

Cartographie optique du génome dans des leucémies aiguës myéloïdes non caractérisées

GFCH
Jeudi 1^{er} février
Laureen Chat

Sélection des cas

Inclusion des cas de juillet 2016 à octobre 2023

- Critères d'inclusion :
LAM au diagnostic ou en rechute avec % blastes > 20%
- 964 Patients de SLS : Adolescent → Sénior
De 16 à 99 ans
Moyenne : 66 ans ; Médiane : 72 ans
N=437 femmes (46%) et n=527 hommes (54%)
- Classification selon l'OMS 2022
- Sélection des LAM non caractérisées

Sélection des cas

		Number of patients	% of patients
Defining cytogenetic or molecular abnormalities	AML-MR **	498	52
	<i>NPM1</i>	232	24
	CBFB::MYH11	40	4
	<i>DDX41</i>	29	3
	<i>RUNX1::RUNX1T1</i>	30	3
	KMT2A-r	29	3
	<i>CEBPA</i>	23	2
	<i>BCR::ABL1</i>	14	1
	<i>MECOM</i> -r	12	1
	NUP98-r	5	1
	<i>PML::RARA</i>	2	<1
	<i>UBTF</i>	3	<1
	<i>DEK::NUP214</i>	1	<1
	<i>NPM1::MLF1</i>	1	<1
No defining genetic abnormality / AML defined by differentiation		45	5
total		964	100%

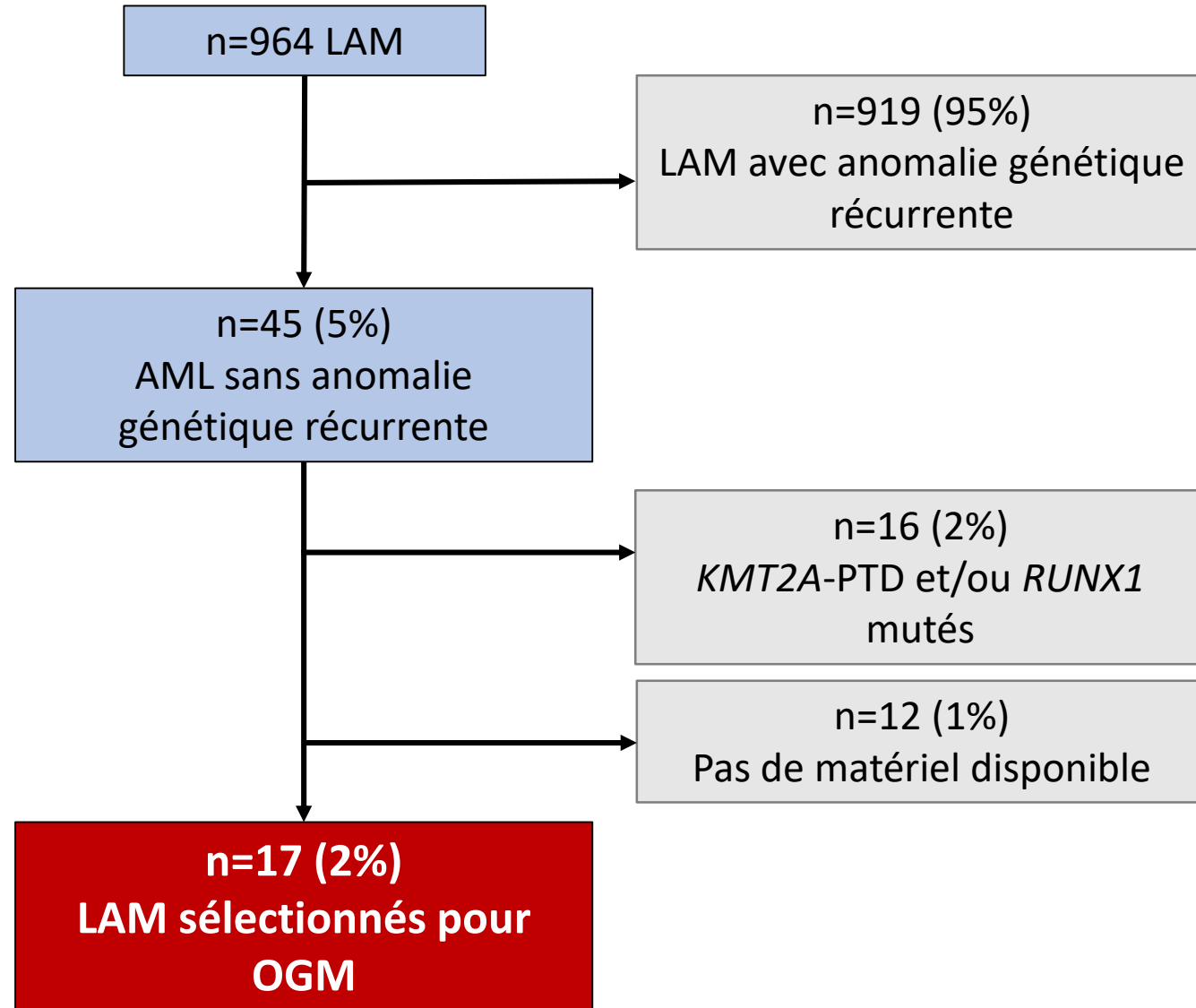
- AML-MR AML : Myelodysplasia-related
- AML with germline pathogenic and somatic *DDX41* variant
- AML with *CEBPA* inframe insertion or deletion in bZip domain.
- AML with *UBTF* tandem duplication

Sélection des cas

AML-MR **		
	Number of patients	% of patients
Gene mutation and/or defining cytogenetic abnormalities (without CK)	338	69
Complex karyotype + <i>TP53</i> bi-allelic alteration	121	25
CK + <i>TP53</i> wt	34	7
CK + <i>TP53</i> mono-allélique	5	1
Total	498	

- Gene mutation in AML-MR group is characterized by ≥ 1 mutations in : *ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*.
- Cytogenetic alteration defining AML-MR :
 - 5q deletion or loss of 5q,
 - monosomy 7, 7q deletion,
 - 11q deletion,
 - 12p deletion,
 - monosomy 13 or 13q deletion,
 - isochromosome 17q,
 - idic(X)(q13).
- Complex karyotype (CK) is defined by ≥ 3 abnormalities in absence of recurrent translocation and hyperdiploid karyotype (>49 chromosomes)

Sélection des cas

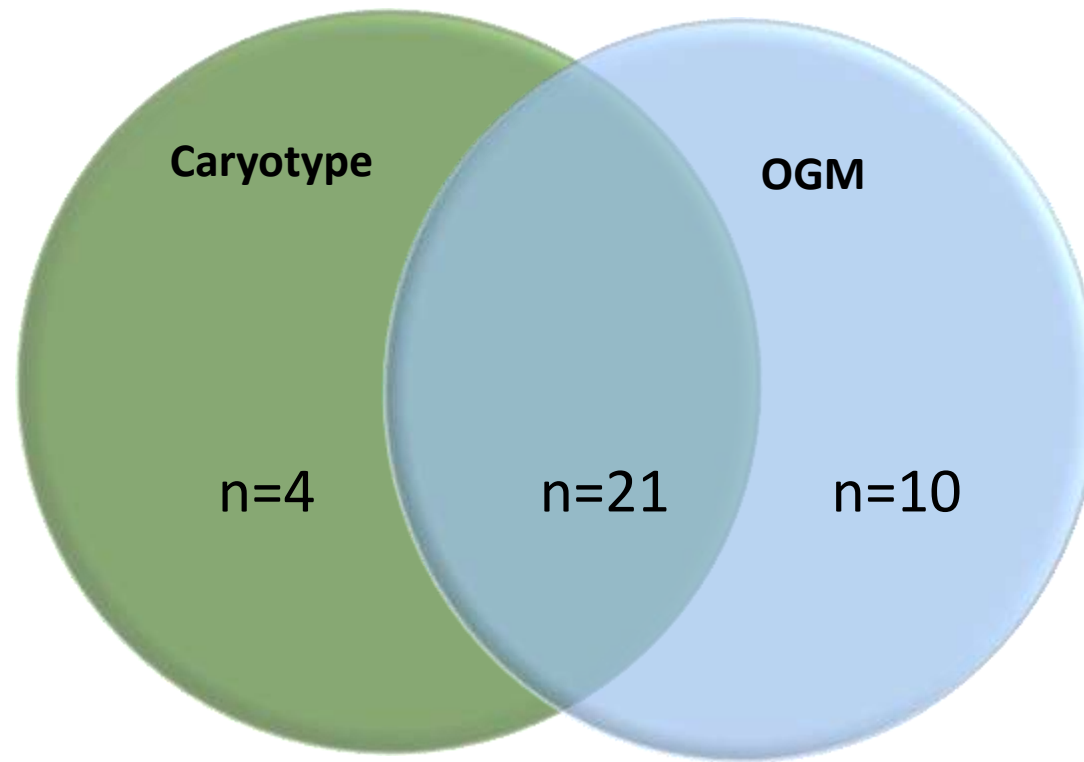


Description des 17 cas

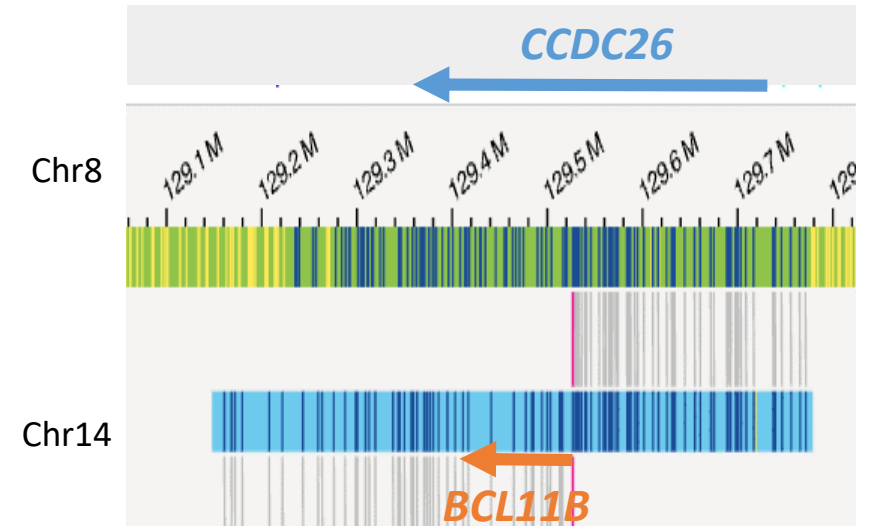
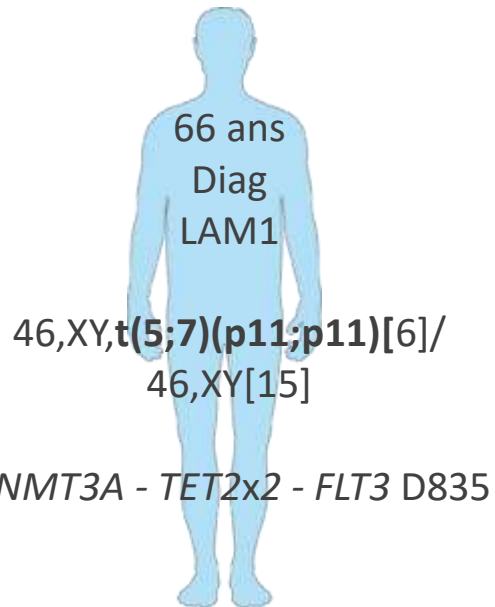
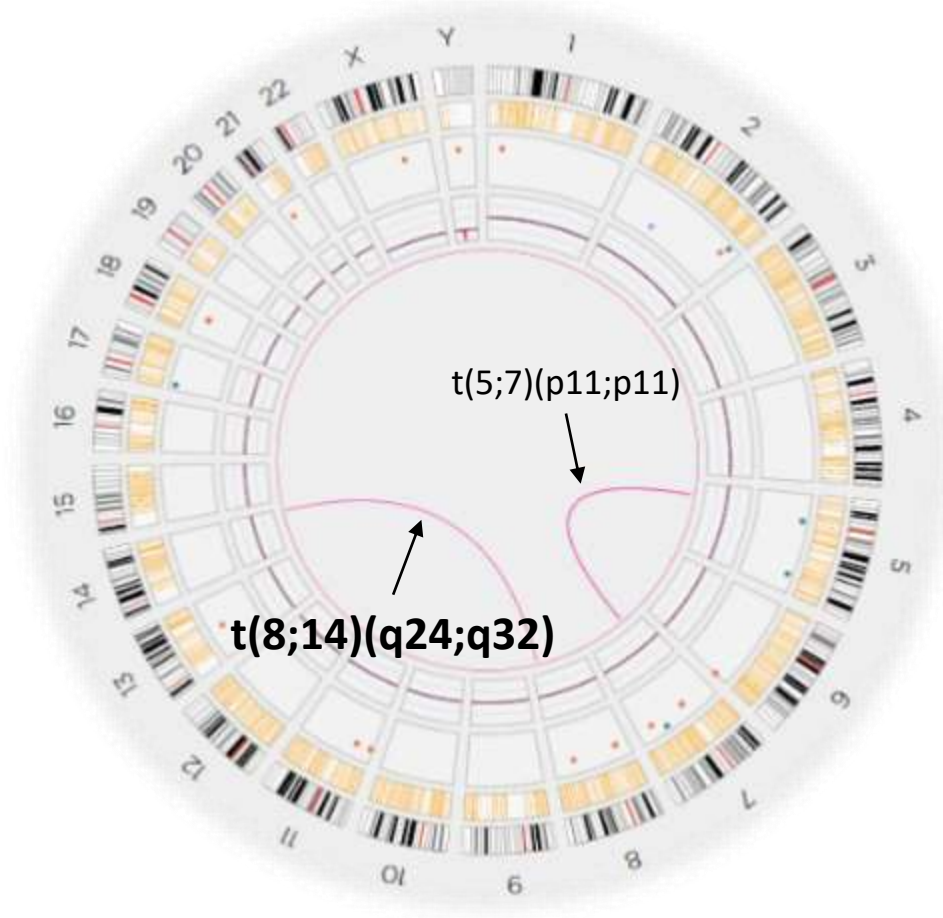
N°Cas	Sexe	Age (ans)	Diag / Rechute	% Blastés	FAB	Caryotype	Gènes mutés
1	M	66	D	77	LAM1	46,XY,t(5;7)(p11;p11)[6]/46,XY[15]	DNMT3A, TET2x2, FLT3 TKD
2	M	44	D	92	LAM0	46,XY[20]	FLT3
3	F	74	R	25	LAM2	6,XX,ins(9;?)(q1?2;?)[3]/46,XX[17]	RAD21, TET2
4	M	54	D	92	LAM0	47,XY,+8[20]/48,idem,+21[4]/46,XY[2]	IDH1, DNMT3A, PFH6
5	F	31	D	74	LAM4	46,XX,t(5;6)(q3?4;p?21)[11]	FLT3
6	M	25	D	82	LAM5	46,XY[20]	WT1, FLT3 ITD
7	F	25	D	56	LAM4	46,XX,?del(9)(q1?1q1?2)	FLT3, IDH1, IDH2, NRAS RIT1
8	F	40	R	94	LAM5	47,XX,+8[21]	WT1, FLT3 TKD & ITD
9	M	25	R	92	LAM1	46,XY,del(11)(p1?1p1?5)[21]/46,XY[1]	FLT3, WT1, PHF6
10	M	67	D	87	LAM0	48,XY,+10,+19,inc[20]	PHF6, FLT3
11	F	58	D	80	LAM5	46,XX[40]	WT1x4, FLT3 ITD
12	F	27	D	28	LAM0	57,XX,i(7)(q10)[14],+3,+8,+8,+9,+10,+11,+12,+13,+?14 or mar,+19,+20[cp19]/46,XX[1]	Absence
13	M	37	D	94	LAM5	47,XY,+?8[4]	FLT3 ITD
14	F	57	D	57	LAM2	47,XX,+4[30]	TET2, WT1
15	M	89	D	47	LAM5	47,XY,+8[3]/46,XY[27]	TET2x2, BRAF, CTCF, PHF6
16	M	30	D	54	LAM4	46,XY[23]	ASXL2, IDH2, DNMT3A
17	M	41	D	33	LAM2	46,XY[20]	WT1, FLT3

Analyse des variants retrouvés en OGM

Au total 35 SVs ont été retrouvés



Une translocation cryptique au caryotype → *BCL11B-r*



Une translocation cryptique au caryotype → *BCL11B-r*



HHS Public Access

Author manuscript

Cancer Discov. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Cancer Discov. 2021 November ; 11(11): 2846–2867. doi:10.1158/2159-8290.CD-21-0145.

Enhancer hijacking drives oncogenic *BCL11B* expression in lineage ambiguous stem cell leukemia

A full list of authors and affiliations appears at the end of the article.

These authors contributed equally to this work.



LAM avec réarrangement de *BCL11B*

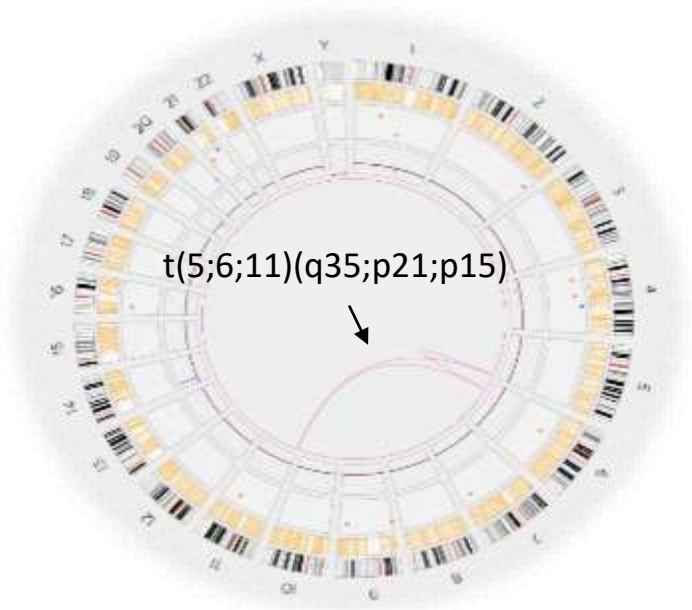
LAM M0 M1

LAL T

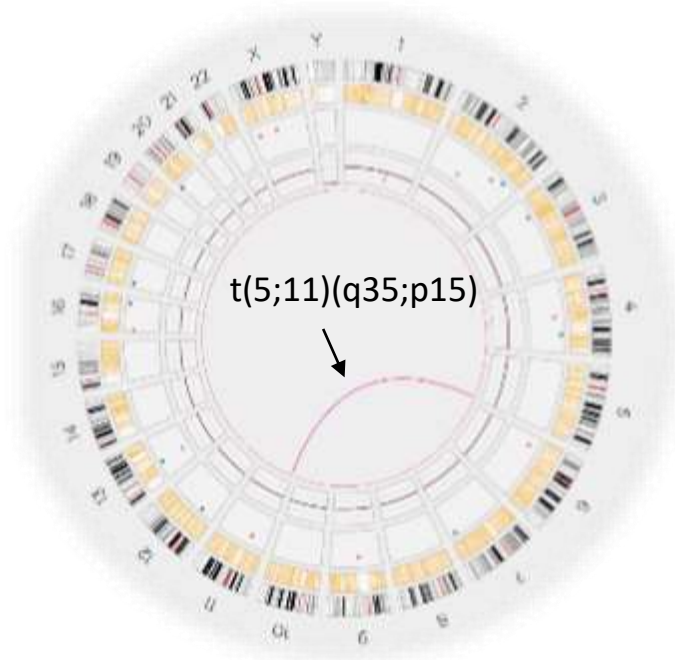
LAL ETP

Mutations associés ++ : *WT1*, *DNMT3A*, *TET2*

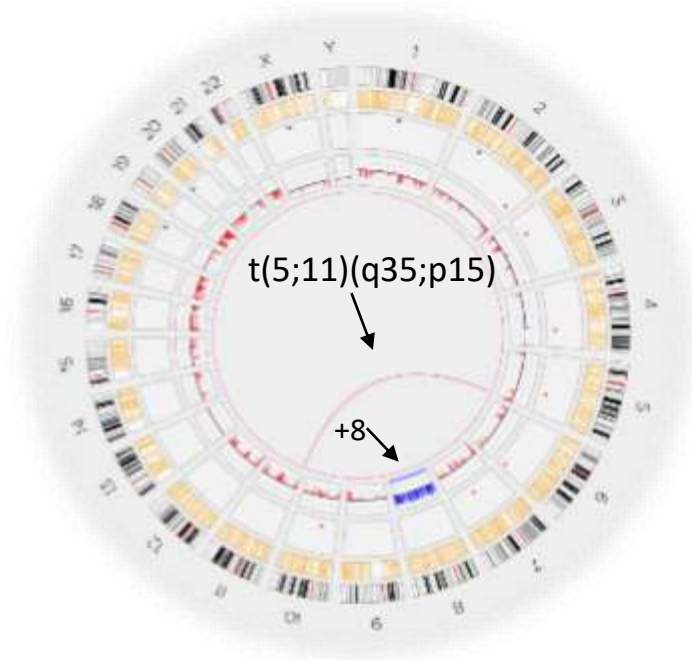
3 cas de translocations cryptiques



31 ans
Diag
LAM4
46,XX,t(5;6)(q3?4;p?21)[11]
FLT3 ITD
Décès 5 mois post diag

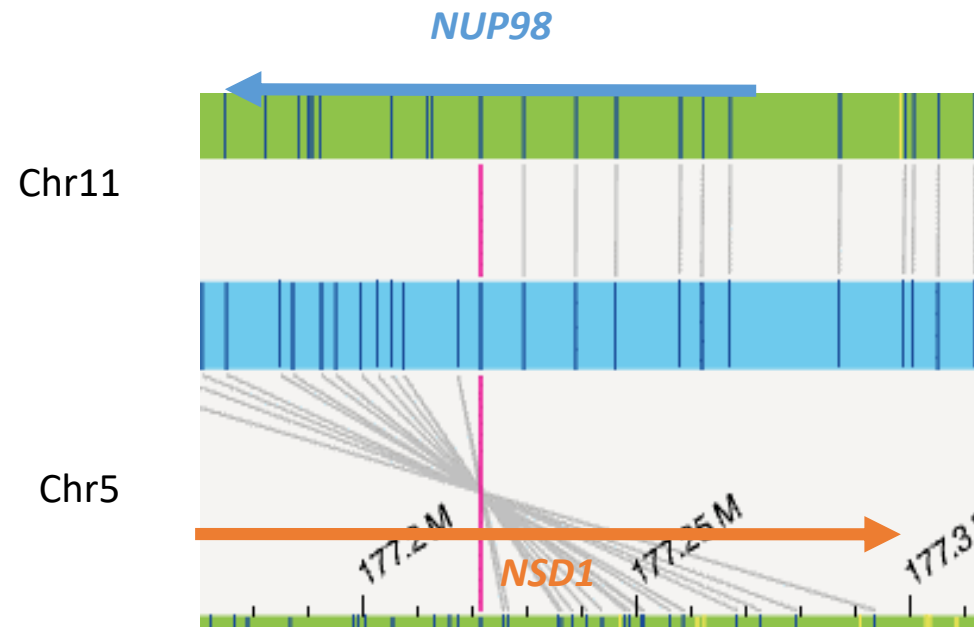
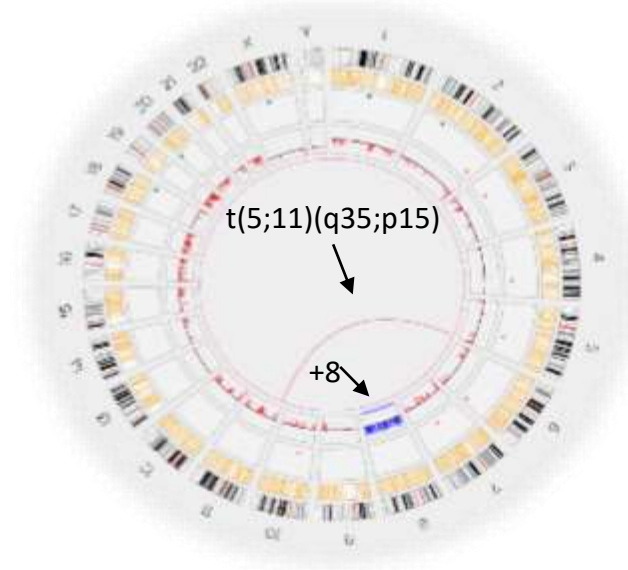
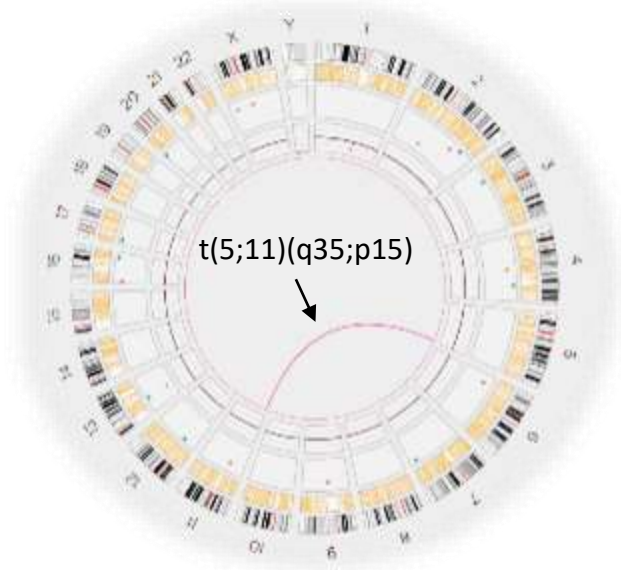


59 ans
Diag
LAM 4
46,XX[40]
FLT3 ITD, *WT1*
Décès 9 mois post diag



37 ans
Diag
LAM4
47,XX,+8[4]
FLT3 ITD
Décès avant induction

3 cas de translocations cryptiques → réarrangement de *NUP98*



LAM avec remaniement de *NUP98*

- *NUP98* : 28 genes partenaires recensés
- *NUP98::NSD1* : Translocation cryptique au caryotype → Intérêt ++ FISH *NUP98*

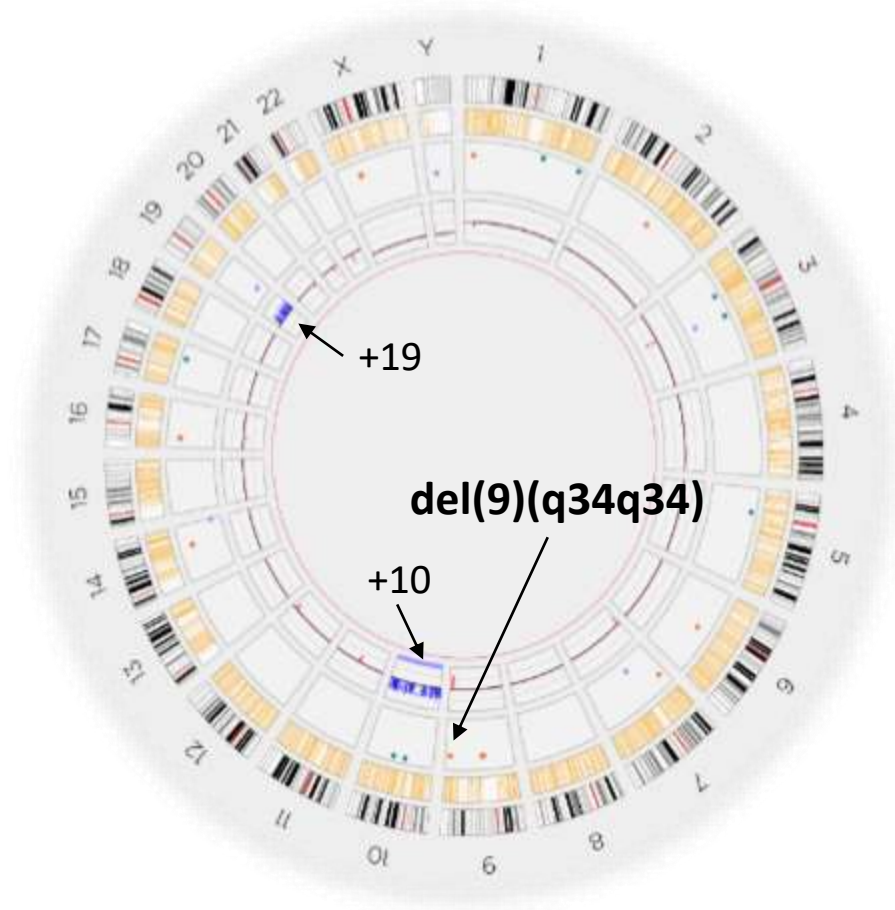
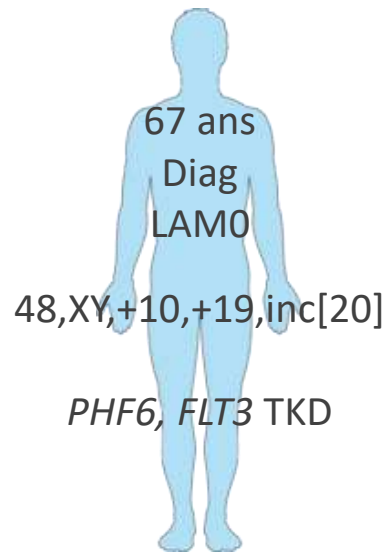
Pédiatrie : 3,8% des LAM et 16,1% des LAM à CN

FISH systématique protocolaire → Mauvais pronostic → Greffe

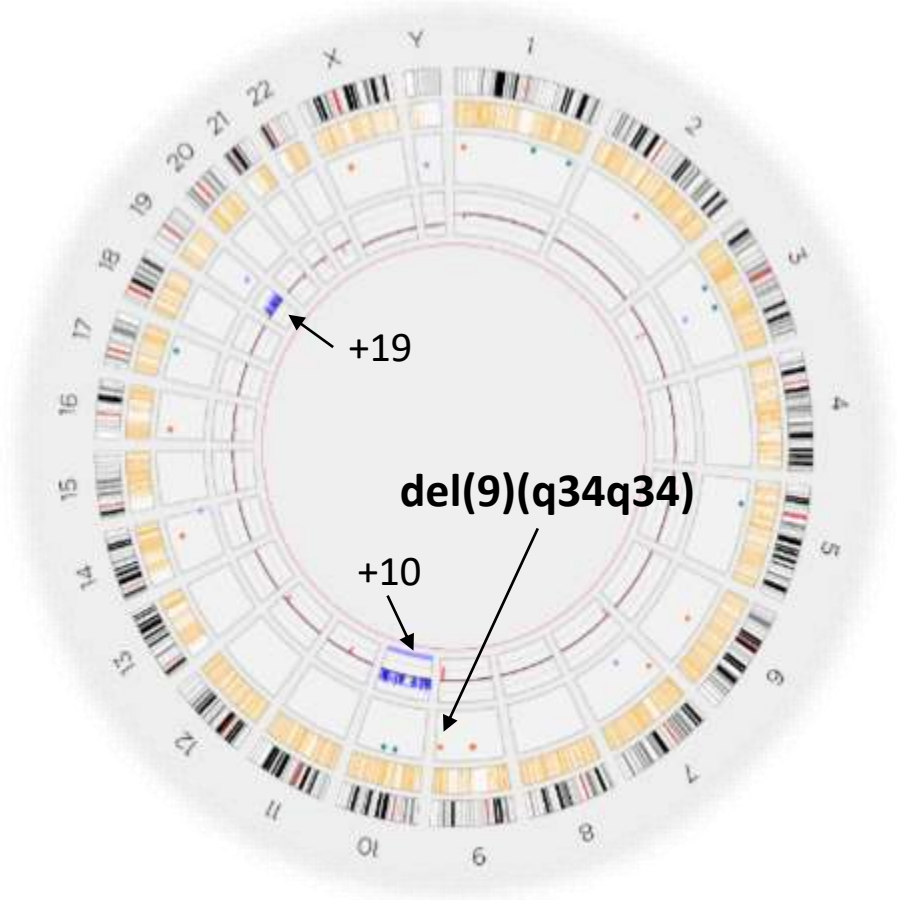
Adultes : 1,5% des LAM

- Caractéristiques des cas de LAM *NUP98* :
 - Âge des patients <40 ans
 - FAB M4/M5
 - FLT3*-ITD ++
 - Mutations *WT1*
 - Pronostic défavorable (Rechute / Réfractaires) mais intermédiaire selon ELN 2022.

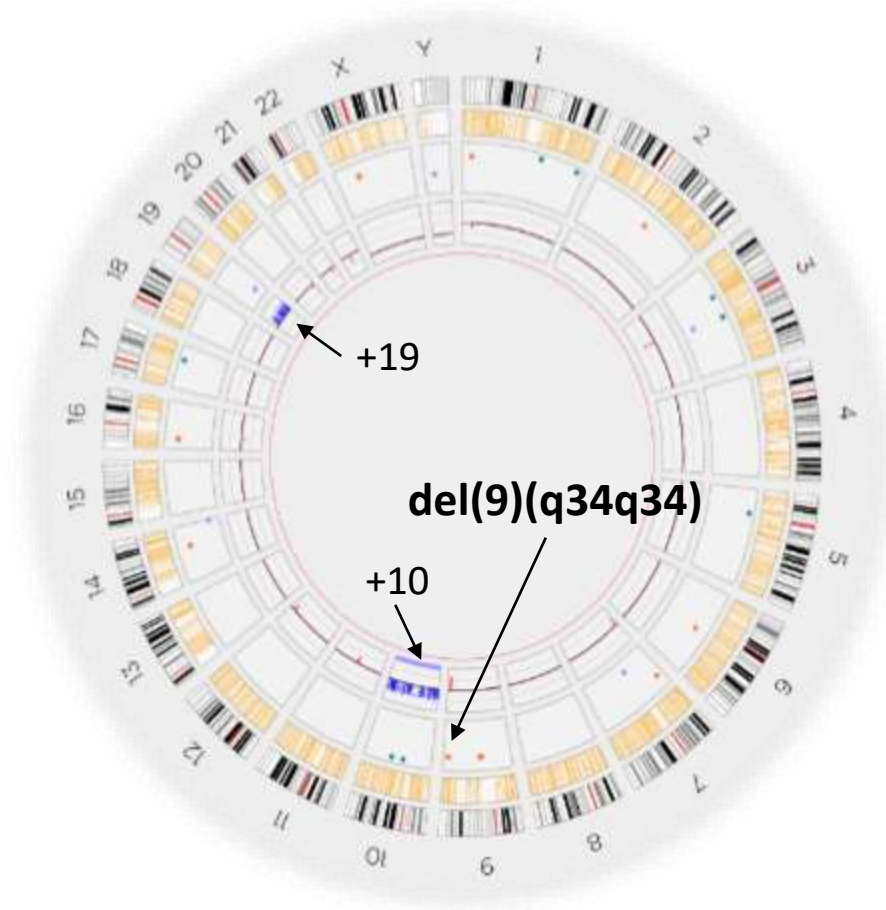
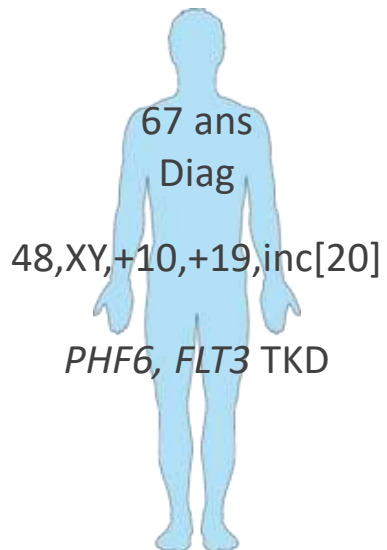
Une délétion cryptique



Une délétion cryptique → SET::NUP214



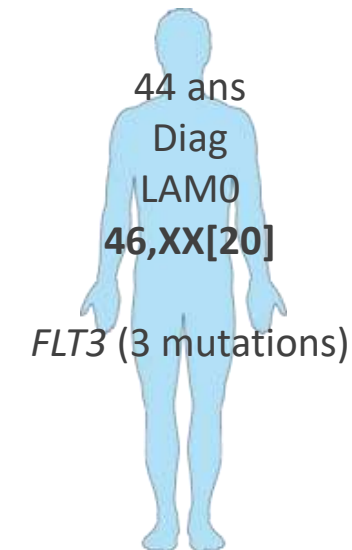
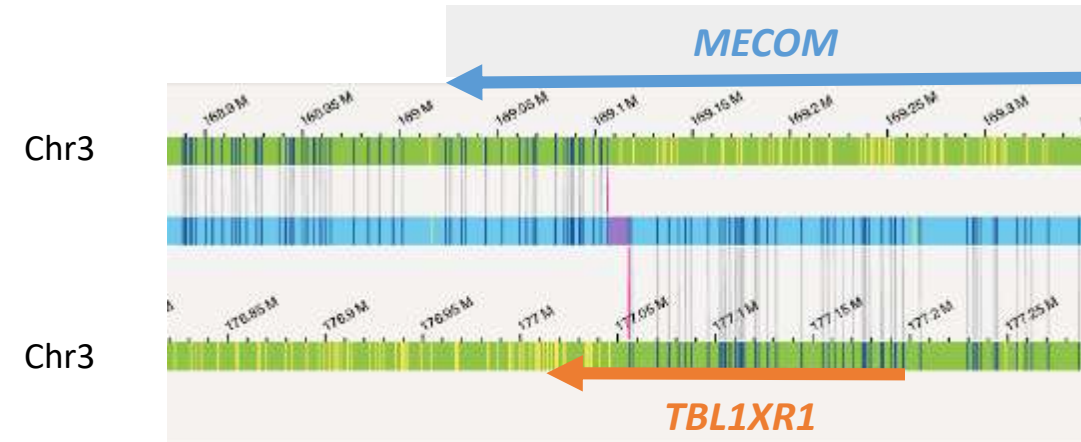
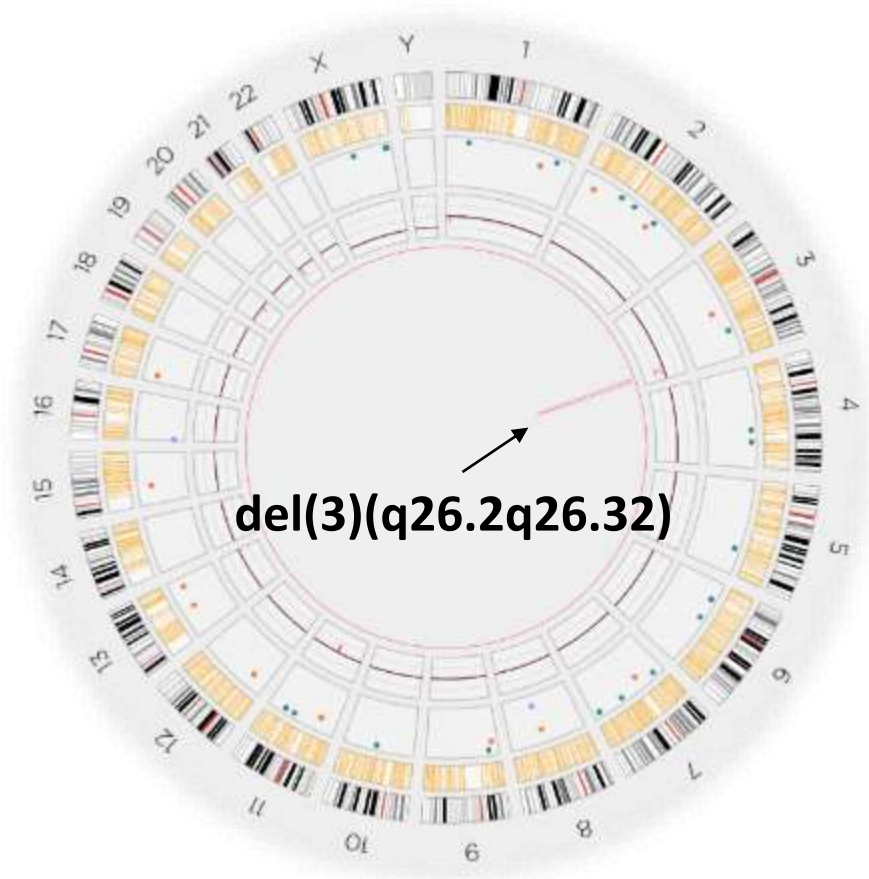
Une délétion cryptique → SET::NUP214



SET-NUP214

- LAL-T
- LAL-ETP (Early T-cell Precursor)
- **LAM : très rare**
- ++ associés aux mutations de *PHF6*
- Mauvais pronostic
- Intérêt de l'allogreffe

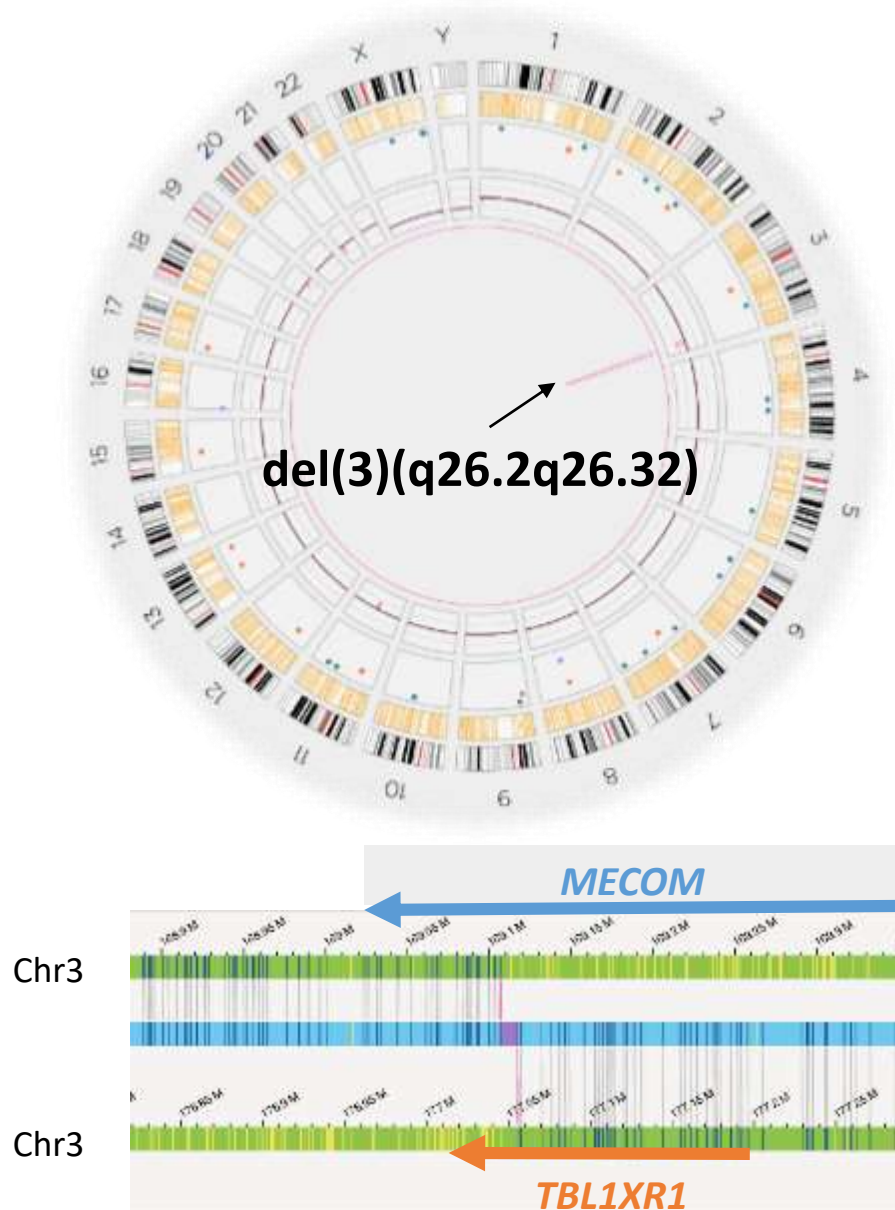
Une délétion cryptique → Transcrit MECOM::TBL1XR1



Une délétion cryptique → Transcrit MECOM::TBL1XR1

Transcrit TBL1XR1::MECOM

- Partie N-term *TBL1XR1* + C-term *MECOM*
 - Réarrangements de *MECOM* : Hyperexpression de *MECOM*
 - *TBL1XR1* :
LAM Promyélocytaire (fusion avec *RARA*),
LAL-B : délétions fréquentes dans les *TEL::AML1*
- MECOM::TBL1XR1 : mécanisme d'action inconnu



S Groeschel, Cell, 2014

J Yi Li et al, AM J Clin Exp Urol, 2015

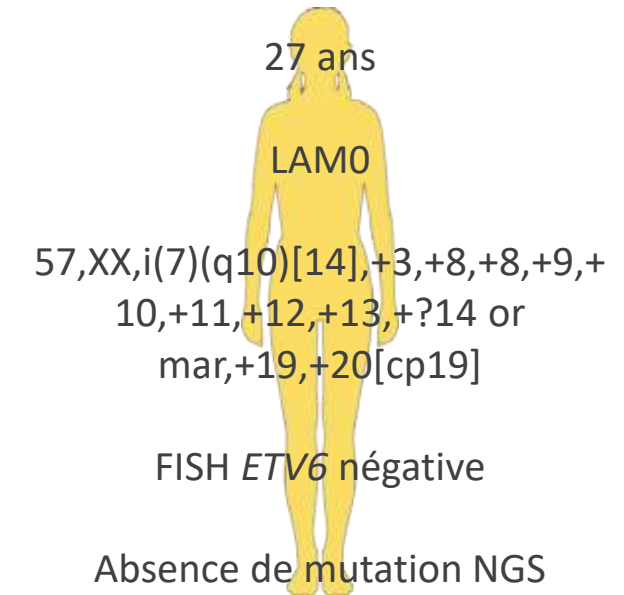
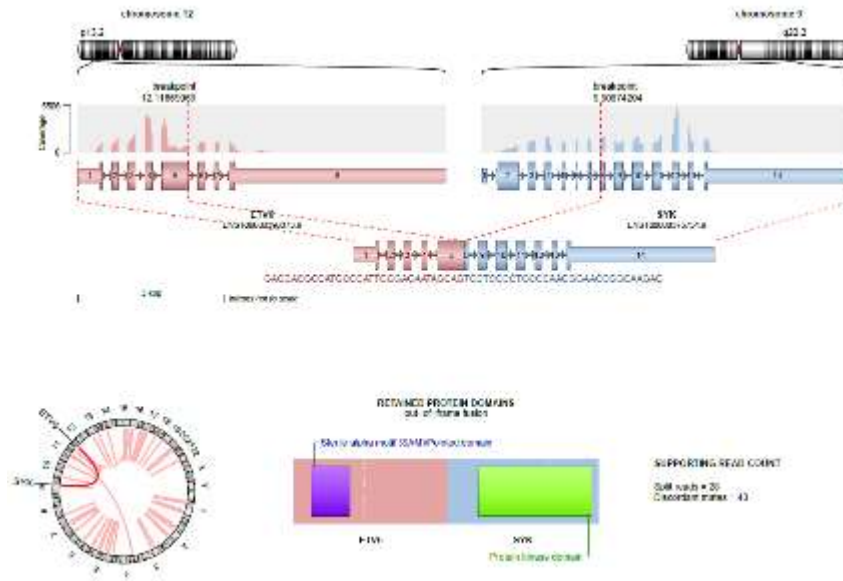
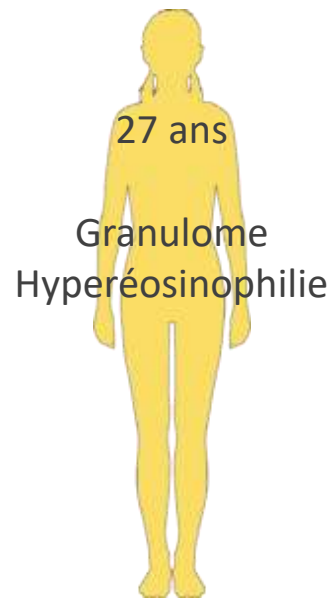
H Parker et al, genes chromosome cancer, 2008

Une insertion cryptique

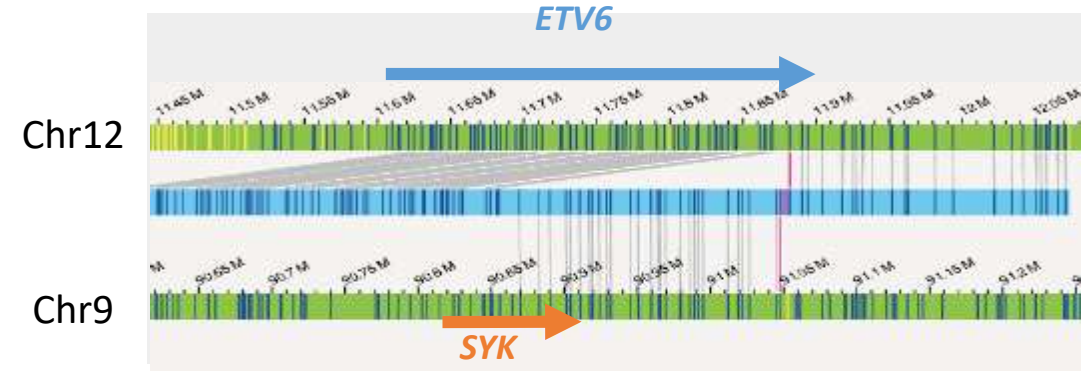
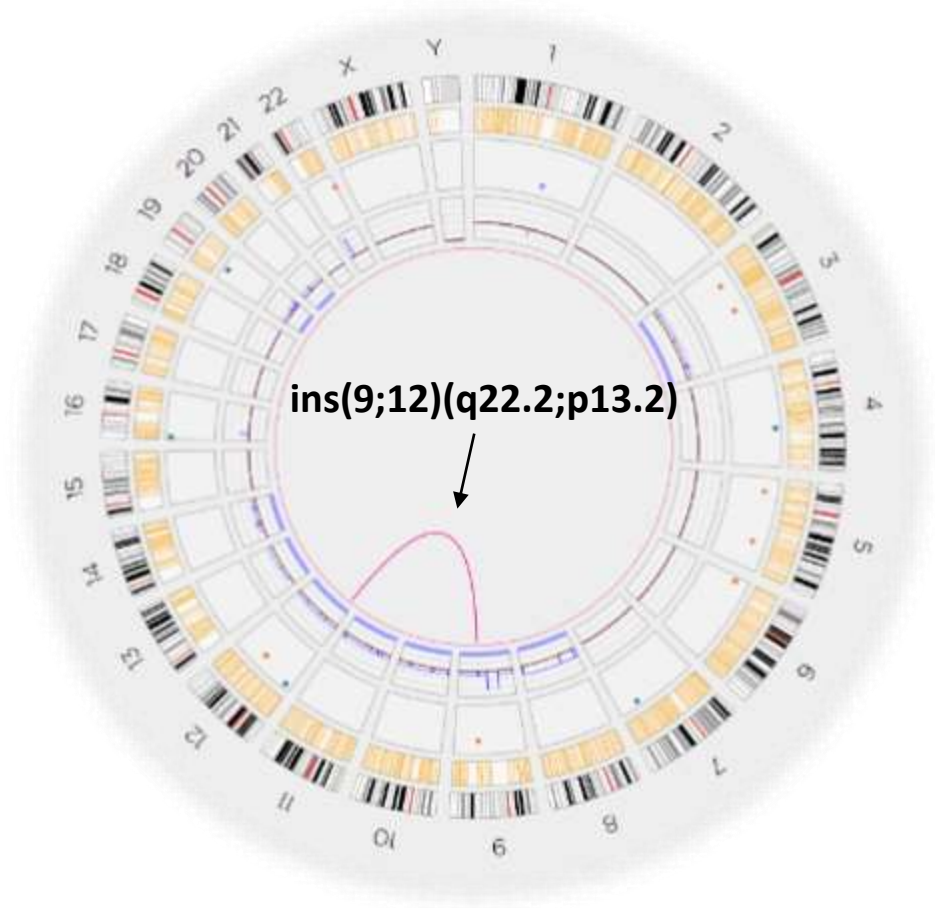
Juillet 2021

Juin 2022

RNAseq lésion cutanée



Une insertion cryptique → Transcrit ETV6::SYK



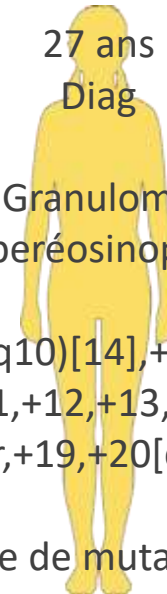
27 ans

Diag

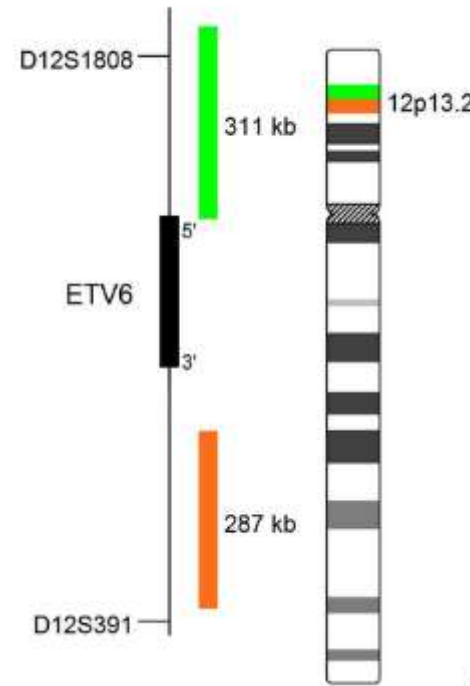
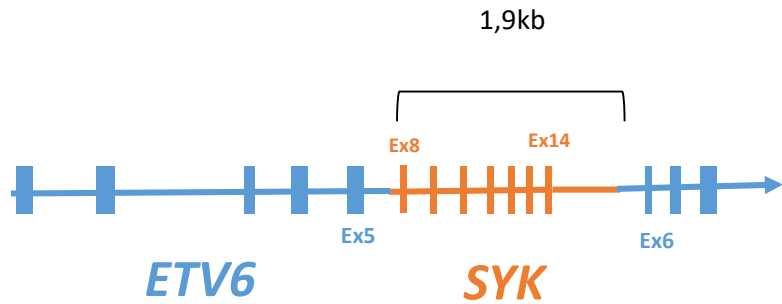
Granulome
Hyperéosinophilie

57,XX,i(7)(q10)[14],+3,+8,+8,+9,+
10,+11,+12,+13,+?14 or
mar,+19,+20[cp19]

Absence de mutation NGS



Une insertion cryptique → Transcrit ETV6::SYK



Remaniement d'ETV6 cryptique en FISH

Une insertion cryptique → Transcrit ETV6::SYK

blood

2001 97: 1050-1055
doi:10.1182/blood.V97.4.1050

Constitutive kinase activation of the *TEL-Syk* fusion gene in myelodysplastic syndrome with t(9;12)(q22;p12)

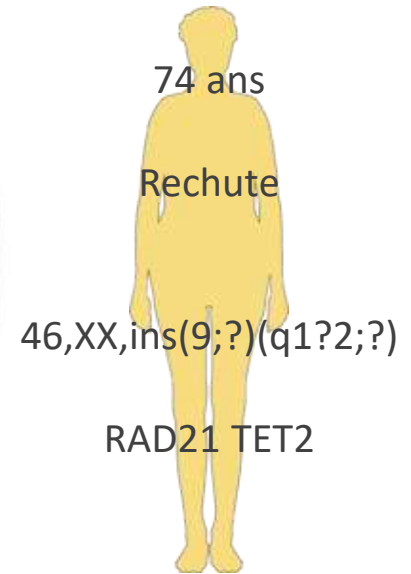
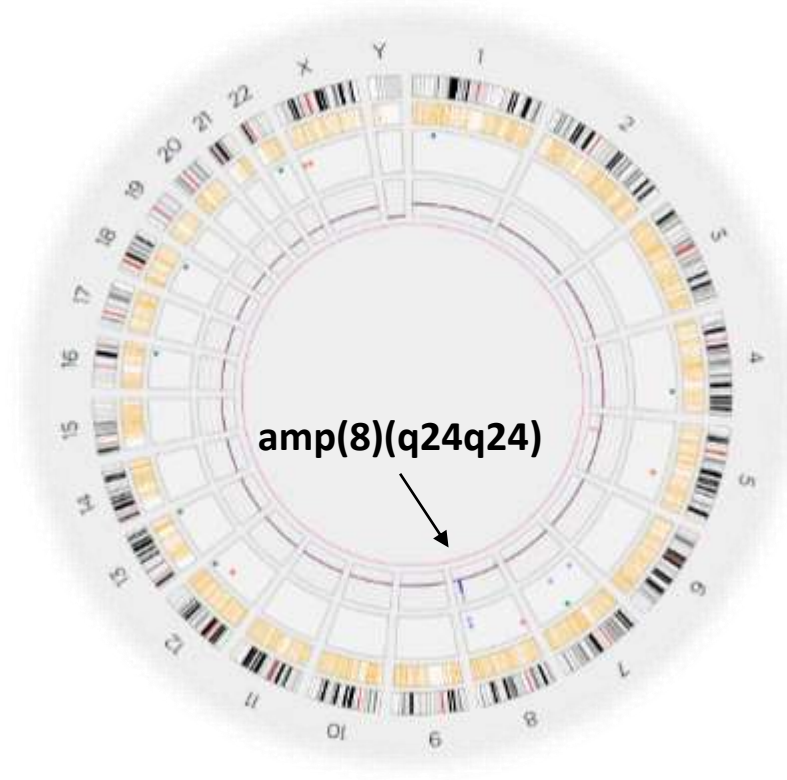
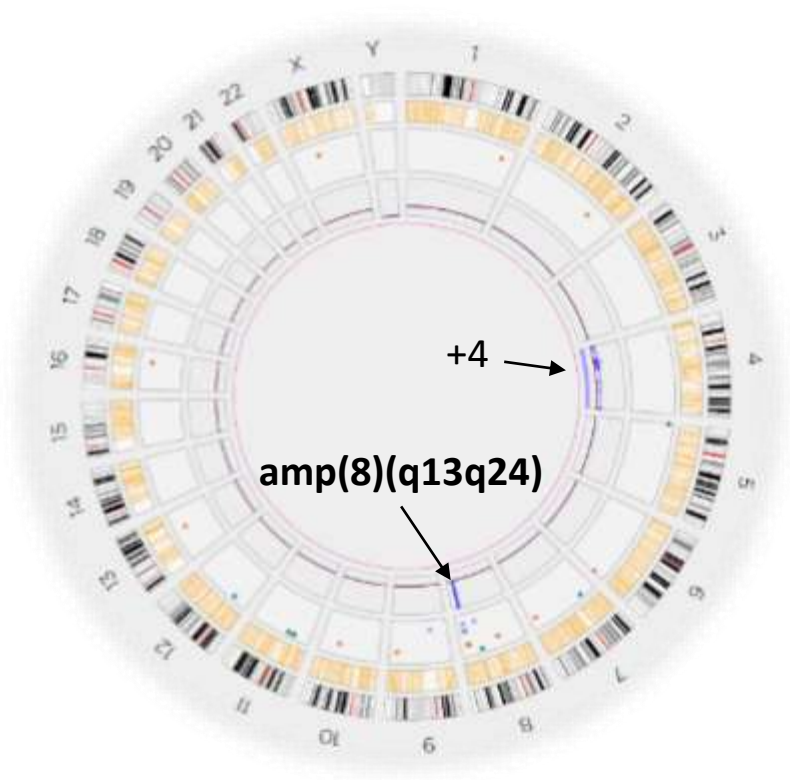
Yoshie Kuno, Akihiro Abe, Nobuhiko Emi, Minako Iida, Toshiya Yokozawa, Masayuki Towatari, Mitsune Tanimoto and Hidehiko Saito

- Toux, **lésions cutanées**
- SMD avec **hyperéosinophilie**
- Evolution rapide en LAM
- t(9;12)(q22;p12)
- FISH : **rearrangement d'ETV6**

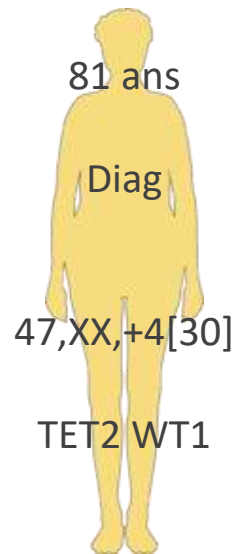
Transcrit ETV6-SYK

- **Activité constitutive SYK (Tyrosine Kinase)**
- **PEC : Inhibiteur de SYK : Fostamatinib**

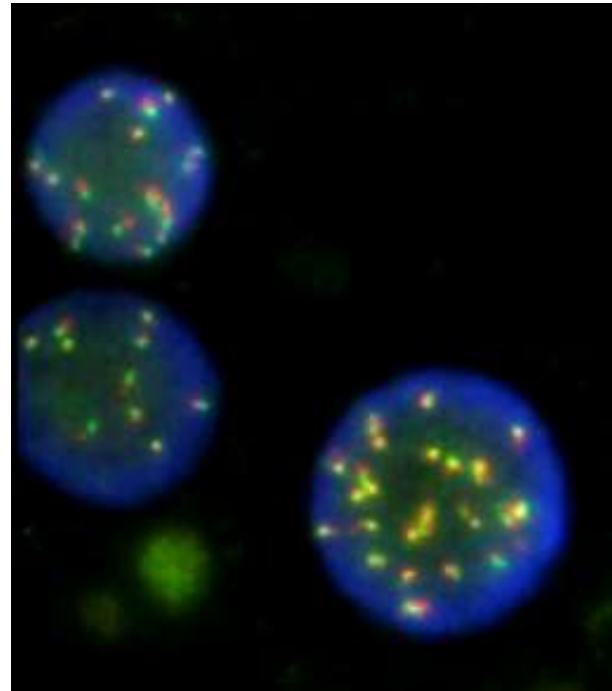
Deux cas d'amplification 8q



Deux cas d'amplification 8q → *MYC* amp



FISH interphasique



→ Amplification de *MYC* sous forme d'épisomes

Amplification de *MYC* dans les LAM

Leukemia (2018) 32:2152–2166
<https://doi.org/10.1038/s41375-018-0033-0>

ARTICLE

Acute myeloid leukemia

Corrected: Correction



***MYC*-containing amplicons in acute myeloid leukemia: genomic structures, evolution, and transcriptional consequences**

Alberto L'Abbate¹ · Doron Tolomeo¹ · Ingrid Cifola² · Marco Severgnini² · Antonella Turchiano¹ · Bartolomeo Augello³ · Gabriella Squeo³ · Pietro D'Addabbo¹ · Debora Traversa¹ · Giulia Daniele¹ · Angelo Lonoce¹ · Mariella Pafundi¹ · Massimo Carella³ · Orazio Palumbo³ · Anna Dolnik⁴ · Dominique Muehlethaler⁵ · Jacqueline Schoumans⁵ · Nadine Van Roy⁶ · Gianluca De Bellis² · Giovanni Martinelli⁷ · Giuseppe Merla³ · Lars Bullinger⁴ · Claudia Haferlach⁸ · Clelia Tiziana Storlazzi¹

- 8q24 amp (*MYC*, *TRIB1*)
- Mauvais pronostic
- Sujets âgés
- Amp ++ dans hsr dmin et ring
- +4

Bilan

Au total sur les 17 LAM non caractérisées passées en OGM :

- *BCL11B-r* (n=1)
 - *TBL1XR1::MECOM* (n=1)
 - *MYC* amplification (n=2)
 - *NUP98::NSD1* (n=3)
 - *SET::NUP214* (n=1)
 - *ETV6::SYK* (n=1)
- } n=9
- 3 patients → *UBTF*
 - 6 restent non caractérisés → NGS nouveau panel