Anomalies clonales de « signification indéterminée » ? Tri15 et -Y

Table 6.03 Recurrent chromosomal abnormalities and their frequencies in myelodysplastic syndrome (MDS) at diagnosis

Chromosomal abnormality	Frequency	
	MDS overall	Therapy-related MDS
Unbalanced		
Gain of chromosome 8[a]	10%	
Loss of chromosome 7 or del(7q)	10%	50%
del(5q)	10%	40%
del(20q)[a]	5–8%	
Loss of Y chromosome[a]	5%	
Isochromosome 17q or t(17p)	3–5%	25–30%
Loss of chromosome 13 or del(13q)	3%	
del(11q)	3%	
del(12p) or t(12p)	3%	
del(9q)	1–2%	
idic(X)(q13)	1–2%	
Balanced		
t(11;16)(q23.3;p13.3)		3%
t(3;21)(q26.2;q22.1)		2%
t(1;3)(p36.3;q21.2)	1%	
t(2;11)(p21;q23.3)	1%	
inv(3)(q21.3q26.2) / t(3;3)(q21.3;q26.2)	1%	
t(6;9)(p23;q34.1)	1%	

Persistant cytopenia without dysplasia
MDS-defining abnormality

[a] As a sole cytogenetic abnormality in the absence of morphological criteria, gain of chromosome 8, del(20q) and loss of Y chromosome are not considered definitive evidence of MDS; in the setting of persistent cytopenia of undetermined origin, the other abnormalities shown in this table are considered presumptive evidence of MDS, even in the absence of definitive morphological features.

Journée du GFCH 01/06/2022
CEC, Pitié-Salpêtrière
Pr F Nguyen Khac

GFCH
Groupe Francophone de Cytogénétique Hématologique

Anomalies clonales de « signification indéterminée » ? Tri15 et -Y

Table 6.03 Recurrent chromosomal abnormalities and their frequencies in myelodysplastic syndrome (MDS) at diagnosis

Chromosomal abnormality	Frequency	
	MDS overall	Therapy-related MDS
Unbalanced		
Gain of chromosome 8[a]	10%	
Loss of chromosome 7 or del(7q)	10%	50%
del(5q)	10%	40%
del(20q)[a]	5–8%	
Loss of Y chromosome[a]	5%	
Isochromosome 17q or t(17p)	3–5%	25–30%
Loss of chromosome 13 or del(13q)	3%	
del(11q)	3%	
del(12p) or t(12p)	3%	
del(9q)	1–2%	
idic(X)(q13)	1–2%	
Balanced		
t(11;16)(q23.3;p13.3)		3%
t(3;21)(q26.2;q22.1)		2%
t(1;3)(p36.3;q21.2)	1%	
t(2;11)(p21;q23.3)	1%	
inv(3)(q21.3q26.2) / t(3;3)(q21.3;q26.2)	1%	
t(6;9)(p23;q34.1)	1%	

Persistant cytopenia without dysplasia
MDS-defining abnormality

[a] As a sole cytogenetic abnormality in the absence of morphological criteria, gain of chromosome 8, del(20q) and loss of Y chromosome are not considered definitive evidence of MDS; in the setting of persistent cytopenia of undetermined origin, the other abnormalities shown in this table are considered presumptive evidence of MDS, even in the absence of definitive morphological features.

Journée du GFCH 01/06/2022
CEC, Pitié-Salpêtrière
Pr F Nguyen Khac

GFCH
Groupe Francophone de Cytogénétique Hématologique

Anomalies clonales de « signification indéterminée » ? Tri15 et -Y

Table 6.03 Recurrent chromosomal abnormalities and their frequencies in myelodysplastic syndrome (MDS) at diagnosis

Chromosomal abnormality	Frequency	
	MDS overall	Therapy-related MDS
Unbalanced		
Gain of chromosome 8[a]	10%	
Loss of chromosome 7 or del(7q)	10%	50%
del(5q)	10%	40%
del(20q)[a]	5–8%	
Loss of Y chromosome[a]	5%	
Isochromosome 17q or t(17p)	3–5%	25–30%
Loss of chromosome 13 or del(13q)	3%	
del(11q)	3%	
del(12p) or t(12p)	3%	
del(9q)	1–2%	
idic(X)(q13)	1–2%	
Balanced		
t(11;16)(q23.3;p13.3)		3%
t(3;21)(q26.2;q22.1)		2%
t(1;3)(p36.3;q21.2)	1%	
t(2;11)(p21;q23.3)	1%	
inv(3)(q21.3q26.2) / t(3;3)(q21.3;q26.2)	1%	
t(6;9)(p23;q34.1)	1%	

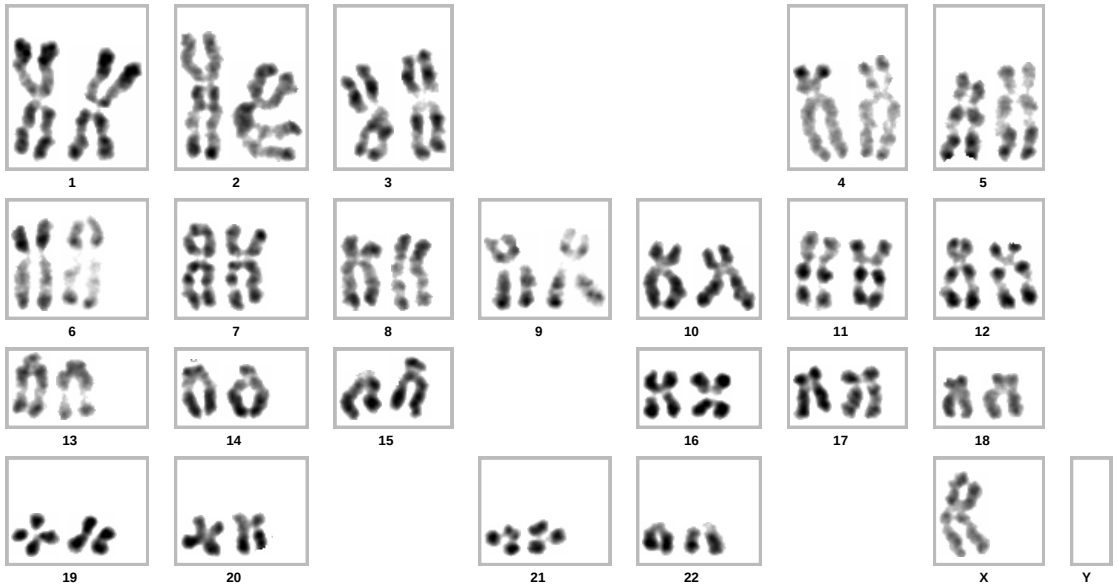
Persistant cytopenia without dysplasia
MDS-defining abnormality

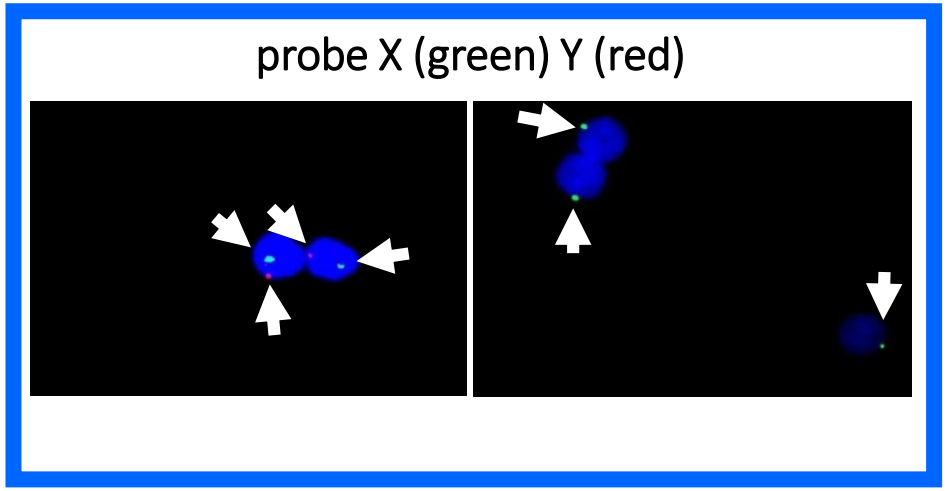
[a] As a sole cytogenetic abnormality in the absence of morphological criteria, gain of chromosome 8, del(20q) and loss of Y chromosome are not considered definitive evidence of MDS; in the setting of persistent cytopenia of undetermined origin, the other abnormalities shown in this table are considered presumptive evidence of MDS, even in the absence of definitive morphological features.

Journée du GFCH 01/06/2022
CEC, Pitié-Salpêtrière
Pr F Nguyen Khac

GFCH
Groupe Francophone de Cytogénétique Hématologique

Perte de l'Y





Chapiro et al., Genes Chromosomes Cancer 2014

ISCN 2020

A clone is defined as a cell population derived from a single progenitor.

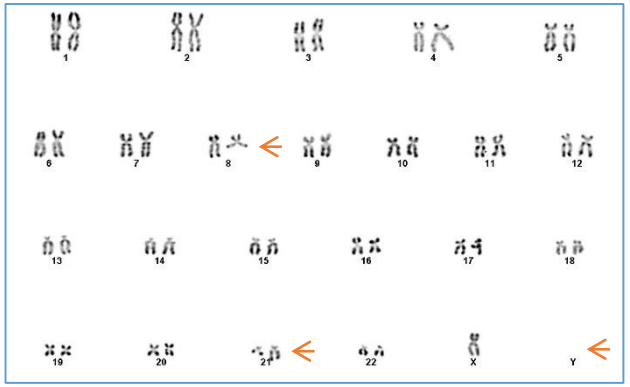
If the abnormality is loss of a chromosome, the same loss must be present in at least 3 cells to be accepted as clonal.

(However, 2 cells with identical losses of one or more chromosomes and the same chromosome gain structural aberration(s) may be considered clonal)

Perte du chromosome Y

➢Hémopathies malignes

- Non spécifique
- LAM, LMC, MDS, MPN
- Association avec t(8;21)(q22;q22) / LAM
- Isolée : bon/très bon pronostic MDS



Pitié-Salpêtrière

Score	0	0.5	1	1.5	2
Blastes moelle	< 5%	5 à 10%	_	11 à 20%	21 à 30%
Caryotype	Bon (normal, -Y, del(5q), del(20q)	Intermédiaire ni bon, ni mauvais	Mauvais (complexe ≥ 3 anomalies) ou anomalies du 7	_	_
Cytopénies Hb < 10 g/dL PN < 1.8 G/L PLQ < 100 G/L	0 ou 1	2 ou 3	_	_	_

Greenberg et al., Blood 1997

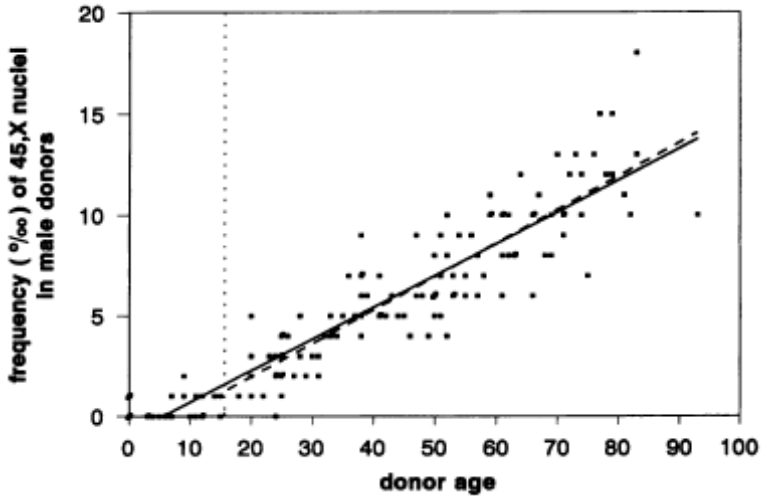
Prognostic subgroup	Defining cytogenetic abnormalities
Very good	Loss of Y chromosome del(11q)
Good	Normal del(5q) del(12p) del(20q) Double, including del(5q)
Intermediate	del(7q) Gain of chromosome 8 Gain of chromosome 19 Isochromosome 17q Single or double abnormalities not specified in other subgroups Two or more independent non-complex clones
Poor	Loss of chromosome 7 inv(3), t(3q) or del(3q) Double including loss of chromosome 7 or del(7q) Complex (3 abnormalities)
Very poor	Complex (>3 abnormalities)

Schanz et al., J Clin Oncol 2012

➢Physiologique

- ~2% sang, ~6% moelle osseuse ?
- Augmente avec l'âge (GWAS sang : 2% <60 ans, 15-40% 70-85 ans, 57% 93 ans)
- N'est pas considérée comme une évidence définitive de MDS (OMS 2016)

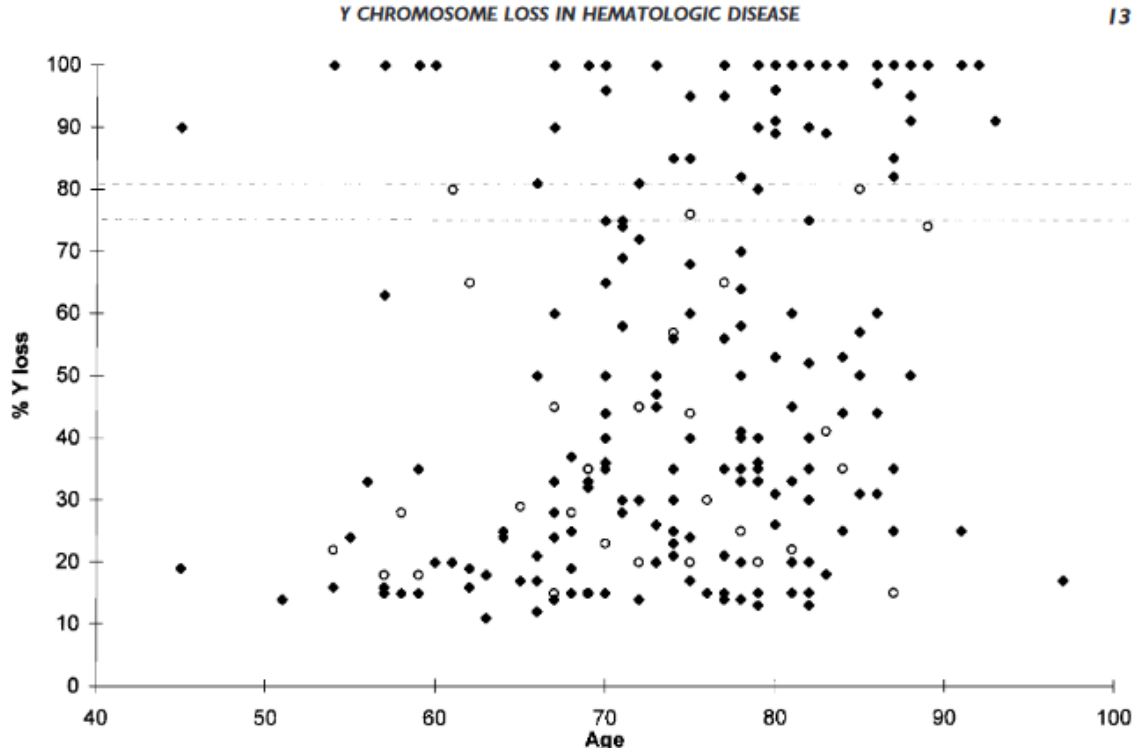
UKCCG, Genes Chromosomes Cancer 1992 ; Wiktor et al., Genes Chromosomes Cancer 2000 ; http://AtlasGeneticsOncology.com ; revue : Guo et al., Human Genetics 2020



Guttenbach et al., Am J Hum Genet 1995

<15 ans: 0,05% cellules

76-80 ans : 1,34% cellules



« controls »

TABLE 3. Association of 75% Y Chromosome Loss with Diagnosis (n = 215)

Group	>75% loss	OR (95% CI)	*P* value	OR (95% CI)[a]	*P* value[a]
Controls (n = 30)	10.0[b]	1.0		1.0	
MDS/RA/CMML (n = 109)	31.2	4.1 (1.2–14.3)	0.028	3.3 (0.9–12.0)	0.070
AML (n = 7)	42.9	6.8 (1.0–45.8)	0.051	6.7 (1.0–46.0)	0.052
MPD/CGL/PV (n = 42)	26.2	3.2 (0.8–12.7)	0.098	3.2 (0.8–12.6)	0.104
B-cell lymphomas and leukemia (n = 27)	22.2	2.6 (0.6–11.5)	0.217	2.7 (0.6–12.1)	0.204
All Cases (n = 185)	29.2	3.7 (1.1–12.7)	0.037	3.4 (1.0–11.8)	0.055

[a]Age-adjusted.
[b]Percent of group with >75% Y loss.

Wiktor et al., Genes Chromosomes Cancer 2000

- Mosaïcisme somatique : perte de l'Y : le plus fréquent

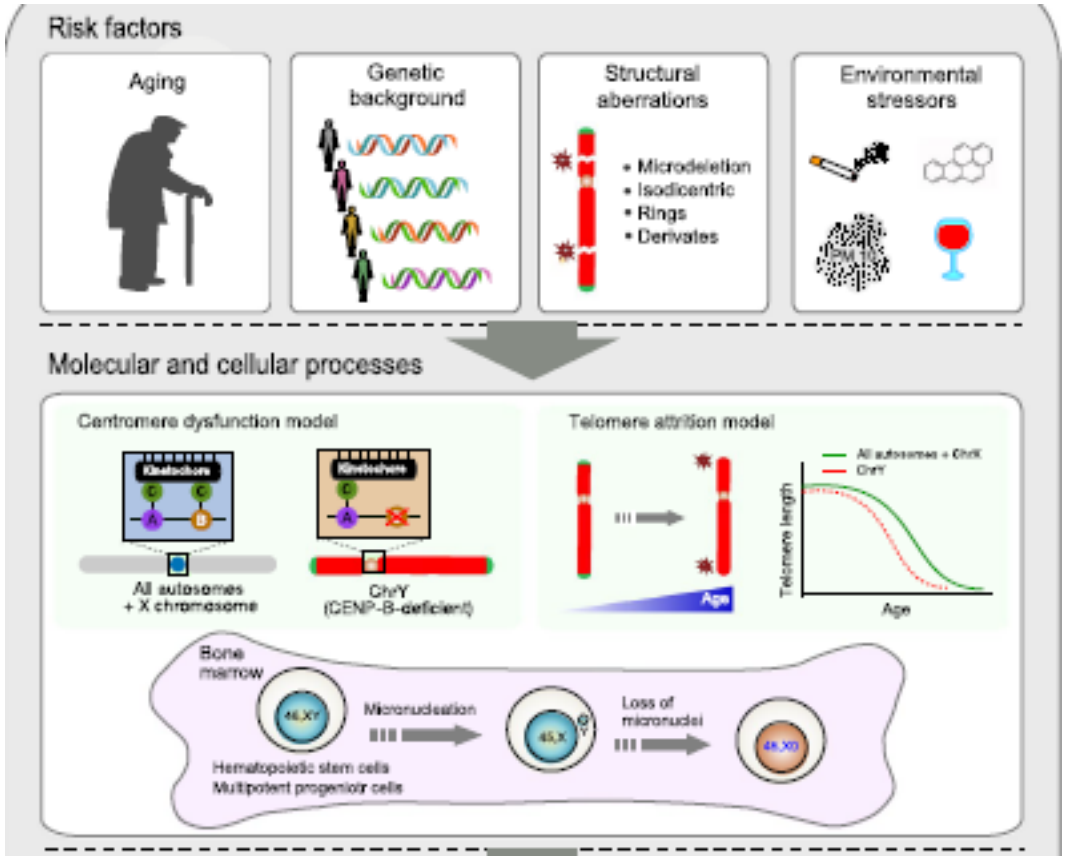
- Aucun gène sur le Y n'est essentiel pour la viabilité des cellules (femmes vivent sans Y )

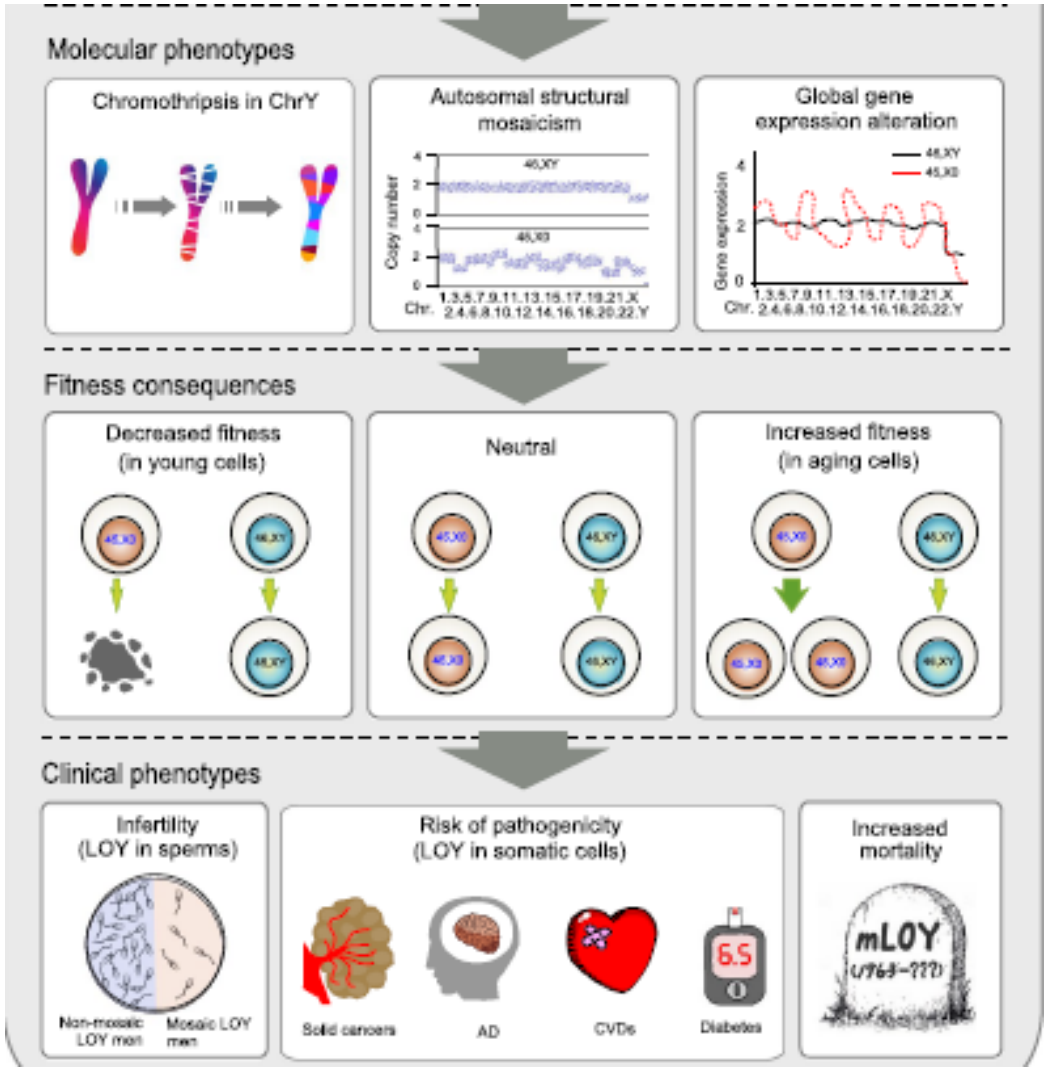
- Facteur de risque :
  - âge +++
  - gènes de susceptibilité
  - tabac, hydrocarbures aromatiques, insecticides, alcool, obésité

- Maladies en relation avec l'âge : cancer, Alzheimer, diabète, maladies cardio-vasculaires

- Hématopoïèse clonale

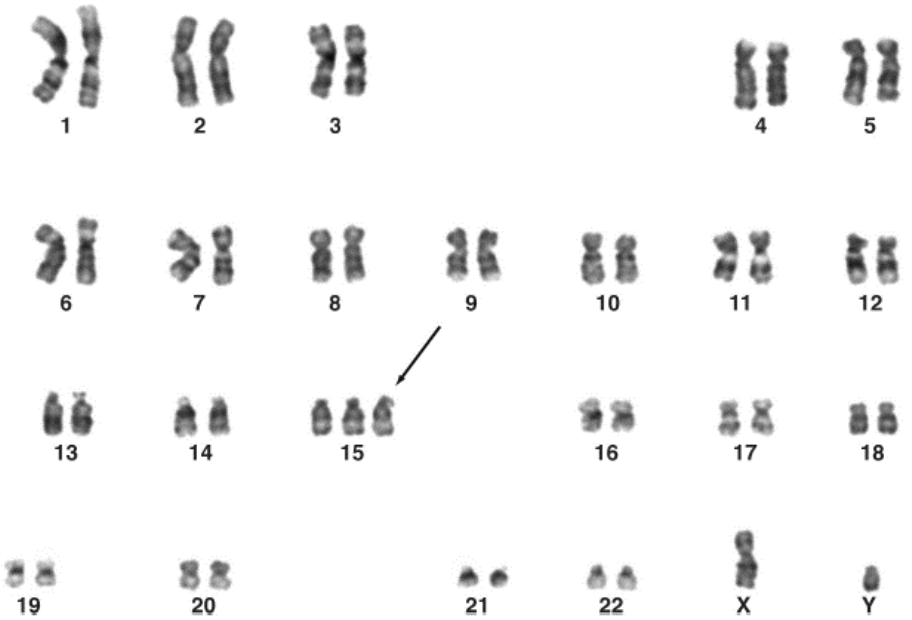
Guo et al., Human Genetics 2020

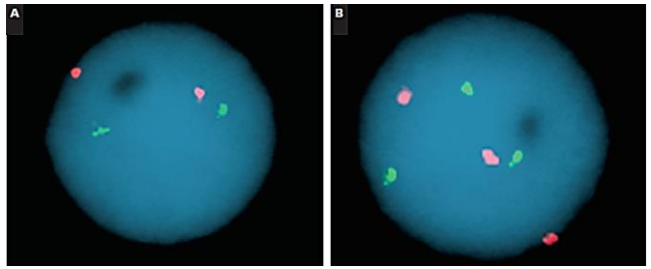




Guo et al., Human Genetics 2020

Trisomie 15





RP11-28912 (15q11.2)+RP11-348A14/RP11-42K15 (15q21.1)

Hanson et al., Am J Clin Pathol 2008

Trisomie 15

- Anomalie non spécifique (LAM, LAL, MDS, LLC, myélome…)
- Isolée : Liée à l'âge ?
  - Patient âgé (≥ 65 ans)
  - Clone mineur
  - Souvent associée à –Y
  - N'est pas considérée comme une évidence définitive de MDS ?
  - >55% des cellules : signification ?

Goswani et al., Leuk Res 2015 ; Hanson et al., Am J Clin Pathol 2008 ; Batanian et al., Cancer Genet Cytogenet 2000 ; Sinclair et al., Cancer Genet Cytogenet 1998 ; Smith et al., Cancer Genet Cytogenet 1996 ; http://AtlasGeneticsOncology.com

2012-2021 Pitié-Salpêtrière

9 patients avec tri15

Pathologie	Age	Echantillon	caryotype	FISH (interphase)	Conclusion
Pancytopénie (myélome)	70	Moelle	47,XX,+15[2]/46,XX[18]	+15 : 37%	+15 isolée
MDS-MLD (LZM : CK sang)	86	Moelle	46,X,-Y,+15[11]/46,XY[9]	nd	+15, -Y Score IPSS : 0,5 Score IPSS-R : 2
MDS-MLD	84	Moelle	46,X,-Y,+15[16]/46,XY[4]	nd	+15, -Y Score IPSS : 0,5 Score IPSS-R : 2
Cytopénie	88	Moelle	45,X,-Y[6]/47,XY,+15[2]/46,XY[12]	(+15 : 2/29 mitoses) -Y : 35%	+15, -Y clones indépendants
MW	80	Moelle	47,XY,der(6)t(3;6)(q11;q11),+15[7]/46,XY[13]	+15 : 12% ; -6q : 11% ; +3q : 8%	+15,+3q,-6q
LAM, MM, LZM, LB			complexes		