

ERCC6L2

Journée nationale du CRMR Aplasies médullaires

Octobre 2023

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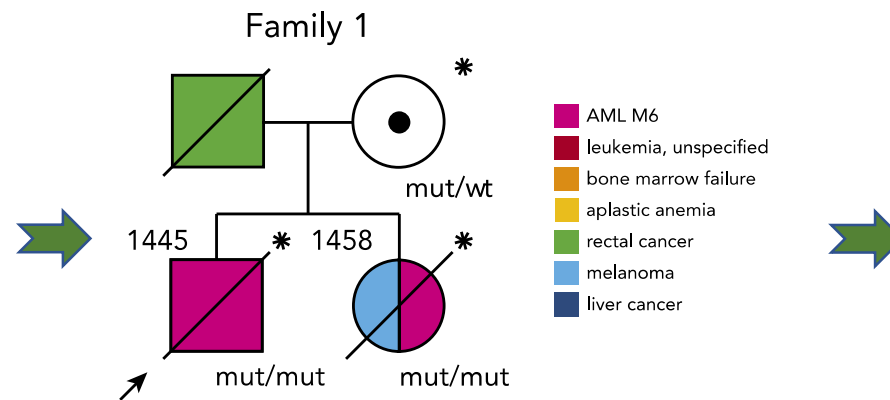


Historique

Features	Case 1 (Family 1)	Case 2 (Family 2)	Case 3
Gender	male	female	female
Age at presentation (years)	12	19	9
Ethnic origin	French	Pakistani	Pakistar
First-cousin parents	yes	yes	yes
Trilineage bone marrow failure	yes ^a	yes ^b	yes ^c
Learning difficulties and/or developmental delay	yes	yes	yes
Microcephaly	yes	yes	no
Cutaneous photosensitivity	no	no	no
Cancer	no	no	no
Mucocutaneous features	no	no	no
Other clinical features	yes ^d	yes ^e	yes ^f
Chromosomal breakage in PB lymphocytes after treatment with DEB or MMC	normal	normal	normal
Telomere length	normal	short	short

2014, Tummala

LOF mutations, AR
BMF, microcéphalie, retard des acquisitions
2 pts



2019, Douglas

LOF mutations, AR
LAM6/MDS, BMF, TP53
8 pts

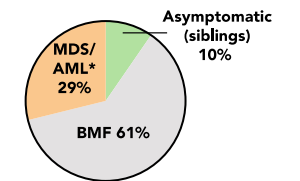
Cohort:

- 52 patients from 35 families
- 9 countries, 11 centers
- 1165 person years

Constitutional features:

- Microcephaly (3/52)
- Neuropsychiatric (4/53)
- Solid tumors (2/52)

Disease at presentation:



* One case with ALL, later progressed to MDS/AML

	BMF N = 32	MDS/AML* N = 15
Age at initial diagnosis, years, median (range)	12 (2-57)	29 (12-65)
Hypocellular marrow	96%	36%
TP53 mutations, percent of cases	83%	100%
TP53 median VAF	12%	38%
Overall survival (3 yrs)	95%	19%
Survival after HSCT (3 yrs)	88%	28%

**CBC does not predict MDS onset
(need for marrow surveillance and TP53 genetics)**

2023, Hakkarainen

LOF mutations, AR
LAM6/MDS, BMF, TP53
52 pts

ERCC6L2 - Fonctions

Helicase, 9q22.32

Expression ubiquitaire (cellules hématopoiétiques & CSM)

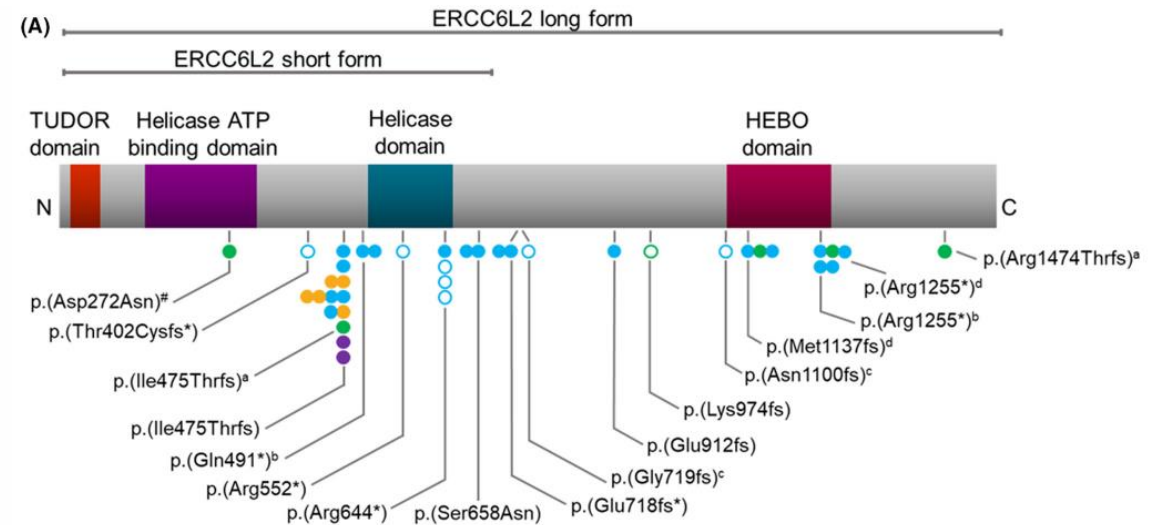
2 isoformes exprimées similaire

Rôles :

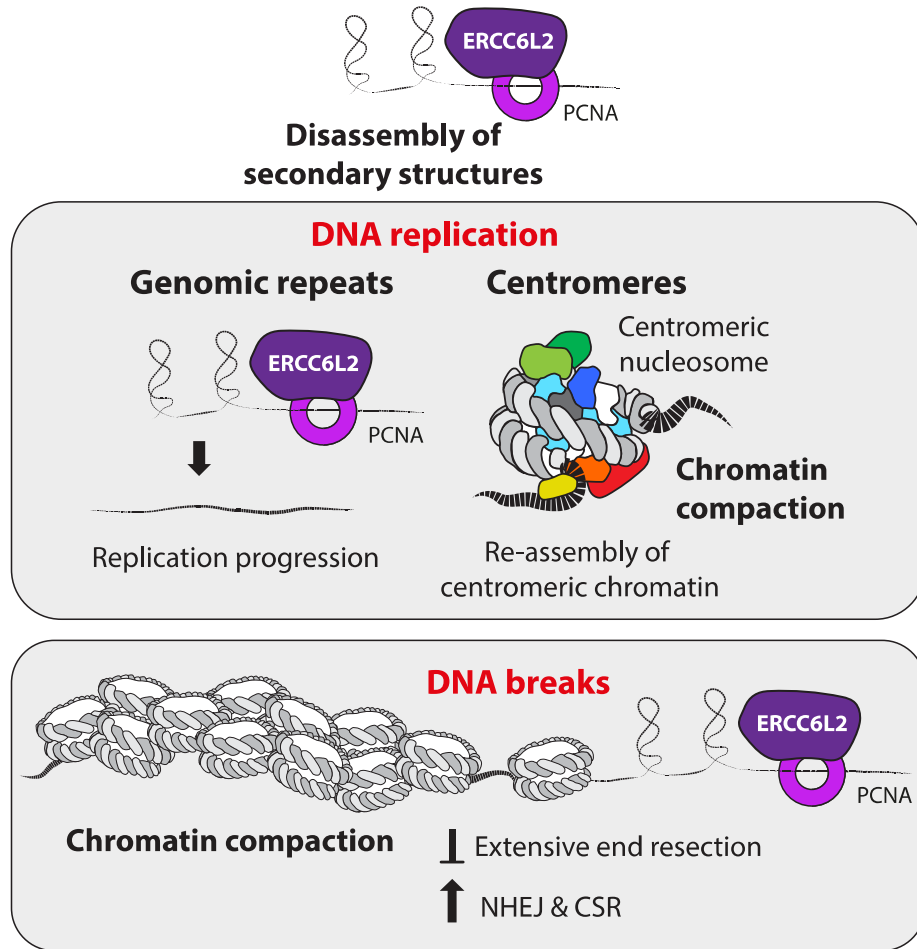
- Décompaction chromatine
- Régulation transcription
- Recombinaison et réparation ADN (class switch)

Hématopoïèse (KO / progeniteurs patients) :

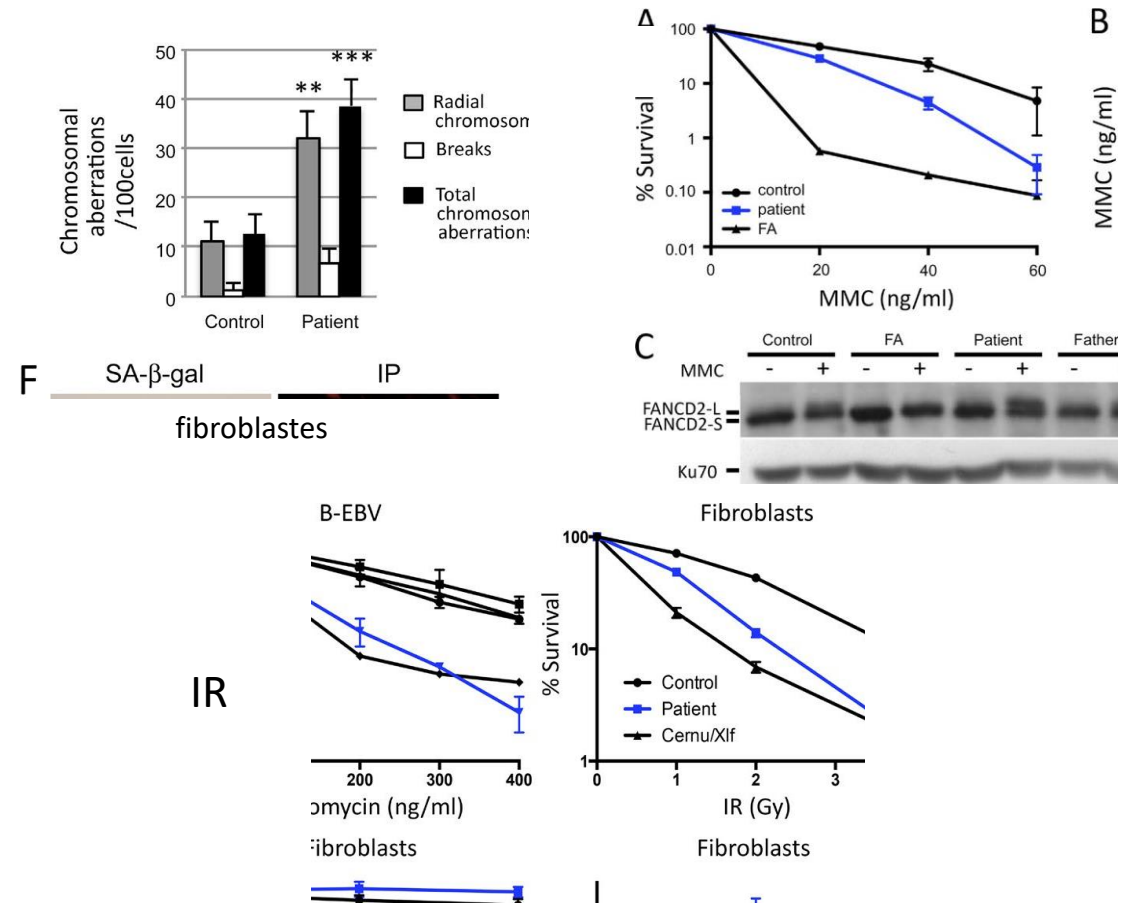
- ✓ réduction clonogenicité CSH
- ✓ retard différenciation erythroïde
- ✓ Activation voie réparation ADN, voie p53 & contrôle cycle cellulaire



Conséquences déficit ERCC6L2



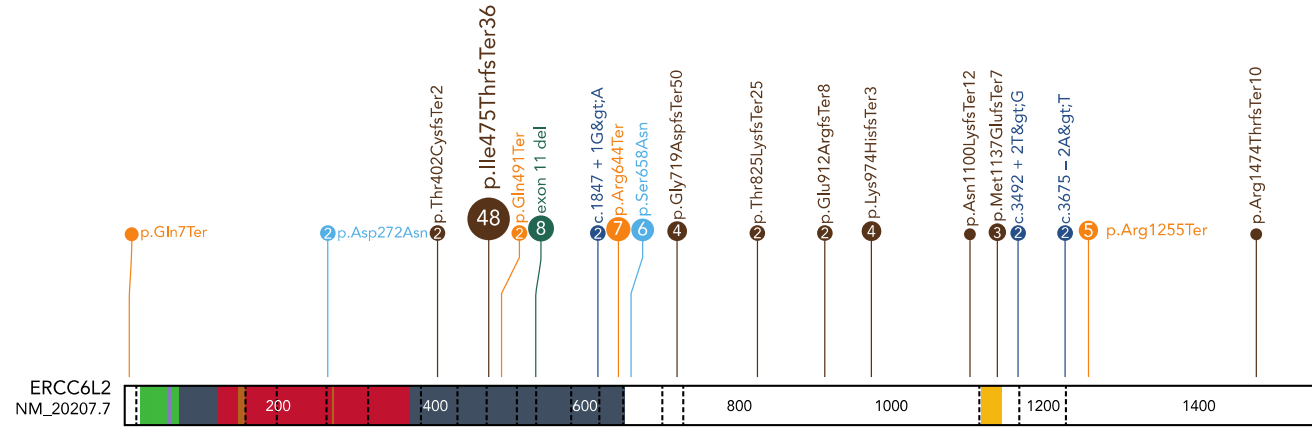
Chimio et/ou radiosensibilité ???



Phénotypes cliniques patients ERCC6L2^{-/-}

Cohorte

- 52 patients (33 déjà rapportés)
- 9 pays, 11 centres
- 23 patients finlandais (22 variant HOZ c.1424delT)
- 25% HEZ composites
- 34% consanguinité
- 5/52 apparentés asymptomatiques

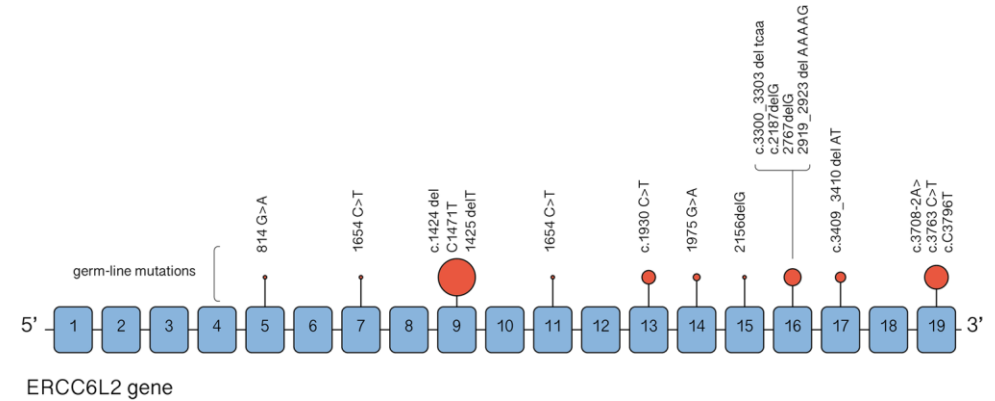


Manifestations extra-hématologiques

- Microcéphalie 3/52 (6%)
- Troubles neuropsychiques 4/52 (8%)
- Tumeurs solides 2/52

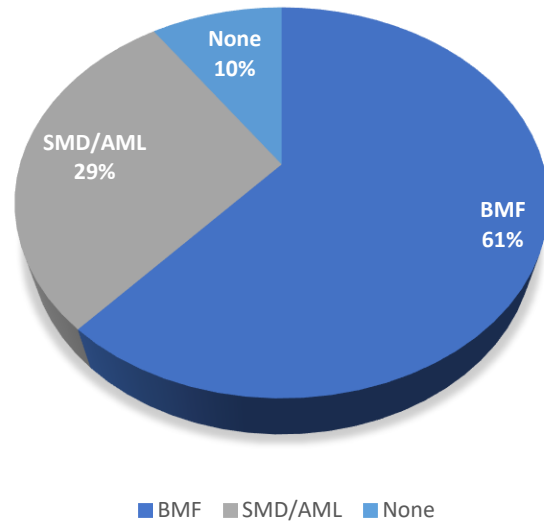
Phénotypes cliniques patients ERCC6L2^{-/-}

ERCC6L2-related disease: a novel entity of bone marrow failure disorder with high risk of clonal evolution



Male	13/31 (42%)
Mean age at presentation	19 years old (2–65)
Thrombocytopenia ($\leq 150,000/\mu\text{L}$)	20/21 (N/A 10)
Leucopenia ($\leq 4500/\mu\text{L}$)/neutropenia ($\leq 1500/\mu\text{L}$)	17/21 (N/A 10)
Anemia (≤ 12 g/dL)	17/21 (N/A 10)
Microcephaly/developmental delay	6/31 (19%)
Short telomeres	4/17 (N/A for 16)
Hypocellular BM	20/30
Development of MDS/AML	10/31 (32%)
Mean age at development of MDS/AML	31.5 years old (2–65)

Phénotypes hématologique patients ERCC6L2^{-/-}



Variable	ERCC6L2 subjects without malignancy, n = 33	ERCC6L2 subjects with malignancy, n = 15	P	Data available, n
Age at diagnosis				
Median, y (range)	12 (2-57)	29 (12-65)	.0007	33; 15
CBC				
Median leukocytes, 1 × 10 ⁹ /L (range)	3.25 (1.3-7.7)	2.85 (1.2-5.8)	.2891	28; 12
Median ANC, 1 × 10 ⁹ /L (range)	1.16 (0.25-3.9)	0.65 (0.1-4.7)	.6350	26; 12
Median hemoglobin, g/dL (range)	10.80 (3.4-15)	10.10 (5.9-14)	.1918	29; 13
Median MCV, fL (range)	101.5 (90-114)	98.0 (87-105)	.3720	8; 5
Median platelets, 1 × 10 ⁹ /L (range)	63.50 (4-195)	80.0 (10-175)	.9623	30; 13
Median reticulocytes, 1 × 10 ⁹ /L (range)	58.0 (33.0-104.1)	29.1 (11.9-98.0)	.0530	15; 6
TP53 status				
N of patients with TP53 clone (%)	15* (84.2)	11 (100)	.1845	19; 11
N of mutations, range	0–4	1–2		18; 11
Median VAF % (range)	12.0 (1.3-36.0)	38.0 (6.0-94.0)	.0020	16; 9
BM				
Hypocellular, n (%)	25 (96)	4 (36)	<.0001	26; 11
Normal, n (%)	1 (4)	2 (18)		
Hypercellular, n (%)	N/A	5 (45)		

Relecture myelo & BOM 19 pts finlandais (13 BMF & 6 AML/SMD) :

- Moelle plutôt erythroblastique
- 70% des BMF dysplasie au moins 1 lignée (MK ou ER)

Hémopathies myéloïdes patients ERCC6L2^{-/-}

MDS/AML

1 LAL T → SMD

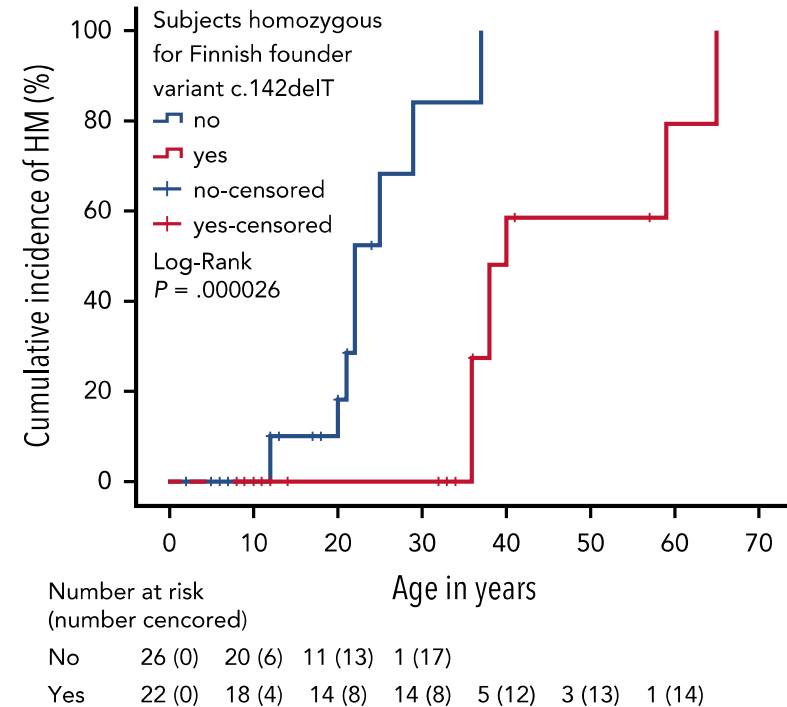
Age médian au diag HM 37 y (12-65)

Mais 22 ans si pts finlandais exclus

SMD/LAM6

Caryotypes complexes

Mutations p53 VAF élevées



Evolution patients ERCC6L2-/-

FU médian court 3 ans

3 pts BMF → MDS/LAM (1 mois à 25 ans post diag)

Survie moyenne 26 ans ; OS à 5 ans 95%

9 allogreffés pour BMF

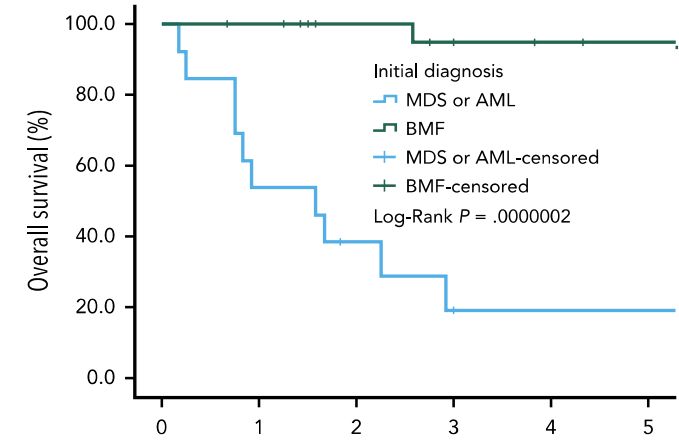
2 décès

13 pts with MDS/LAM & FU

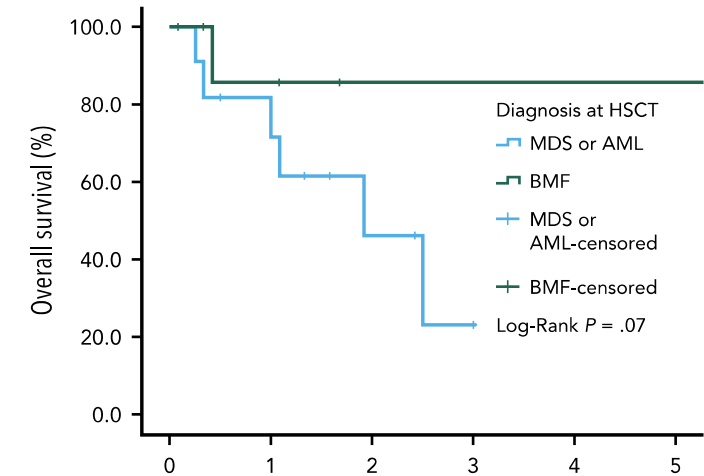
6 LAM CT induction : 50% remission (rechute post HSCT)

OS médiane 1,6 an

OS 3 ans : 19%

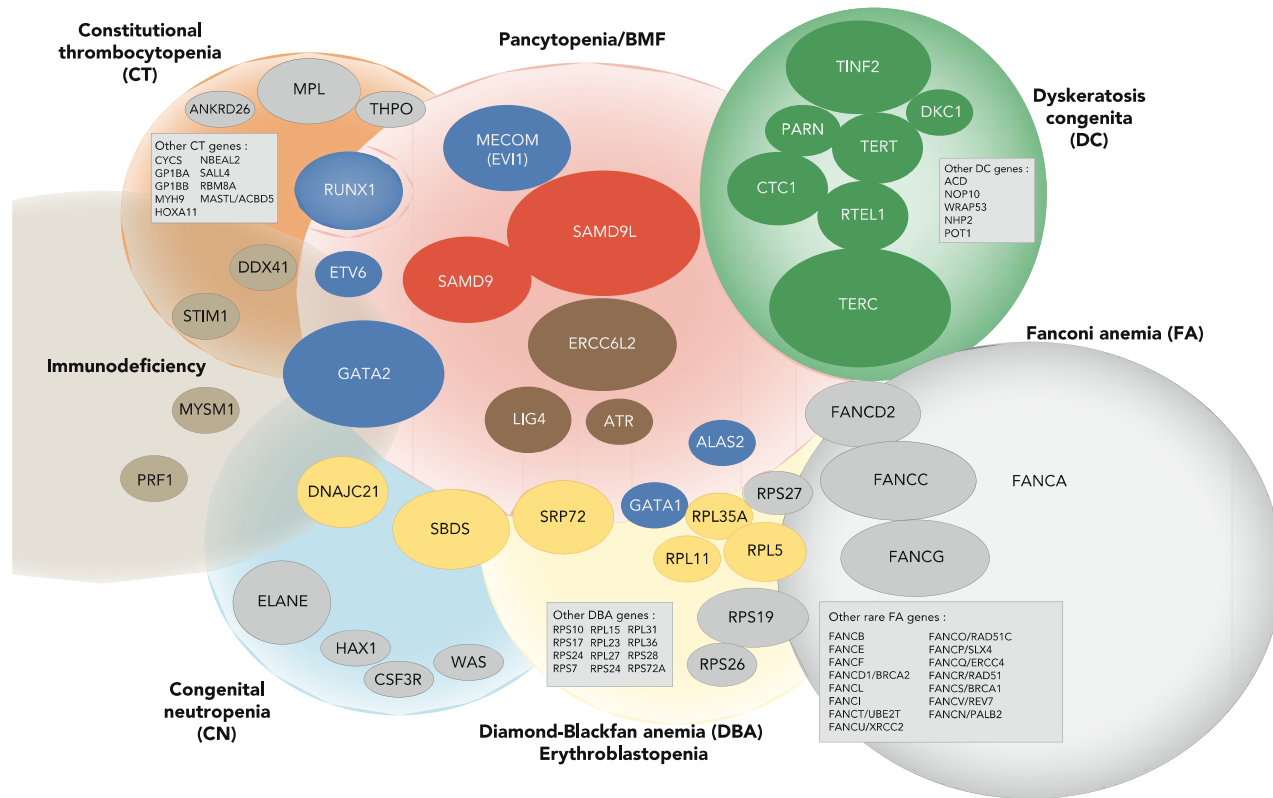


	0	1	2	3	4	5
BMF	26 (0)	25 (6)	20 (7)	18 (9)	16 (10)	15 (24)
MDS or AML	13 (0)	7 (1)	4 (1)	2 (2)	1 (2)	1 (3)



	0	1	2	3	4	5
BMF	9 (0)	6 (2)	4 (4)	4 (4)	4 (4)	4 (4)
MDS or AML	11 (0)	8 (1)	3 (3)	1 (5)		

Conclusion ERCC6L2^{-/-}



Cause rare BMF

- 7/179 patients
- 1 pts depuis
- Age varié : enfants / AJA
- Microcéphalie
- BMF :
 - Mutations de p53 a faible VAF
 - Dysplasie erythro/mega

Conclusion ERCC6L2^{-/-}

- Pronostic très bon si allogreffe pour BMF
- Pronostic catastrophique si évolution vers SMD/LAM
- Allogreffe pré-emptive ???
- Modalités allogreffe : Chimiosensibilité ? Radiosensibilité ?
 - France tous patients allogreffés pour BMF avec conditionnement FA like
 - Pas de toxicité des conditionnements
 - 1 patiente PTLD réfractaire post allo : RT curative avec radiodermite majeure
 - 1 patiente néoplasie mammaire : toxicité majeure radiothérapie après chir



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