Number of mitosis with monosomy 7?**
  - **FISH analysis: precise % of nuclei with monosomy 7**
  - **molecular analysis (doable on blood samples?) with 2 aspects:**
    - **additional somatic events (NGS for myeloid genes)? What is the VAF?**
    - **detection of SGR**

NB: patience required!

Other phenotypes associated with *SAMD9* & *SAMD9L* variants

***SAMD9*: normophosphatemic familial tumoral calcinosis** — *Topaz & al, Am J Hum Gent 2006*

Phenotype: *calcium depositions in skin and mucosae + severe and recurrent skin infections*

Deleterious variants & biallelic: transmission autosomic and recessive

***SAMD9L*-associated autoinflammatory disease** — *De Jesus & al, JCI 2020*

High IFN-response –gene score

Acquired frameshift mutations

***SAMD9 & SAMD9L*: MDS in adults patients** — *Nagata & al, Blood 2018*

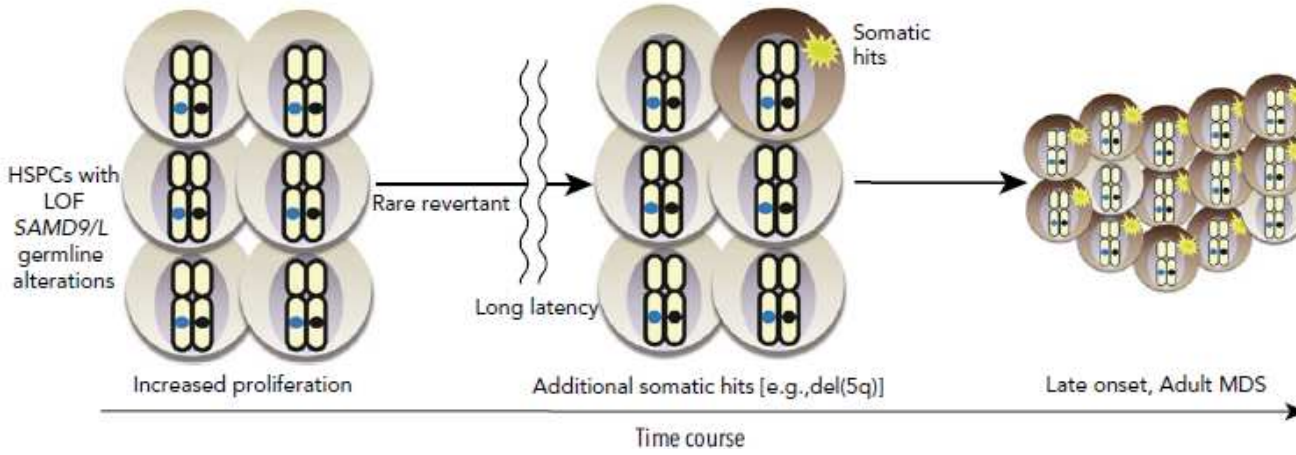
Germinal LOF mutations

N = 799 adults pts with MDS/BMF

☞24 pts and 26 variants (MDS: 4%: BMF: 3%)

Localized mostly in the N-ter coding part

Monosomy 7: rare



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SAMD9 & *SAMD9L* syndrome: take-home messages

New and not so rare ***(same frequency as GATA2 syndrome)*** **IBMF syndrome**

Extra-hematological phenotype may be absent (40 to 50%) and if present:

- **Is not specific for one gene**
- **Is variable with time:** ***ex: ataxia in the elderly***

Must be looked for in every child with monosomy 7 or del(7q)

High frequency of VUS : do not exclude class 3 variants!

Very high frequency of SGR making the indication for up-front HSCT difficult
(especially when the child lacks a good donor)

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Prospective studies needed!

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Congenital Thrombocytopenia and interstitial 3q26 microdeletions

	Nielsen et al. [2012]	Present case [2015]
Genotype		
Aberration	Del(3)(q26.2)	Del(3)(3q26.2q26.31)
Size	751.3 kb	4.52 Mb
# Refseq genes	3	31
MECOM deleted?	Completely	Exon 1 & exon 2
TERC deleted?	No	Completely
Phenotype		
Dysmorphic features	No	Yes
Respiratory problems	No	Yes
Cong. thrombocytopenia	Yes (8×10^9/L)	Yes (41×10^9/L)
Increased thrombopoietin	Yes (596 E/ml)	Yes (770 E/ml)
Neutropenia	Yes (age: 2 months)	No
Bone marrow aplasia	Yes (age: 2 months)	No
Bone marrow dysplasia	No	No
Alive	Yes (healthy at 5 ½ year of age)	No (died at 28 days of age)

NB: HSCT at 4m of age

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MECOM included in the deletion

Nielsen & al, J Med Genet 2012
Bouman & al, Am J Med Genet 2015

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Mutations in *MECOM*, encoding oncoprotein *EVI1*, cause RadioUlnar Synostosis with Amegacaryocytic Thrombocytopenia

RUSAT syndrome:

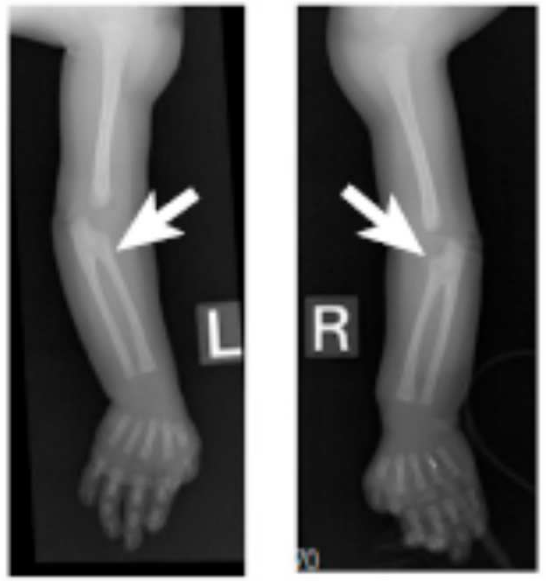
1st identified gene: *HOXA11* (2 families)

1 pt with RUSAT and w/o mutation ☞ WES:
***de novo* missense mutation in *MECOM*: c.266A>G / p.Thr756Ala**

2 other pts with RUSAT and missense mutations

Common characteristics of mutations:

- monoallelic
- de novo
- within a hostpot: 8th zinc finger motif sequence



Niihori & al, AM J Human Genet 2015

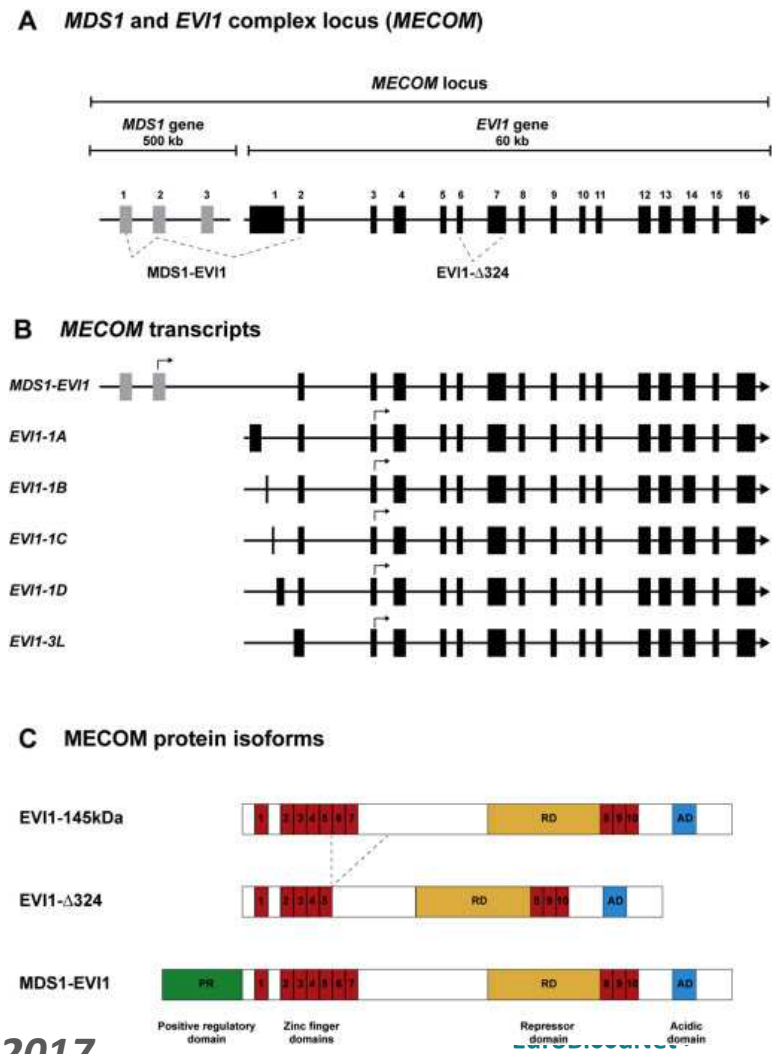
Table 1. Clinical Manifestations in Individuals with Mutations in *MECOM*

Individual	TRS1	TRS2[4]	TRS3[5]
Clinical Information			
Family history	simplex	simplex	simplex
Gender	female	female	male
Age at last clinical examination	3 years 2 months	8 years 9 months	8 years 0 months
Height (SD)	90.3 cm (−0.95)	113.7 cm (−2.5)	112 cm (−2.42)
Weight (SD)	11.8 kg (−1.07)	16.6 kg (−2.1)	17.8 kg (−1.63)
Gestational age	35 weeks	37 weeks	31 weeks
Birth weight	2,160 g	2,058 g	2,180 g
Leukocyte count at birth	6,780/μl	17,100/μl	3,220/μl
Hemoglobin count at birth	4.0 g/dl	12.9 g/dl	2.7 g/dl
Platelet count at birth	5,000/μl	8,000/μl	89,000/μl
Initial clinical presentation	neonatal asphyxia	systemic petechiae	fetal hydrops
HSC transplantation	CBT, 4 months	uBMT, 18 months	uBMT, 8 months
Radioulnar synostosis	blt	blt	blt
Finger abnormality	blt bony defect of the intermediate phalanges of the fifth digits, blt brachymesophalangia of the fourth digits	blt clinodactyly of the fifth digits	overlapping fingers without abnormalities of bone
Hearing	normal	sensorineural hearing impairment: Rt 55 dB, Lt 33.75 dB	prelingual sensorineural hearing impairment: Rt 60 dB, Lt 25 dB
Psychomotor development	normal	normal	mild intellectual disability (IQ 67)
Other	none	cleft palate, dysarthria	hydrocele testicle

MECOM locus

MDS1 and EVI1 COMplex locus:

- 2 genes: *MDS1* & *EVI1*
- 6 differents transcripts
- 2 major mRNA and protein species: EVI1 and MDS1/EVI1
- EVI1 is a regulator of gene expression involved in maintenance and expansion of normal HSC and is a known oncogene (myeloid leukemia & solid tumors)
- *MECOM* is also involved in embryonic development



Maicas & al, BBA 2017

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Network Hematological Diseases (ERN EuroBloodNet)

N = 6 pts

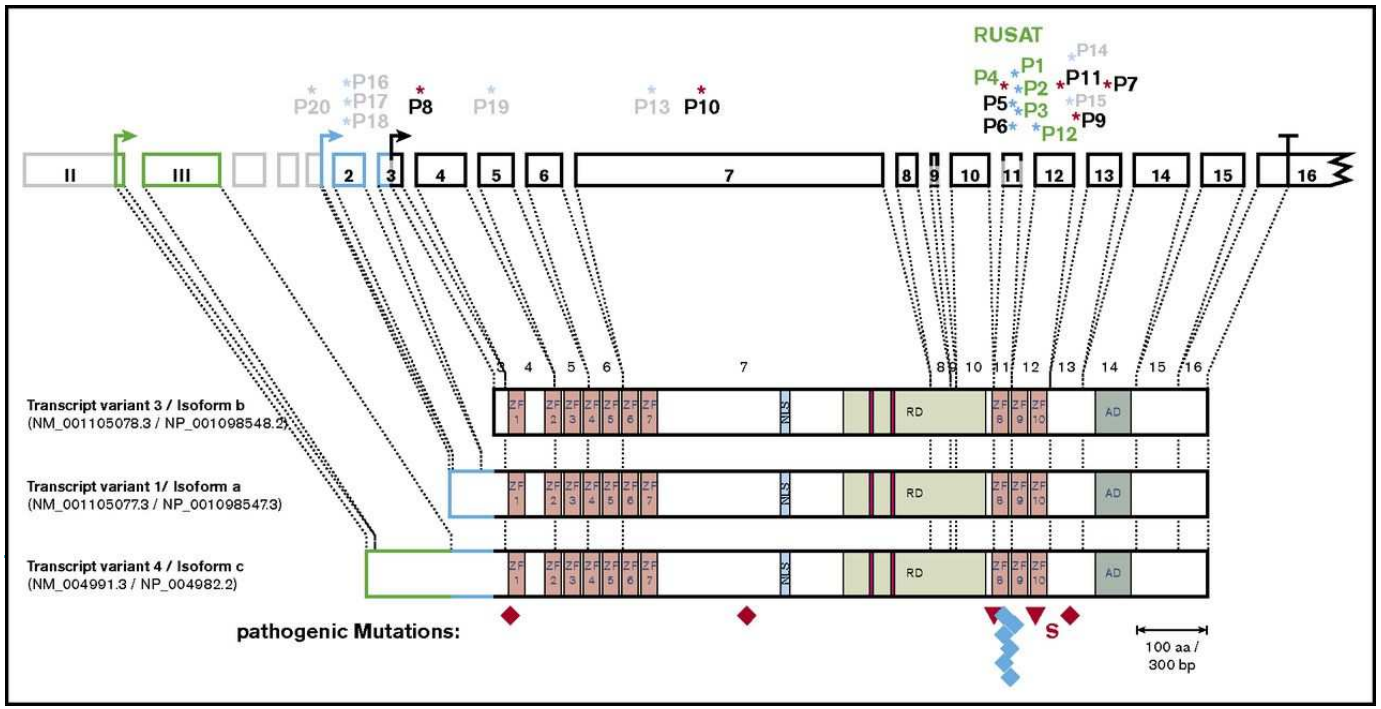
	UB004	UB036	UB093	UB100	UB104	UB153
Nucleic acid change	c.C2248T	c.G2334T	c.G1930T	c.1302_1306del	c.2900_2903del	c.2208-1G>A
Amino acid change	p.R750W	p.R778S	p.E644X	p.K434fs	p.D967fs	—
Sex	M	F	M	F	F	F
Age	18 mo	6 mo	3 mo	Neonatal	9 mo	9 mo
Family history	Simplex	Simplex	Simplex	Simplex	Simplex	Simplex
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-associated syndrome: a heterogeneous inherited BMF syndrome with amegakaryocytic thrombocytopenia

N = 151 patients with CAMT phenotype but no mutation in *MPL*

☞ **20 with heterozygous *MECOM* variants: 6 mutations in the previously reported hotspot**
7 in other regions of the gene
7 sn variations present in public databases

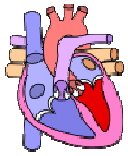


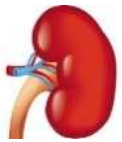
Truncating mutation / frameshift

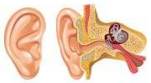
Truncating mutation / misense

Missense mutation

Germeshausen & al, Blood advances, 2018







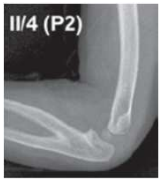


Table 2. Clinical characteristics of patients with MECOM mutations with high certainty of pathogenicity

Patient	Sex	Hematological course	HSCT (age in months)	RUS	Other skeletal malformations	Other malformations	Hearing	Other/remarks	Family history	MECOM mutation (transcript variant 3)
P1	M	Congenital TP and anemia, progressive BMF	MUD (11)	Y	Hypoplasia of middle and end phalanx D5	N	Normal		RUS in family members	c.2251C>T, p.His751Tyr
P2	M	Congenital TP, progressive BMF	First: MFD (8); second: MUD (21)	Y	N	N	Impaired (hearing aids)		RUS and RUSAT in family members	c.2276A>T, p.Gln759Leu
P3	M	Severely pancytopenic at birth but spontaneous amelioration during first weeks of life, persisting mild TP	N	Y	Clinodactyly D5, hypoplasia of middle phalanx D5	N	ND			c.2278C>T, p.Pro760Ser
P4	F	Congenital TP and anemia, progressive BMF	MUD (7)	Y	Toe malposition D2 bilateral	Cystic kidney (left), duplex kidney (right), urinary obstruction with megaureter (left)	Normal	Hypogammaglobulinemia	N	c.2208-1_2208delGA, loss of splice acceptor site
P5	F	Severe congenital pancytopenia, progressive BMF	Died as a result of sepsis before HSCT	N	N	Hepatomegaly and mild bilateral renal calyceal dilatation	ND	Severe infections, B-cell deficiency	N	c.2248C>T, p.Arg750Trp
P6	F	Severe congenital pancytopenia, extremely hypocellular BM	MUD (5), TRD	N	N	N	ND	Severe bacterial and fungal infections, GI bleeding	Healthy parents, 1 sister with Pierre Robin sequence, 1 sister with craniosynostosis	c.2248C>T, p.Arg750Trp
P7	M	Congenital TP and anemia, progressive BMF	MUD (4), TRD	N	Brachymesophalangy D5	Subpulmonary VSD, aortic coarctation	Normal			c.2542C>T, p.Arg848Ter
P8	F	Congenital TP and anemia, progressive BMF	UCB (3)	N	N	ASD, small cleft palate	ND	Precocious puberty, cognitive deficits		c.69C>A, p.Cys23Ter
P9	M	Fetal adrenal hemorrhage (w30) resulting from TP, fast progression to pancytopenia and BMF	MUD (10.5), TRD	N	Thumb under D2	N		Severe bacterial and fungal infections		c.2455+1G>C, loss of splice donor site
P10	M	Pancytopenia	MFD (156)	N	Floating elbow, clinodactyly D5	Tetralogy of Fallot	Congenital hearing loss		Niece with severe BMF (HSCT: MUD at age 8 mo); father hearing impaired	c.1114C>T, p.Gln372Ter
P11	F	Congenital TP, progressive BMF	MUD (16)	N	Hip dysplasia (left)	N	Inconspicuous	Gynecomastia in infancy (Tanner stage B3)	N	c.2419_2420insA, p.Arg807Lysfs*7
P12	M	Mild TP at age 1 y, progressive BMF	MUD (85)	Y	Clinodactyly D5, brachydactyly D1 and D2, small patellae	N	Bilateral deafness		N	c.2296T>C, p.Cys766Arg

HSCT outcome was positive unless otherwise indicated.
ASD, atrial septal defect; F, female; GI, gastrointestinal; M, male; MFD, matched family donor; MUD, matched unrelated donor; ND, no data; TP, thrombocytopenia; TRD, transplantation-related death; UCB, unrelated cord blood.

Early BMT: 8/10 < 12 m

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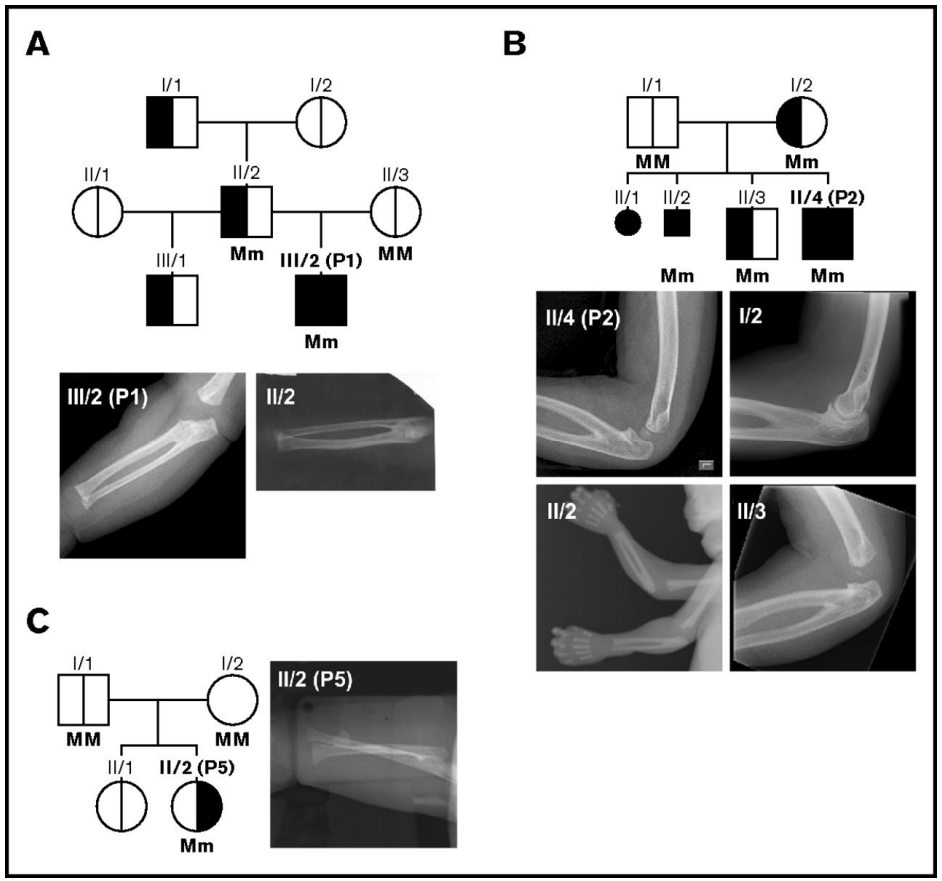
Autosomal dominant inheritance in some families (A & B)



M: wild type
m: mutated

: RUS

: CAMT/AA

Family analysis in 11/13 pts:

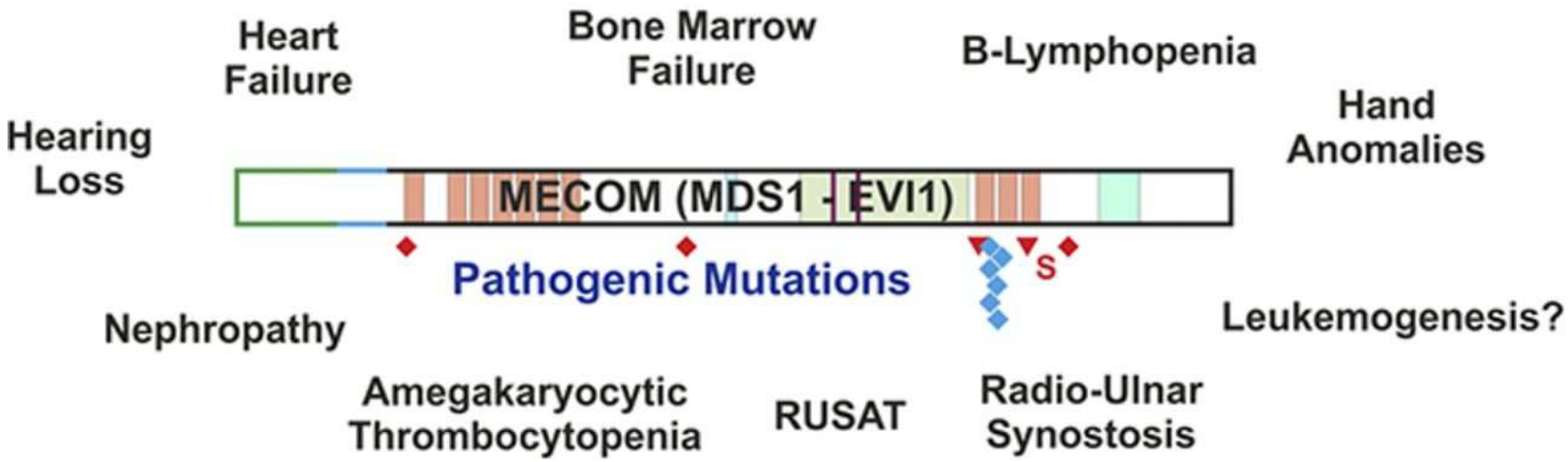
- **3 families with transmission**
- **4 with mutation + in a non-affected subject**
- **4 *de novo* mutations**

To note: variable expression in members of one family

Somatic mosaicism in pts with no BMF?

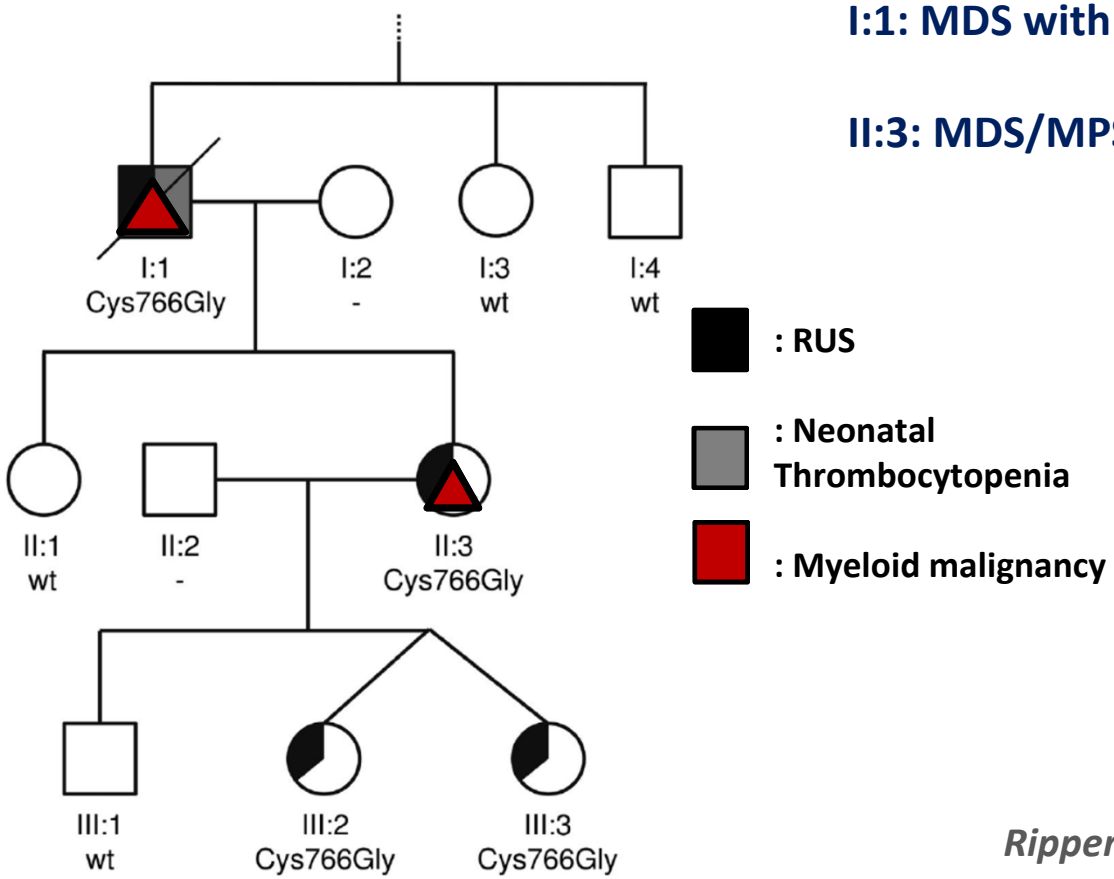
Germeshausen & al, Blood advances, 2018

MECOM syndrome



(Germeshausen & al, Blood advances, 2018)

MDS1 and *EVI1* complex locus (*MECOM*): a novel candidate gene for hereditary hematological malignancies



I:1: MDS with blast excess diagnosed at the age of 73

II:3: MDS/MPS neoplasm unclassified diagnosed at the age of 48

To note: early HSCT may explain the paucity of cases

Ripperger & al, Haematologica 2018

MECOM syndrome: take-home messages

GENETIC ASPECTS:

Monoallelic mutations
and mostly *de novo* mutations : **no familial history & no place for consanguinity…**

Frequency of large deletions : **phenotype may be specially severe**
☞ ***contiguous genes syndrome***
: **genetic diagnosis may be falsely negative**

CLINICAL ASPECTS:

Many different phenotypes : **high degree of suspicion including in pt w/o RUS**

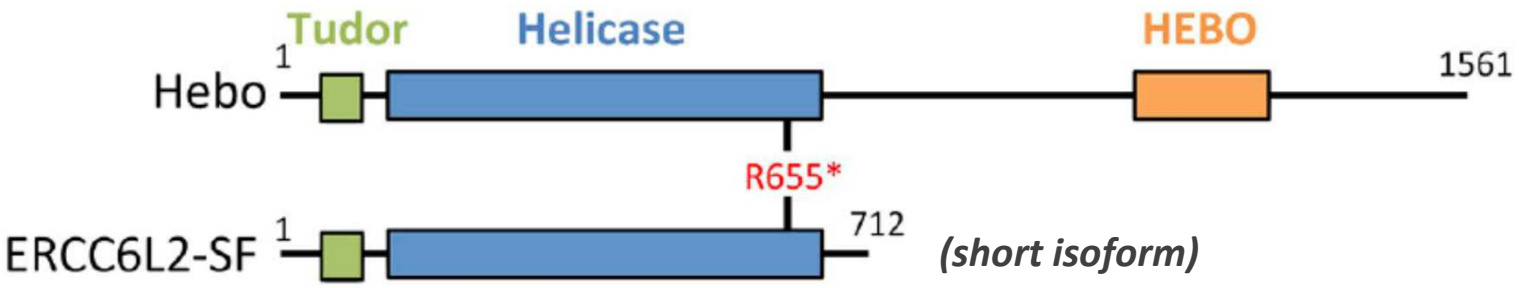
Very early BMF : **prototypic BMF in infant +++**

ERCC6L2 syndrome

1st report by Tummala & al in 2014: 2 cases from 2 different families

	Index Cases in This Study					
Features	**Case 1 (Family 1)**	**Case 2 (Family 2)**	**Case 3**	**FA**	**CS**	**DC**
Gender	male	female	female	male and female	male and female	male and female
Age at presentation (years)	12	19	9	-	-	-
Ethnic origin	French	Pakistani	Pakistani	varied	varied	varied
First-cousin parents	yes	yes	yes	some	some	some
Trilineage bone marrow failure	yes[a]	yes[b]	yes[c]	yes	no	yes
Learning difficulties and/or developmental delay	yes	yes	yes	yes	yes	yes
Microcephaly	yes	yes	no	yes	yes	yes
Cutaneous photosensitivity	no	no	no	no	some	some
Cancer	no	no	no	yes	no	yes
Mucocutaneous features	no	no	no	some	some	yes
Other clinical features	yes[d]	yes[e]	yes[f]	yes[g]	yes[h]	yes[i]
Chromosomal breakage in PB lymphocytes after treatment with DEB or MMC	normal	normal	normal	increased	normal	normal
Telomere length	normal	short	short	short	?	very short

ERCC6L2 and Hebo

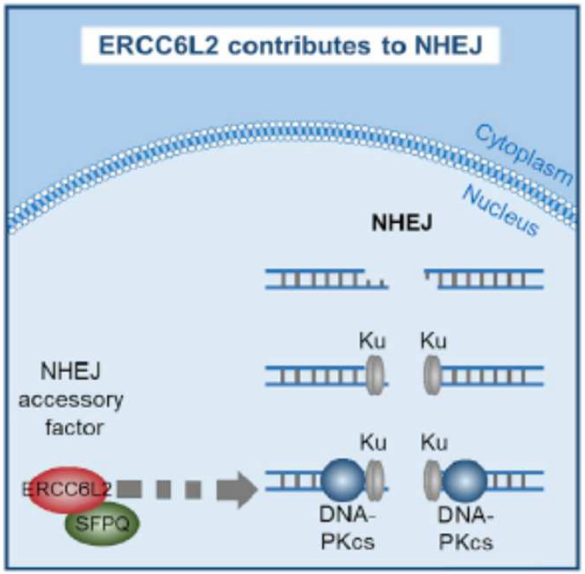


Protein involved in DNA repair: patients have a double strand break repair defect

Recruitment to DNAdsb in a NBS1-dependent manner.

In vitro complementation need the presence of the HEBO domain

Classified as an accessory NHEJ gene through interaction with SFPQ



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Zhang et al, J Exp Med 2016
Francica et al, Cell 2020

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, × 10⁹/L	64	<150	107	101	48	38	4
ANC, × 10⁹/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

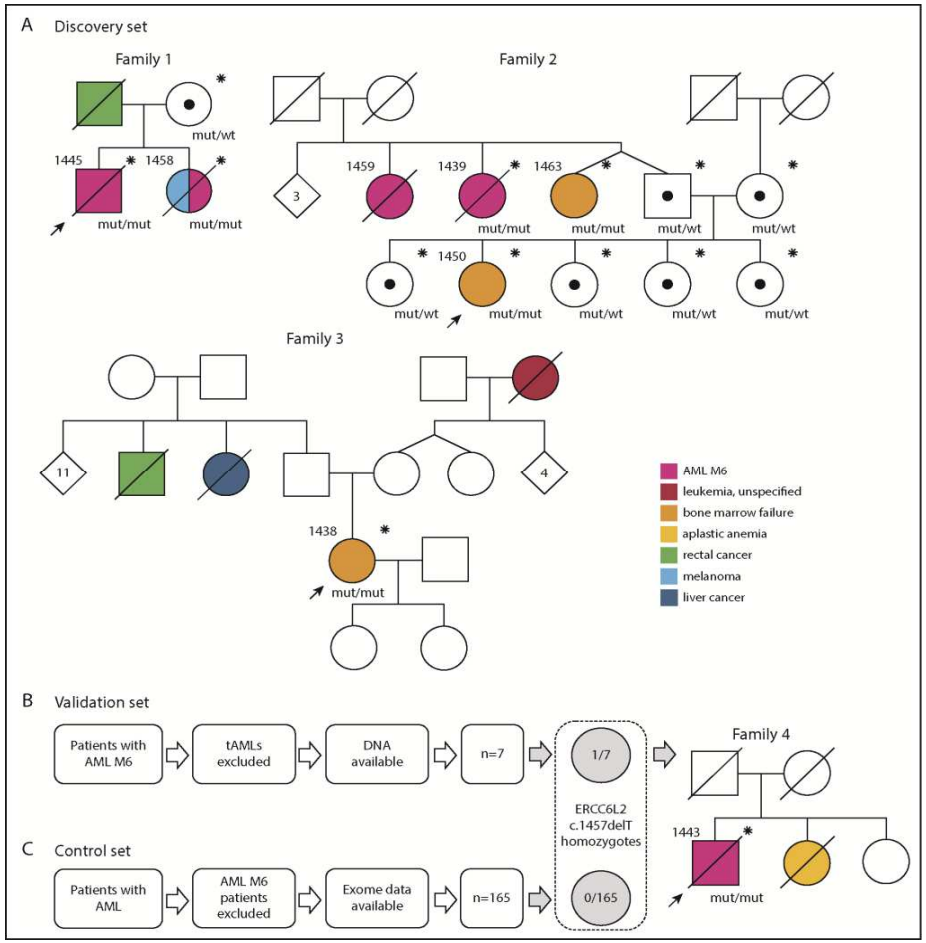
HSCT: only 3/7 (AYA pts)

1/7 AML (age 43)

Bluteau & al, Blood 2018

TO THE EDITOR:

ERCC6L2 defines a novel entity within inherited acute myeloid leukemia



Discovery set: 3 families:

AML6: n = 4 (+1 AML w/o precision)

Validation set:

AML6 (t-AML excluded): 1/7

Control set:

AML other FAB subtypes: 0/165

☞ AML6 +++; association with monosomy 7 & *TP53* mutations

NB1: median age at diagnosis: 49 yr

NB2: no previous BMF history

Douglas & al, Blood 2019

Patients with *ERCC6L2* mutations: hematological outcomes

Review presented at ASH: N = 46: 31 published cases + 15 new cases:

EPIDEMIOLOGY	21 cases from North-Eastern Finland with the same biallelic mutations ☞ Founder effect
HEMATOLOGY (1) **Cytopenias**	Median age at 1st referral to hematologist: 18 yr [6-65] Mild and fluctuating cytopenias with hypoplastic BM *(more severe cases reported in children)*
HEMATOLOGY (2) **Clonal hematopoiesis**	Investigated patient (n = 17): ➔ all with 1 to 4 *TP53* clones
HEMATOLOGY (3) **MDS & AML: 40%**	MDS: N = 9 AML: N = 9 including 6 pts with AML6 ▪ median age at AML: 37 yr [20-65] ▪ Complex karyotype ▪ Very poor prognosis

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Hakkarainen & al, ASH 2021

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ERCC6L2 syndrome: take-home messages

New rare IBMF subtype with defective DNA repair (NHEJ)

☞ you may have some breaks at chromosomal breakage analysis

Extra-hematological phenotype:

- **mostly microcephaly and developmental delay (1 case with ataxia) but not present in every patient**
- **Still to be described?**

To have in mind in front of every patient (mostly adults) with AML6

Conclusion

More and more IBMFs

More and more fascinating stories on Somatic Genetic Rescue in HSC

For my young colleagues: do not worry! We still need help for prospective studies on already known IBMF syndromes and to discover new ones!

Thank you for your attention

thierry.leblanc@aphp.fr

MaRIH network: Reference centres for rare Immunological and hematological diseases

Acknowledgments: Aplastic anemia French group
- *Pediatric site: Jean-Hugues DALLE & Thierry LEBLANC*
- *Adult site: Flore SICRE de FONTBRUNE & Régis PEFFAULT DE LA TOUR*
- *Hematology lab: Lise LARCHER & Jean SOULIER*

Patients associations

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