Hôpitaux de Toulouse

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE
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Biologie des mutations IDH dans les hémopathies myéloïdes

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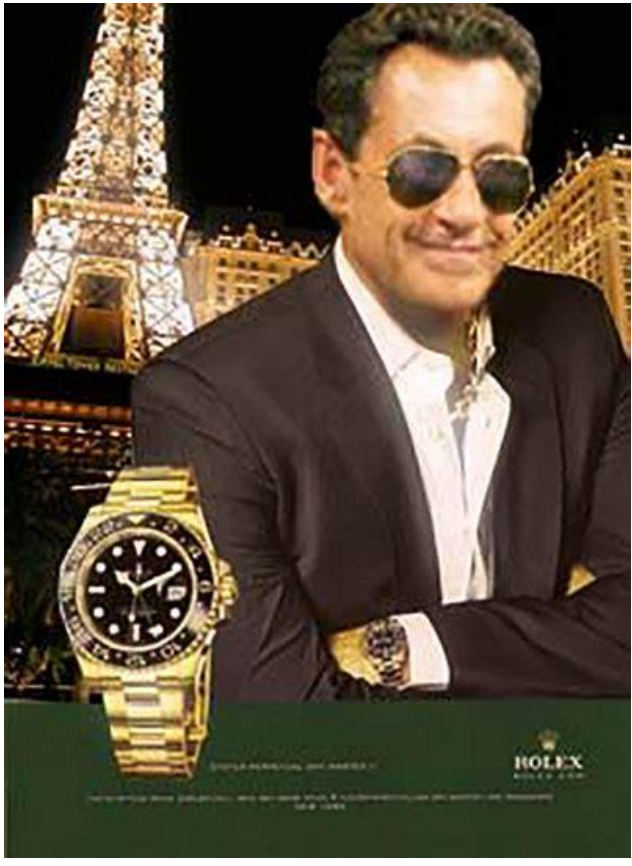
Conflits d’intérêt

- Même pas…

De la Rolex au clochard, 10 phrases cultes de Jacques Séguéla



Biologie des mutations IDH dans les hémopathies myéloïdes

LES MUTATIONS IDH

Mutations IDH1
Première dans le cancer colorectal

The Genomic Landscapes of Human Breast and Colorectal Cancers

Laura D. Wood,[1*] D. Williams Parsons,[1*] Siân Jones,[1*] Jimmy Lin,[1*] Tobias Sjöblom,[1*†] Rebecca J. Leary,[1] Dong Shen,[1] Simina M. Boca,[1,2] Thomas Barber,[1‡] Janine Ptak,[1] Natalie Silliman,[1] Steve Szabo,[1] Zoltan Dezso,[3] Vadim Ustyanksky,[3] Tatiana Nikolskaya,[3,4] Yuri Nikolsky,[3] Rachel Karchin,[5] Paul A. Wilson,[5] Joshua S. Kaminker,[6] Zemin Zhang,[6] Randal Croshaw,[7] Joseph Willis,[8] Dawn Dawson,[8] Michail Shipitsin,[9] James K. V. Willson,[10] Saraswati Sukumar,[11] Kornelia Polyak,[9] Ben Ho Park,[11] Charit L. Pethiyagoda,[12] P. V. Krishna Pant,[12] Dennis G. Ballinger,[12] Andrew B. Sparks,[12§] James Hartigan,[13] Douglas R. Smith,[13] Erick Suh,[13] Nickolas Papadopoulos,[1] Phillip Buckhaults,[7] Sanford D. Markowitz,[14] Giovanni Parmigiani,[1‖] Kenneth W. Kinzler,[1‖] Victor E. Velculescu,[1‖] Bert Vogelstein[1‖]

Human cancer is caused by the accumulation of mutations in oncogenes and tumor suppressor genes. To catalog the genetic changes that occur during tumorigenesis, we isolated DNA from 11 breast and 11 colorectal tumors and determined the sequences of the genes in the Reference Sequence database in these samples. Based on analysis of exons representing 20,857 transcripts from 18,191 genes, we conclude that the genomic landscapes of breast and colorectal cancers are composed of a handful of commonly mutated gene "mountains" and a much larger number of gene "hills" that are mutated at low frequency. We describe statistical and bioinformatic tools that may help identify mutations with a role in tumorigenesis. These results have implications for understanding the nature and heterogeneity of human cancers and for using personal genomics for tumor diagnosis and therapy.

table S3. Somatic mutations discovered in RefSeq genes

Gene	RefSeq Accession	Tumor	Tumor Type	Screen	Nucleotide (genomic)[#]	Nucleotide (cDNA)[§]	Amino acid (protein)[¶]
IDH1	NM_005896.2	Mx22	Colorectal	Discovery	g.chr2:208938619C>T	c.394C>T	p.R132C
IFNA2	NM_000605.2	B3C	Breast	Discovery	g.chr9:21374799C>T	c.530C>T	p.S177L
IFNB1	NM_002176.1	B9C	Breast	Discovery	g.chr9:21067377G>T	c.492G>T	p.W164C
IGFBP3	NM_000598.2	Hx218	Colorectal	Validation	g.chr7:45727781C>T	c.754C>T	p.R252C
IGFBP3	NM_000598.2	Mx27	Colorectal	Discovery	g.chr7:45733960C>T	c.20C>T	p.T7M
IGSF22	NM_173588	Mx27	Colorectal	Discovery	g.chr11:18693782G>A	c.1304G>A	p.R435H
IGSF22	NM_173588	Hx218	Colorectal	Validation	g.chr11:18694908G>A	c.1189G>A	p.G397S

Une mutation parmi 2694 autres

Wood LD et al. Science. 2007;318(5853):1108-13.

Mutations IDH1
Récurrence dans le glioblastome

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons,[1,2]* Siân Jones,[1]* Xiaosong Zhang,[1]* Jimmy Cheng-Ho Lin,[1]* Rebecca J. Leary,[1]* Philipp Angenendt,[1]* Parminder Mankoo,[3] Hannah Carter,[3] I-Mei Siu,[4] Gary L. Gallia,[4] Alessandro Olivi,[4] Roger McLendon,[5] B. Ahmed Rasheed,[5] Stephen Keir,[5] Tatiana Nikolskaya,[6] Yuri Nikolsky,[7] Dana A. Busam,[8] Hanna Tekleab,[8] Luis A. Diaz Jr.,[1] James Hartigan,[9] Doug R. Smith,[9] Robert L. Strausberg,[8] Suely Kazue Nagahashi Marie,[10] Sueli Mieko Oba Shinjo,[10] Hai Yan,[5] Gregory J. Riggins,[4] Darell D. Bigner,[5] Rachel Karchin,[3] Nick Papadopoulos,[1] Giovanni Parmigiani,[1] Bert Vogelstein,[1]† Victor E. Velculescu,[1]† Kenneth W. Kinzler[1]†

Glioblastoma multiforme (GBM) is the most common and lethal type of brain cancer. To identify the genetic alterations in GBMs, we sequenced 20,661 protein coding genes, determined the presence of amplifications and deletions using high-density oligonucleotide arrays, and performed gene expression analyses using next-generation sequencing technologies in 22 human tumor samples. This comprehensive analysis led to the discovery of a variety of genes that were not known to be altered in GBMs. Most notably, we found recurrent mutations in the active site of isocitrate dehydrogenase 1 (*IDH1*) in 12% of GBM patients. Mutations in *IDH1* occurred in a large fraction of young patients and in most patients with secondary GBMs and were associated with an increase in overall survival. These studies demonstrate the value of unbiased genomic analyses in the characterization of human brain cancer and identify a potentially useful genetic alteration for the classification and targeted therapy of GBMs.

Table 2. Most frequently altered GBM *CAN*-genes. All *CAN*-genes are listed in table S7.

Gene	Point mutations*		Amplifications†		Homozygous deletions†		Fraction of tumors with any alteration (%)	Passenger probability‡
	No. of tumors	Fraction of tumors (%)	No. of tumors	Fraction of tumors (%)	No. of tumors	Fraction of tumors (%)		
CDKN2A	0/22	0	0/22	0	11/22	50	50	<0.01
TP53	37/105	35	0/22	0	1/22	5	40	<0.01
EGFR	15/105	14	5/22	23	0/22	0	37	<0.01
PTEN	27/105	26	0/22	0	1/22	5	30	<0.01
NF1	16/105	15	0/22	0	0/22	0	15	0.04
CDK4	0/22	0	3/22	14	0/22	0	14	<0.01
RB1	8/105	8	0/22	0	1/22	5	13	0.03
IDH1	12/105	11	0/22	0	0/22	0	11	<0.01
PIK3CA	10/105	10	0/22	0	0/22	0	10	0.10
PIK3R1	8/105	8	0/22	0	0/22	0	8	0.10

*Fraction of tumors with point mutations indicates the fraction of mutated GBMs out of the 105 samples in the Discovery and Prevalence Screens. CDKN2A and CDK4 were not analyzed for point mutations in the Prevalence Screen because no sequence alterations were detected in these genes in the Discovery Screen. †Fraction of tumors with amplifications and deletions indicates the number of tumors with these types of alterations in the 22 Discovery Screen samples. ‡Passenger probability indicates the probability obtained using the average of the lower and upper bound background mutation rates (*12*).

Table 4. Characteristics of GBM patients with IDH1 mutations

Patient ID	Patient age (years)*	Sex	Recurrent GBM†	Secondary GBM‡	Overall survival (years)§	IDH1 mutation		Mutation of TP53	Mutation of PTEN, RB1, EGFR, or NF1
						Nucleotide	Amino acid		
Br10P	30	F	No	No	2.2	G395A	R132H	Yes	No
Br11P	32	M	No	No	4.1	G395A	R132H	Yes	No
Br12P	31	M	No	No	1.6	G395A	R132H	Yes	No
Br104X	29	F	No	No	4.0	C394A	R132S	Yes	No
Br106X	36	M	No	No	3.8	G395A	R132H	Yes	No
Br122X	53	M	No	No	7.8	G395A	R132H	No	No
Br123X	34	M	No	Yes	4.9	G395A	R132H	Yes	No
Br237T	26	M	No	Yes	2.6	G395A	R132H	Yes	No
Br211T	28	F	No	Yes	0.3	G395A	R132H	Yes	No
Br27P	32	M	Yes	Yes	1.2	G395A	R132H	Yes	No
Br129X	25	M	Yes	Yes	3.2	C394A	R132S	No	No
Br29P	42	F	Yes	Unknown	Unknown	G395A	R132H	Yes	No
IDH1 mutant patients (n=12)	33.2	67% M	25%	42%	3.8	100%	100%	83%	0%
IDH1 wild-type patients (n=93)	53.3	65% M	16%	1%	1.1	0%	0%	27%	60%

*Patient age refers to age at which the sample was obtained. †Recurrent GBM designates a GBM which was resected >3 months after a prior diagnosis of GBM. ‡Secondary GBM designates a GBM which was resected > 1 year after a prior diagnosis of a lower grade glioma (WHO I-III). §Overall survival was calculated using date of GBM diagnosis and date of death or last patient contact: Patients Br10P and Br11P were alive at last contact. Median survival for IDH1 mutant patients and IDH1 wild-type patients was calculated using logrank test. Previous pathologic diagnoses in secondary GBM patients were oligodendroglioma (WHO grade II) in Br123X, low grade glioma (WHO grade I-II) in Br237T and Br211T, anaplastic astrocytoma (WHO grade III) in Br27P, and anaplastic oligodendroglioma (WHO grade III) in Br129X. Mean age and median survival are listed for the groups of IDH1-mutated and IDH1-wild-type patients.

Parsons DW et al. Science. 2008;321(5897):1807-12.

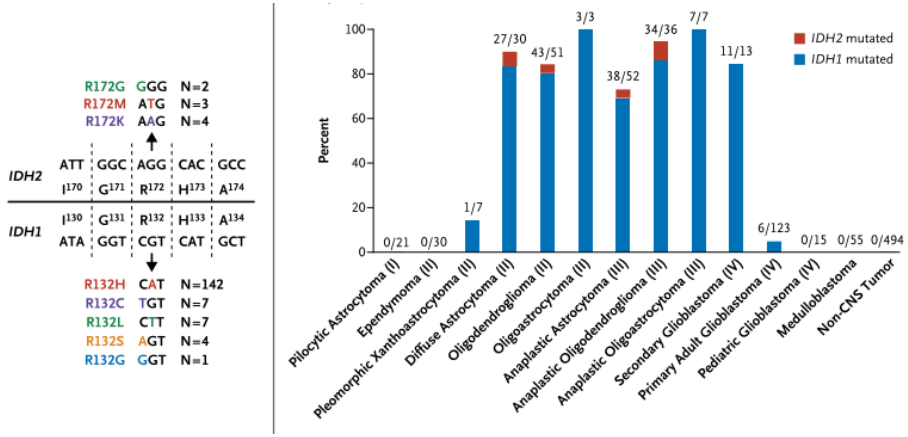
Mutations IDH1 et IDH2 Gliomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IDH1 and *IDH2* Mutations in Gliomas

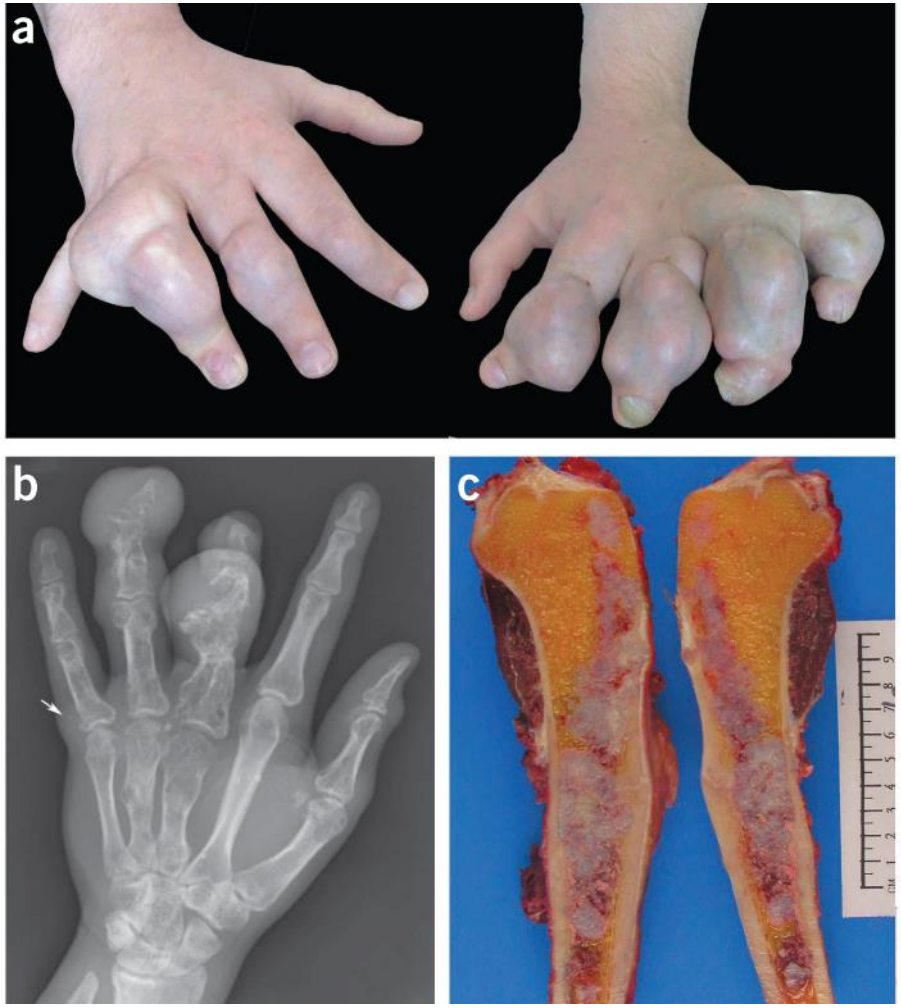
Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

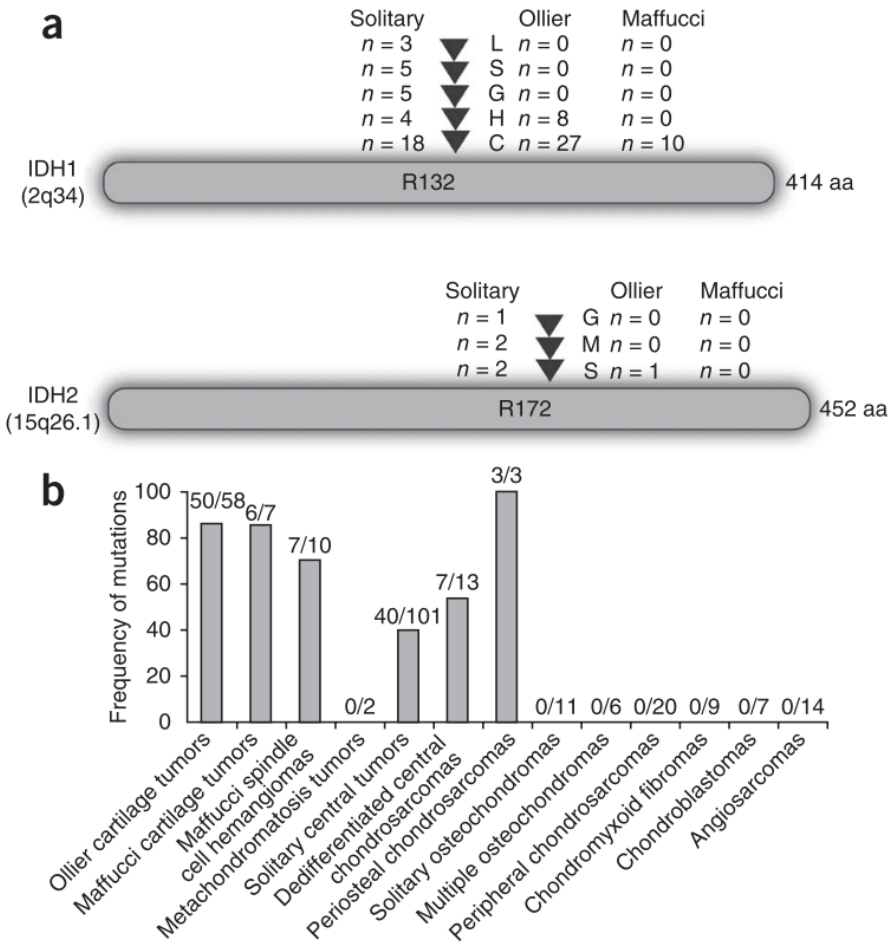


Tumor Classification†	No. of Tumors Analyzed	Median Age of Patient‡	Male Sex	Median Survival	Tumors with *IDH* Mutations		
					IDH1	*IDH2*	Combined
		yr	%	*mo*	*no.*		%
Astrocytic tumors							
Pilocytic astrocytoma (grade I)	21	5	48	ND	0	0	0
Subependymal giant-cell astrocytoma (grade I)	2	16	100	ND	0	NA	0
Diffuse astrocytoma (grade II)	30	34	53	132	25	2	90
Pleomorphic xanthoastrocytoma (grade II)	7	11	14	44	1	NA	14
Anaplastic astrocytoma (grade III)	52	38	67	51	36	2	73
Secondary glioblastoma (grade IV)¶	13	33	70	16	11	0	85
Primary adult glioblastoma (grade IV)	123	59	60	15	6	0	5
Primary pediatric glioblastoma (grade IV)	15	5	60	8	0	0	0
Oligodendroglial tumors							
Oligodendroglioma (grade II)	51	37	63	135	41	2	84
Anaplastic oligodendroglioma (grade III)	36	45	64	84	31	3	94
Oligoastrocytic tumors							
Oligoastrocytoma (grade II)	3	38	67	ND	3	NA	100
Anaplastic oligoastrocytoma (grade III)	7	30	57	ND	7	NA	100
Ependymoma (grade II)	30	5.5	45	ND	0	0	0
Medulloblastoma (grade IV)	55	7	65	27	0	0	0

Yan H et al. N Engl J Med. 2009;360(8):765-73.

Mutations IDH1 et IDH2
Tumeurs cartilagineuses





Amary MF et al.Nat Genet. 2011;43(12):1262-5.

Pansuriya TC et al. Nat Genet. 2011;43(12):1256-61.

Mutation IDH1 LAM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

Elaine R. Mardis, Ph.D., Li Ding, Ph.D., David J. Dooling, Ph.D.,

ABSTRACT

BACKGROUND

The full complement of DNA mutations that are responsible for the pathogenesis of acute myeloid leukemia (AML) is not yet known.

METHODS

We used massively parallel DNA sequencing to obtain a very high level of coverage (approximately 98%) of a primary, cytogenetically normal, de novo genome for AML with minimal maturation (AML-M1) and a matched normal skin genome.

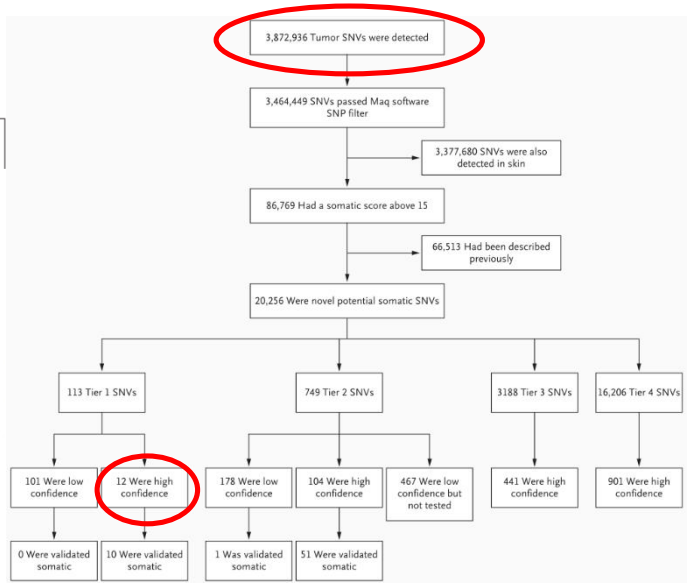


Table 2. Tier 1 Mutations.*

Annotated Gene	Mutation Type	Annotation	SIFT Prediction	Conservation Score	Base Conservation	Variant Frequency			Best Probe†
						Skin	Tumor	cDNA	
						%			
CDC42	Missense	S30L	Tolerated	597	1	1.03	49.27	46.3	27,990
NRAS	Missense	G12D	Deleterious	616	1	0.66	43.00	42.0	7,468
IDH1	Missense	R132C	Deleterious	445	1	0.81	46.06	63.9	11,400
IMPG2	Missense	G834D	Deleterious	472	0.018	0.67	46.22	0.4	NA
ANKRD26	Missense	K1300N	Deleterious	444	1	0.70	51.73	33.1	514
LTA4H	Missense	F107S	Tolerated	539	0.946	0.68	45.28	47.9	12,138
FREM2	Missense	Q2077E	Tolerated	464	1	0.37	48.92	0‡	NA
C19orf62	Splice-site	Exon 5-1	NA	444	1	0.27	38.71	38.8	5,021
SRRM1	Silent	P691	NA	553	0.988	0.97	46.61	ND	12,858
PCDHA6	Silent	A731	NA	NS	0.423	0.66	49.75	ND	Absent
SET130	In-frame insertion	Codon 177 in-frame ins L	NA	513	1	0.28	28.57	52.0	15,298
NPM1	Frame-shift insertion	W288fs	NA	689	1	0	45.46	85.4	27,150

Table 3. Characteristics of the Patients, According to *IDH1* Genotype.*

Variable	Without *IDH1* Mutation (N=172)	With *IDH1* Mutation (N=16)	P Value
Age at study entry — yr	46.3±15.8	48.9±15.4	0.52†
Race — no. (%)‡			0.88§
White	140 (81)	13 (81)	
Black	14 (8)	1 (6)	
Other	18 (10)	2 (12)	
Male sex — no. (%)	101 (59)	9 (56)	1.00§
Bone marrow blasts at diagnosis — %	69.3±18.1	76.7±16.4	0.12†
Cytogenetic profile — no. (%)			0.001§
Normal	67 (39)	13 (81)	
Other	105 (61)	3 (19)	
Cytogenetic risk group — no./total no. (%)¶			0.001§
Favorable	58/169 (34)	0/16	
Intermediate or normal	97/169 (57)	16/16 (100)	
Poor	14/169 (8)	0/16	
AML-M3 subtype — no. (%)	40 (23)	0/16	0.03§
Underwent transplantation — no. (%)	27 (16)	3 (19)	0.72§
Mutation — no. (%)			
NPM1	36 (21)	7 (44)	0.06§
FLT3			
Internal tandem duplication	36 (21)	4 (25)	0.75§
D835	10 (6)	1 (6)	1.00§
RAS	19 (11)	1 (6)	1.00§

Mardis ER et al. N Engl J Med. 2009;361(11):1058-66.

Mutations IDH1 et IDH2 LAM

VOLUME 28 · NUMBER 14 · MAY 10 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

IDH1 and *IDH2* Gene Mutations Identify Novel Molecular Subsets Within De Novo Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study

Guido Marcucci, Kati Maharry, Yue-Zhong Wu, Michael D. Radmacher, Krzysztof Mrózek, Dean Margeson, Kelsi B. Holland, Susan P. Whitman, Heiko Becker, Sebastian Schwind, Klaus H. Metzeler, Bayard L. Powell, Thomas H. Carter, Jonathan E. Kolitz, Meir Wetzler, Andrew J. Carroll, Maria R. Baer, Michael A. Caligiuri, Richard A. Larson, and Clara D. Bloomfield

VOLUME 28 · NUMBER 22 · AUGUST 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

IDH1 and *IDH2* Mutations Are Frequent Genetic Alterations in Acute Myeloid Leukemia and Confer Adverse Prognosis in Cytogenetically Normal Acute Myeloid Leukemia With *NPM1* Mutation Without *FLT3* Internal Tandem Duplication

Peter Paschka, Richard F. Schlenk, Verena I. Gaidzik, Marianne Habdank, Jan Krönke, Lars Bullinger, Daniela Späth, Sabine Kayser, Manuela Zucknick, Katharina Götze, Heinz-A. Horst, Ulrich Germing, Hartmut Döhner, and Konstanze Döhner

CLINICAL TRIALS AND OBSERVATIONS

IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis in adults younger than 60 years and unmutated *NPM1* status

Susanne Schnittger,[1] Claudia Haferlach,[1] Madlen Ulke,[1] Tamara Alpermann,[1] Wolfgang Kern,[1] and Torsten Haferlach[1]

[1]Munich Leukemia Laboratory, Munich, Germany

MYELOID NEOPLASIA

Brief report

The prognostic significance of *IDH1* mutations in younger adult patients with acute myeloid leukemia is dependent on *FLT3*/ITD status

Claire L. Green,[1] Catherine M. Evans,[1] Robert K. Hills,[2] Alan K. Burnett,[2] David C. Linch,[1] and Rosemary E. Gale[1]

[1]Department of Haematology, UCL Cancer Institute, London, United Kingdom; and [2]Department of Haematology, Cardiff University School of Medicine, Cardiff, United Kingdom

MYELOID NEOPLASIA

Brief report

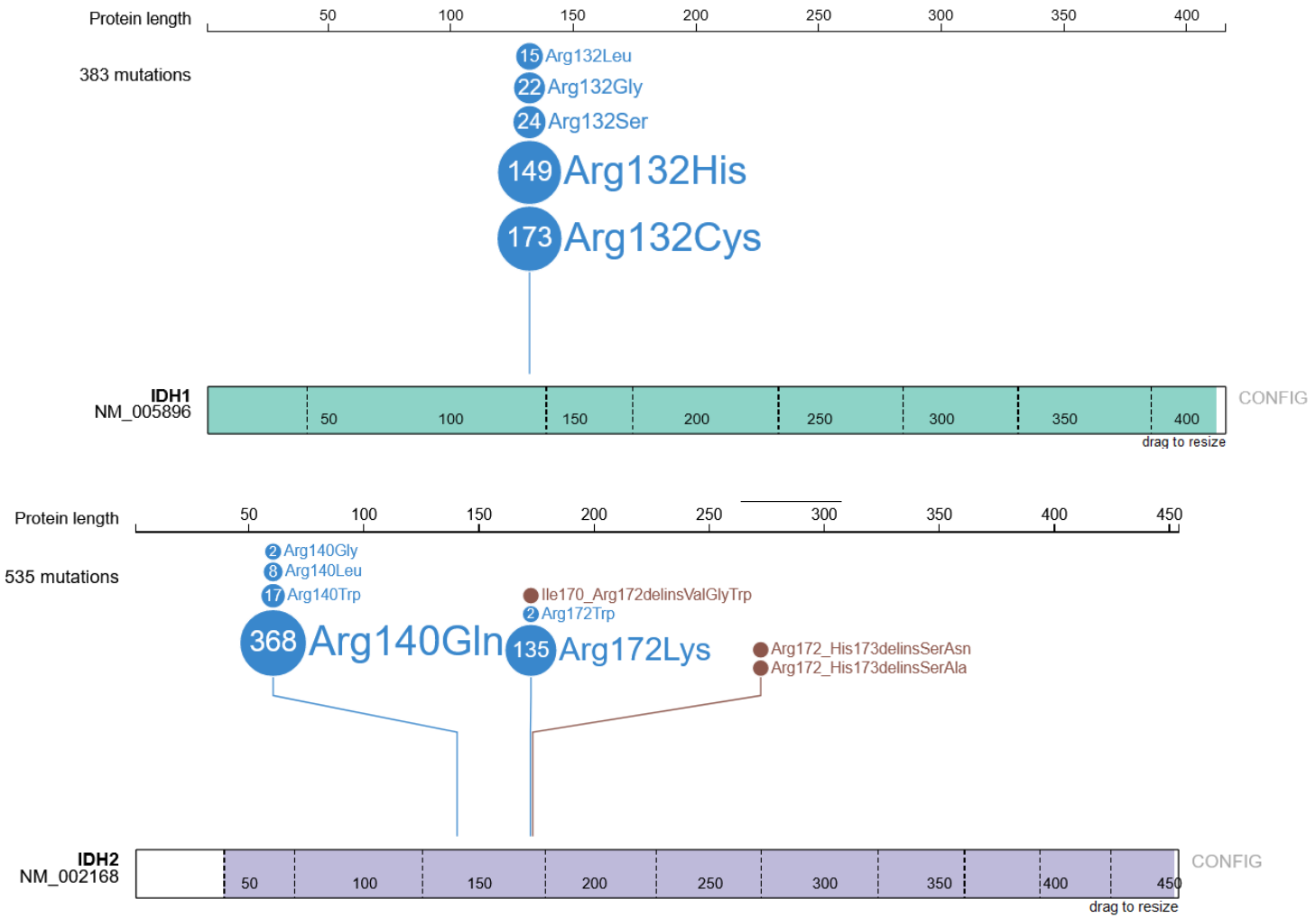
Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value

Saman Abbas,[1] Sanne Lugthart,[1] François G. Kavelaars,[1] Anita Schelen,[1] Jasper E. Koenders,[1] Annelieke Zeilemaker,[1] Wim J. L. van Putten,[2] Anita W. Rijneveld,[1] Bob Löwenberg,[1] and Peter J. M. Valk[1]

Departments of [1]Hematology and [2]Trials and Statistics, Erasmus University Medical Center, Rotterdam, The Netherlands

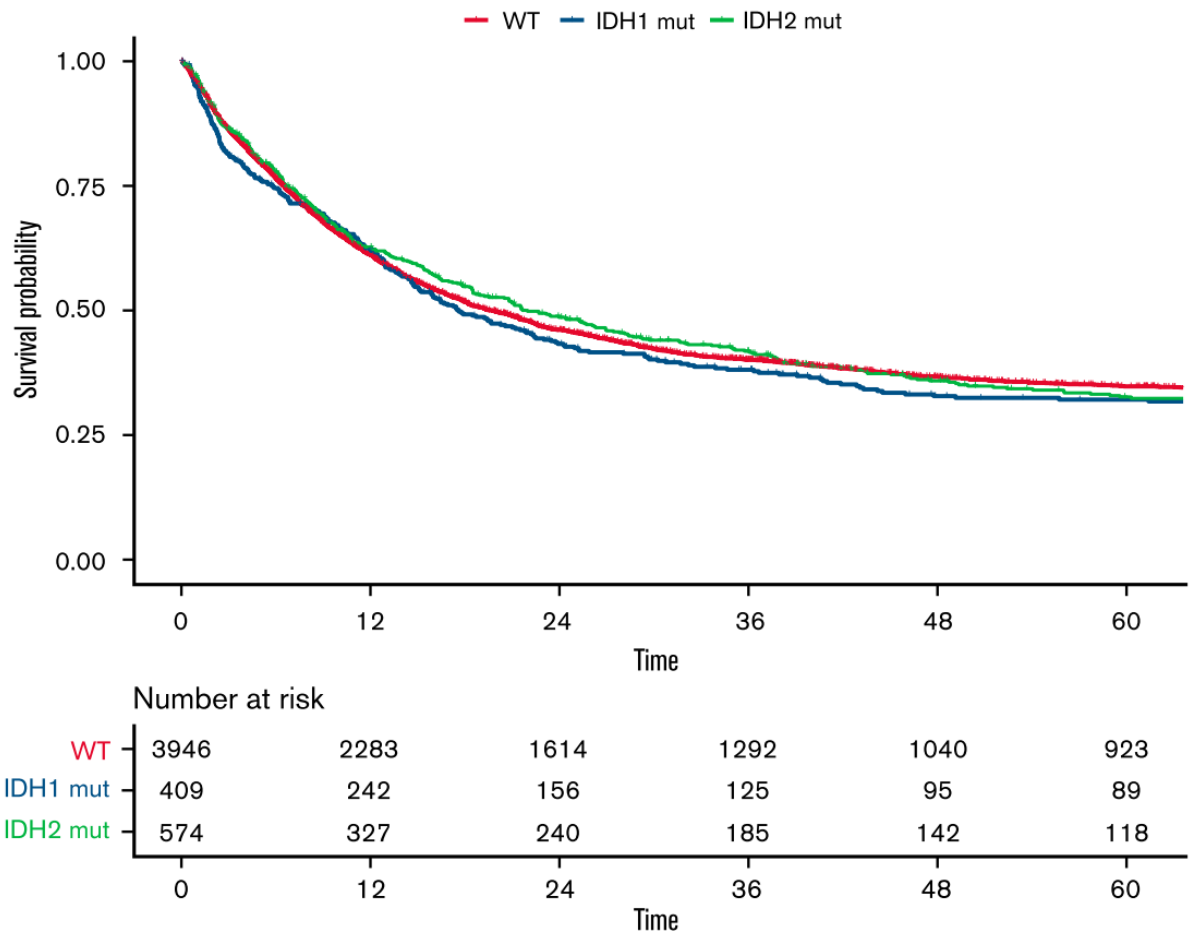
Abbas S et al. Blood. 2010;116(12):2122-6.
Green CL et al. Blood. 2010;116(15):2779-82.
Marcucci G et al. J Clin Oncol. 2010;28(14):2348-55.
Paschka P et al. J Clin Oncol. 2010;28(22):3636-43.
Schnittger S et al. 2010;116(25):5486-96.

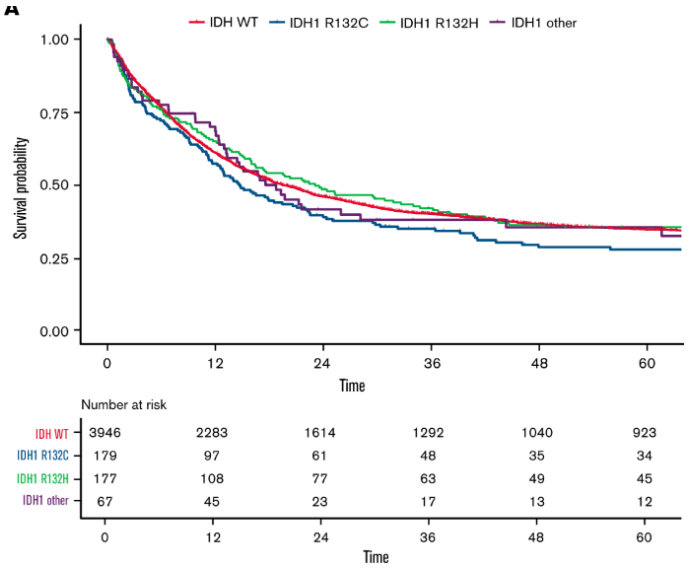
Mutations IDH1 et IDH2 LAM

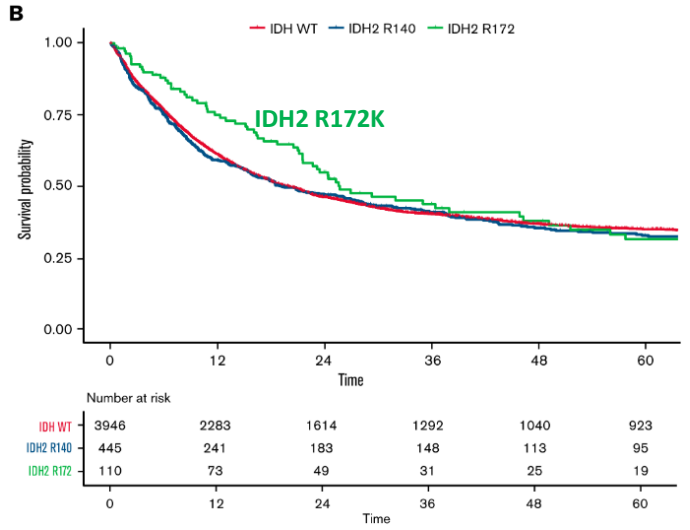


CHU de Toulouse, données non publiées

Mutations IDH1 et IDH2
LAM, Survie globale





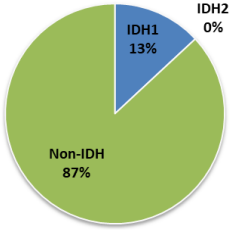


Middeke JM et al. Blood Adv. 2022;6(5):1394-405.

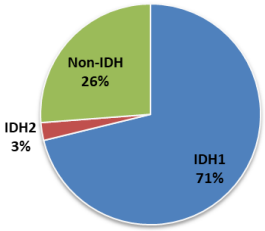
Les mutations IDH sont fréquentes

Tumeurs IDH1

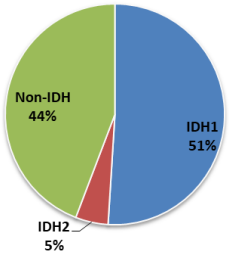
Cholangiocarcinome



Gliome

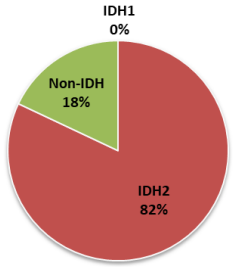


Chondrosarcome

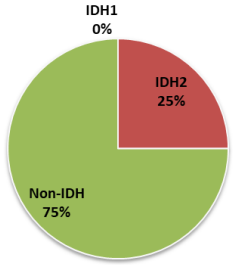


Tumeurs IDH2

Carcinome sino-nasal indifférencié

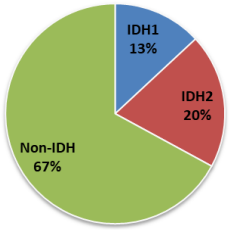


Lymphome T angio-immunoblastique



Tumeurs IDH1/IDH2

LAM

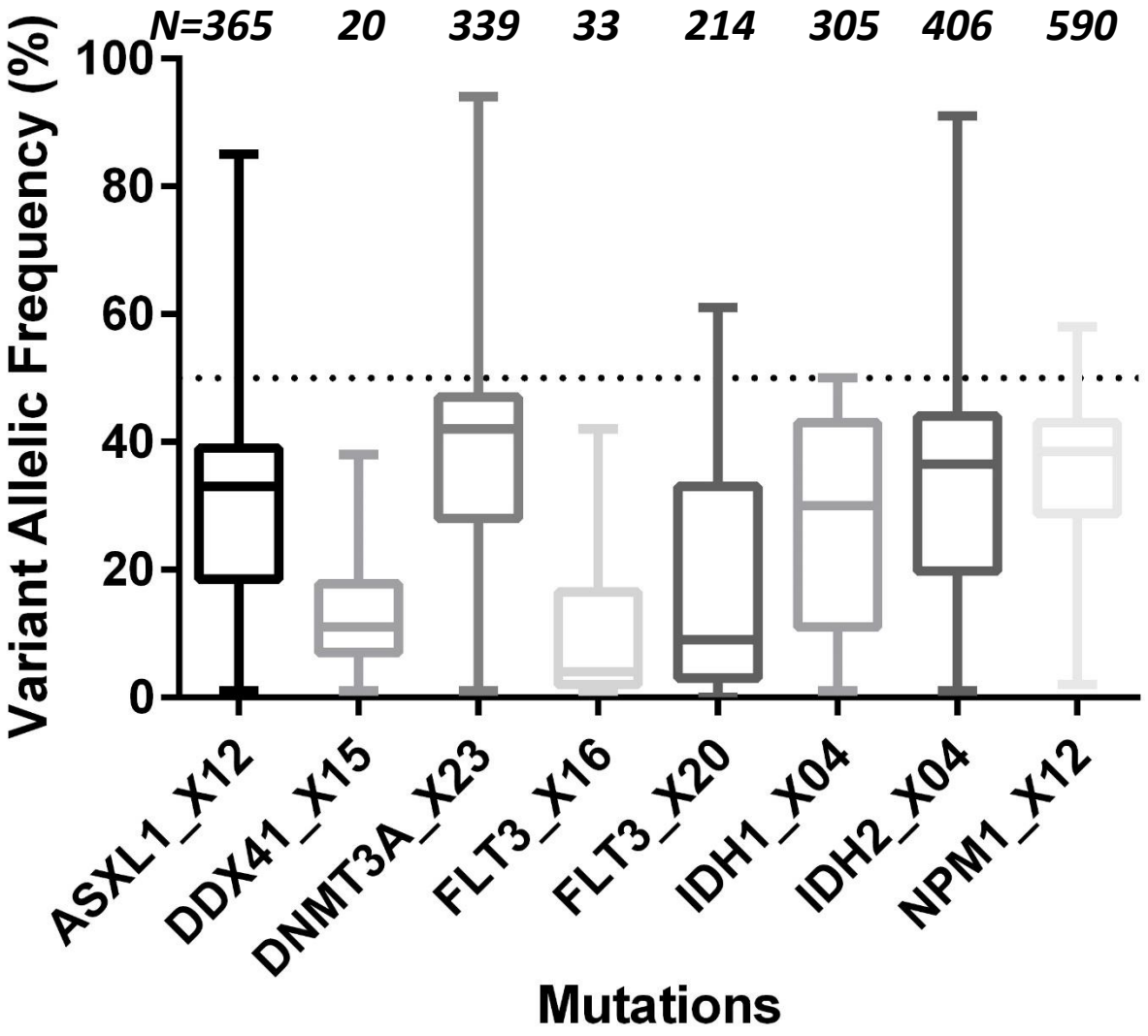


Pirozzi CJ, Yan H. Nat Rev Clin Oncol. 2021;18(10):645-61.

Biologie des mutations IDH dans les hémopathies myéloïdes

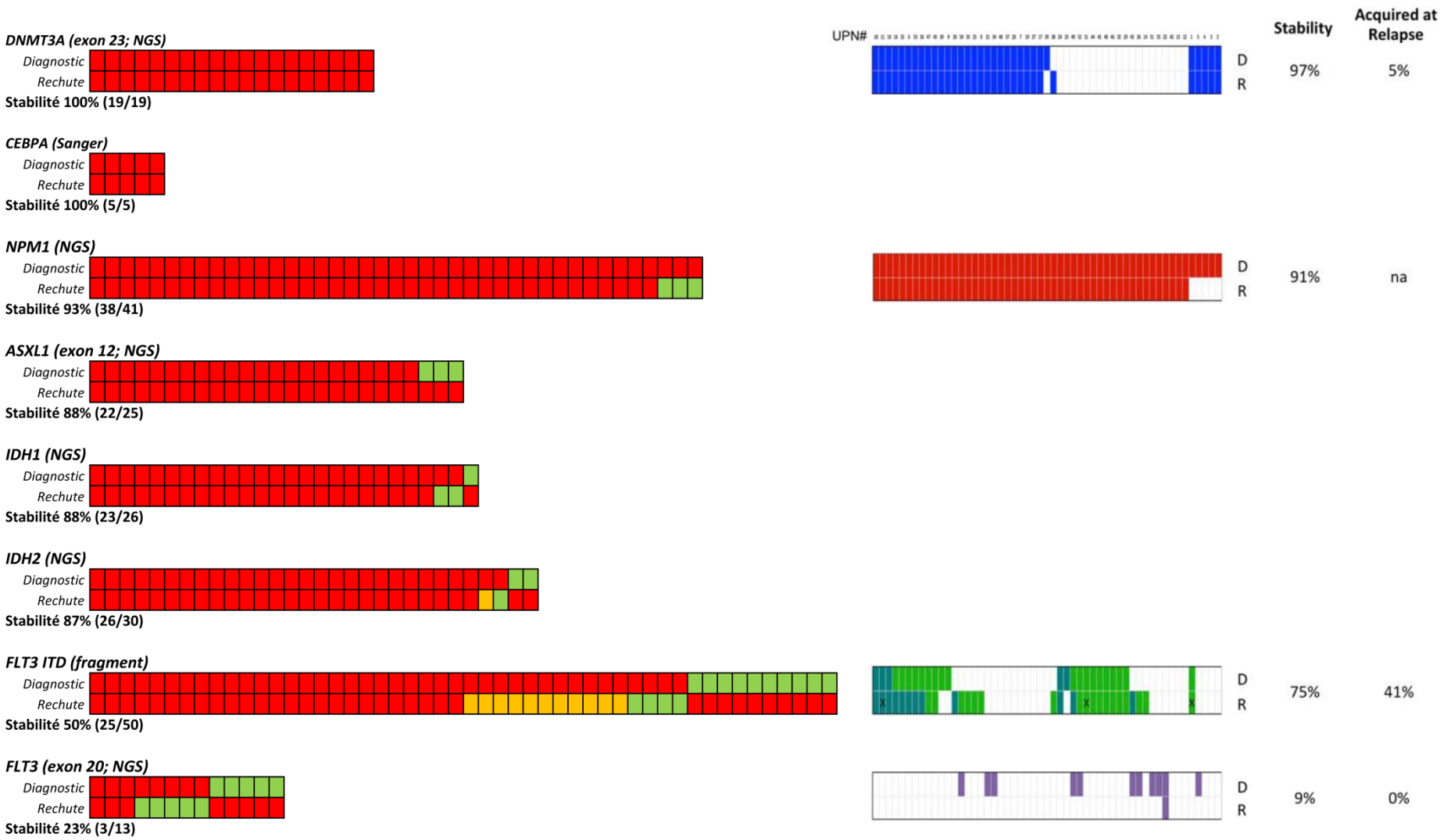
CLONAL OU SOUS-CLONAL

Les mutations IDH sont hétérozygotes



CHU de Toulouse, données non publiées

Stabilité des mutations à la rechute

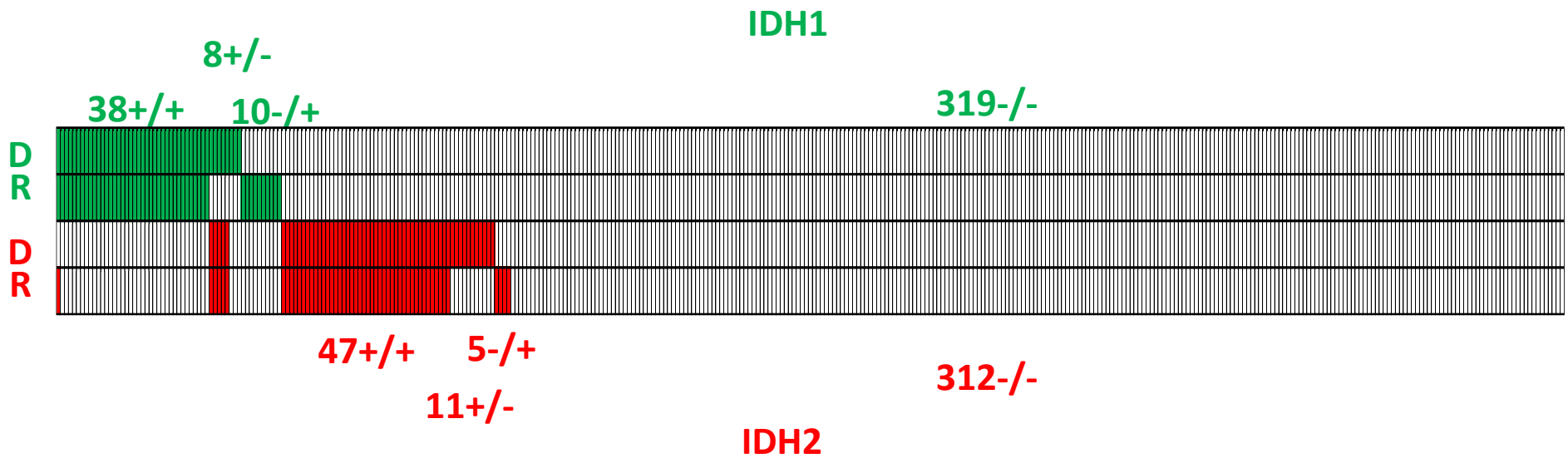


CHU de Toulouse, données non publiées

Krönke et al, Blood. 2013;122(1):100-108

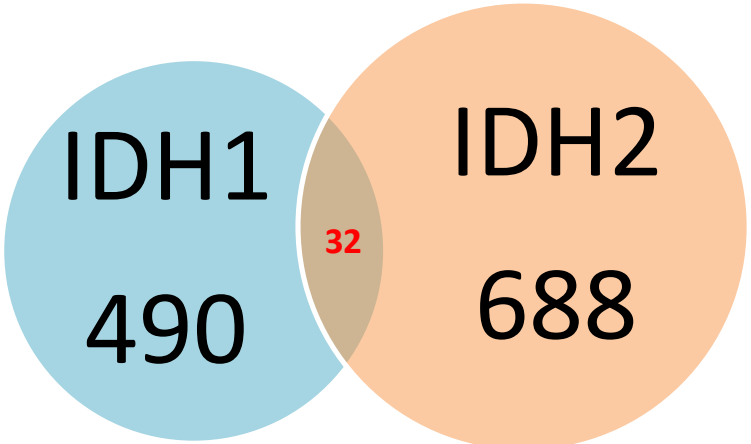
Stabilité des mutations IDH

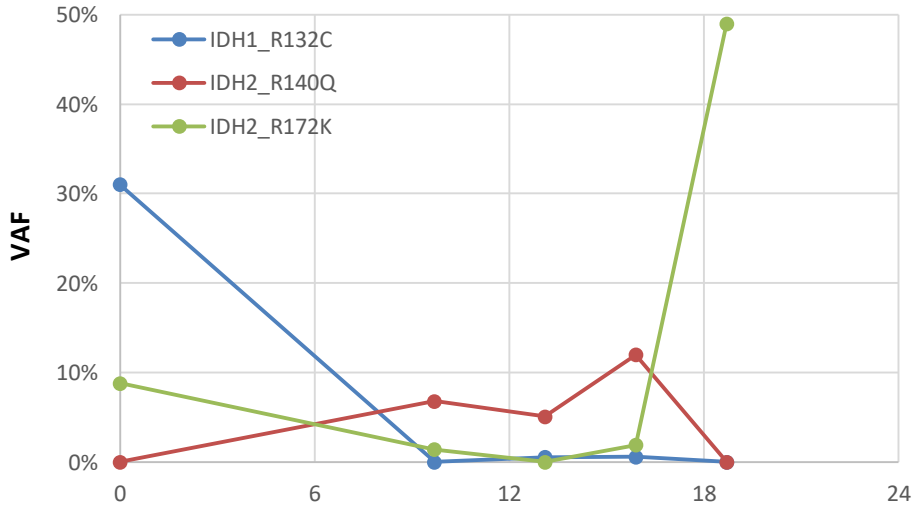
Comparaison analyses IDH1 et IDH2 au diagnostic et à la rechute
>6 mois du diagnostic; 375 LAM

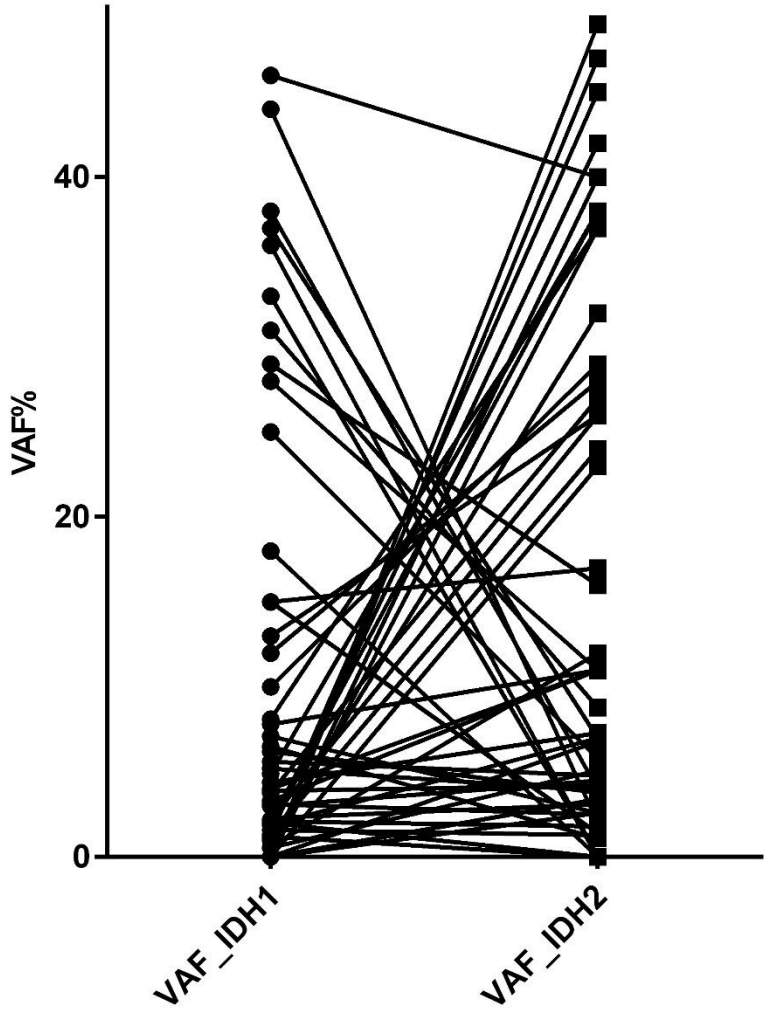


CHU de Toulouse, données non publiées

Mutations IDH1 et IDH2
Co-mutations





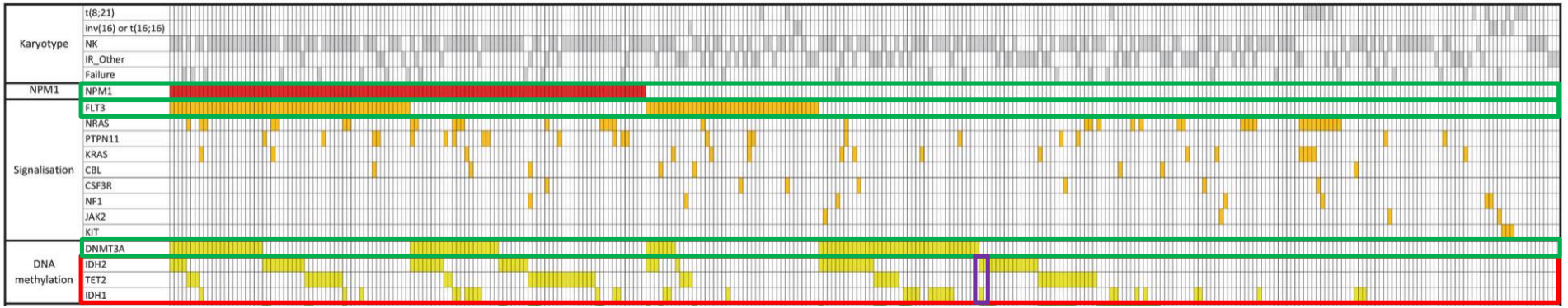


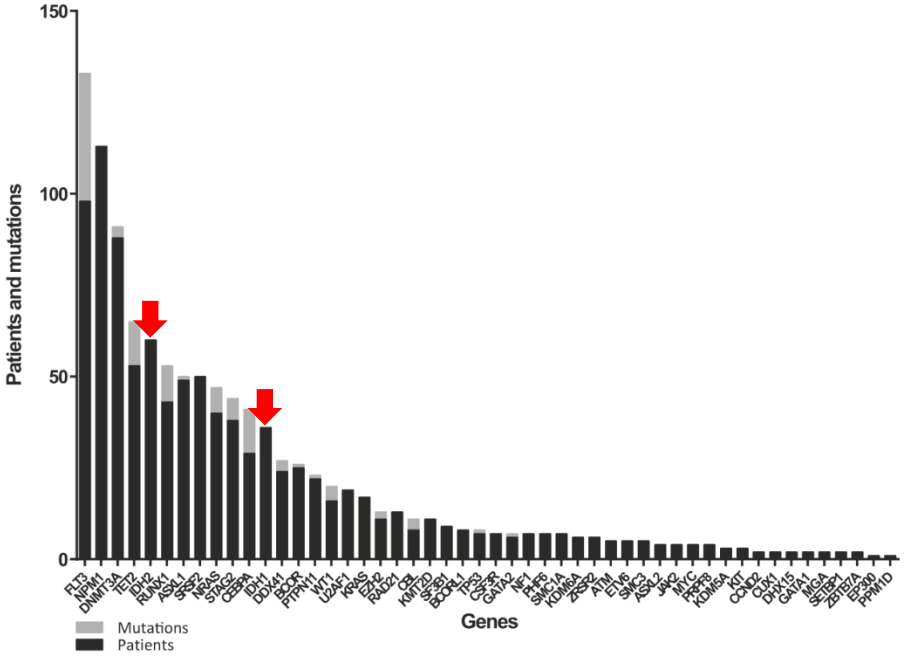
CHU de Toulouse, données non publiées

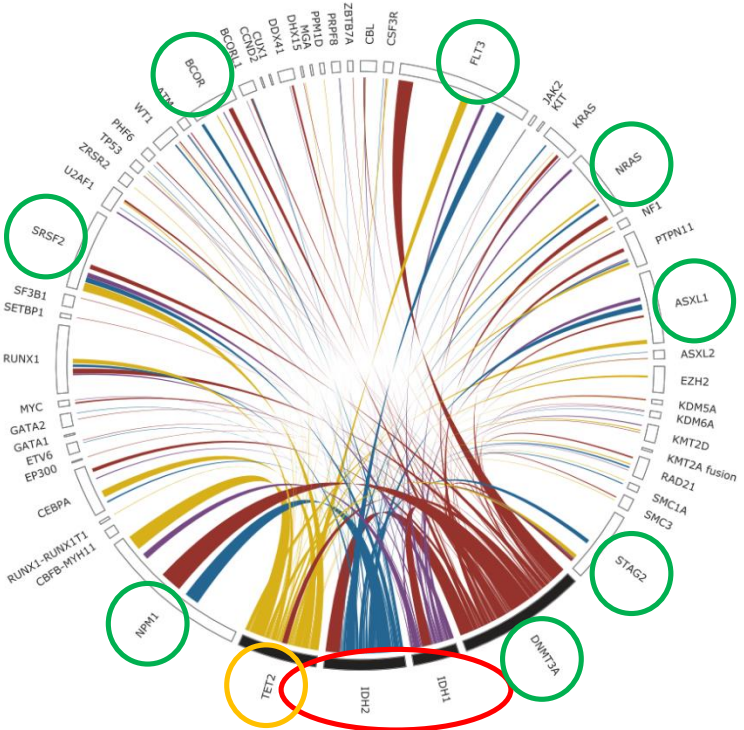
Biologie des mutations IDH dans les hémopathies myéloïdes

LES CO-MUTATIONS IDH

Mutations IDH1 et IDH2
Co-mutations LAMSA-2007

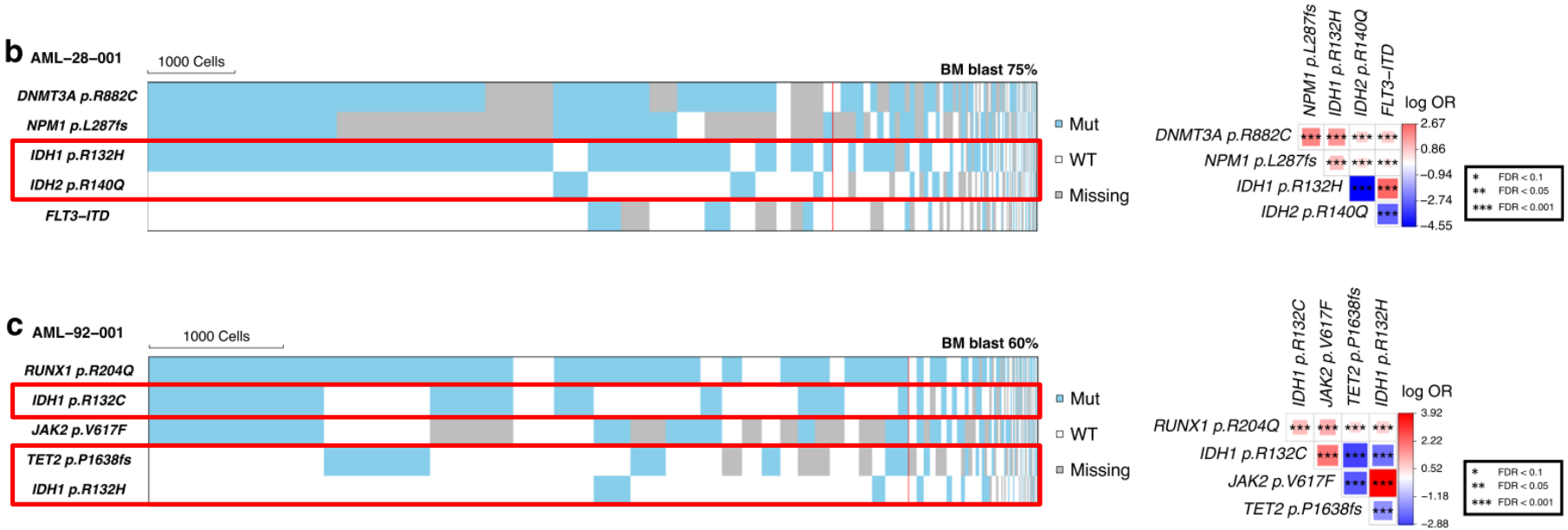






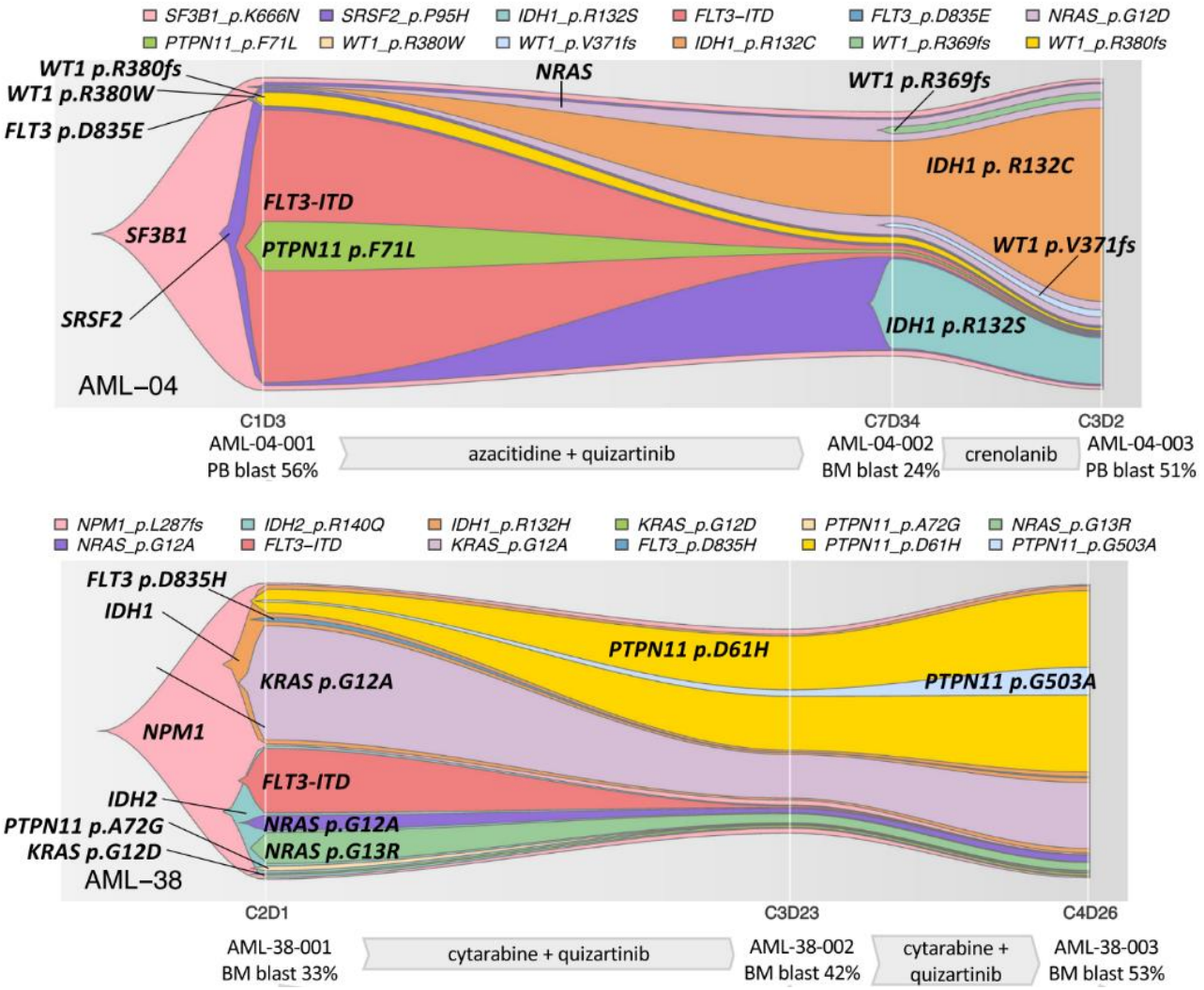
Largeaud L et al. Leukemia. 2021;35(5):1291-300.

Mutations IDH et TET2 exclusives



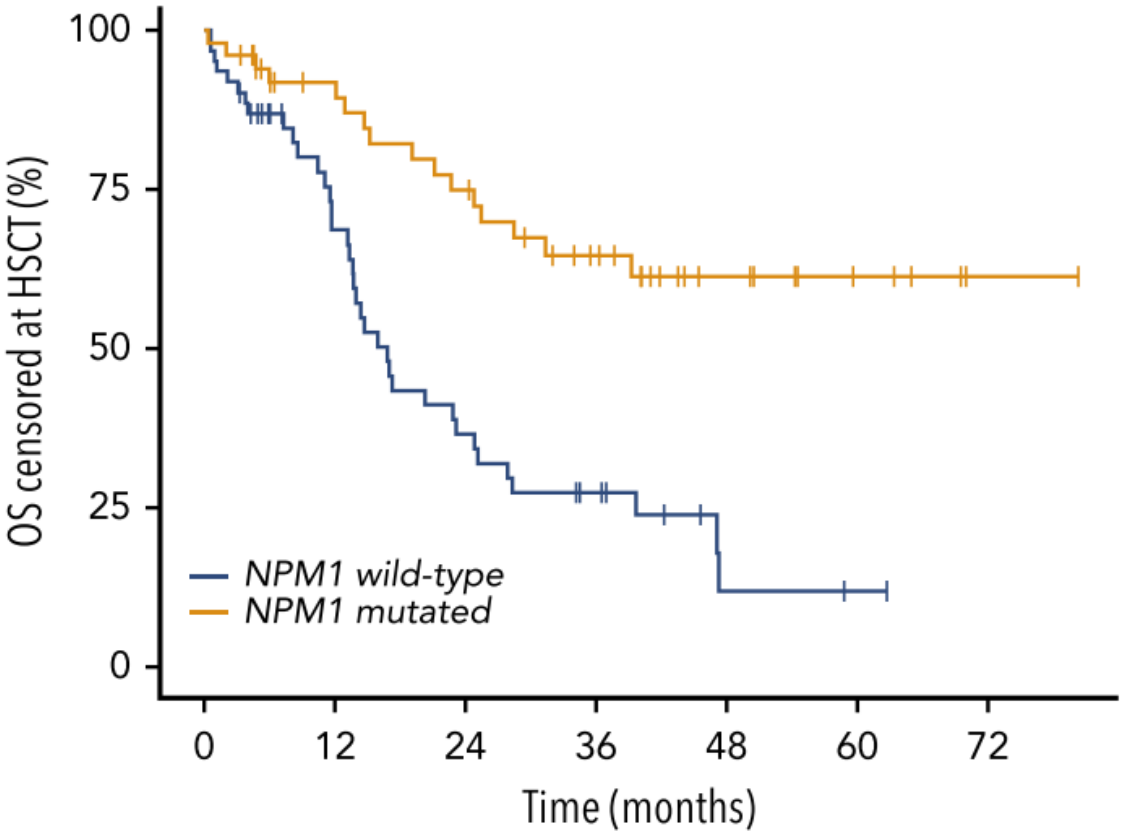
Morita K et al. Nat Commun. 2020;11(1):5327.

Mutations IDH1 et IDH2 Co-mutations



Morita K et al. Nat Commun. 2020;11(1):5327.

Mutations IDH1 et IDH2
Co-mutation NPM1 favorable



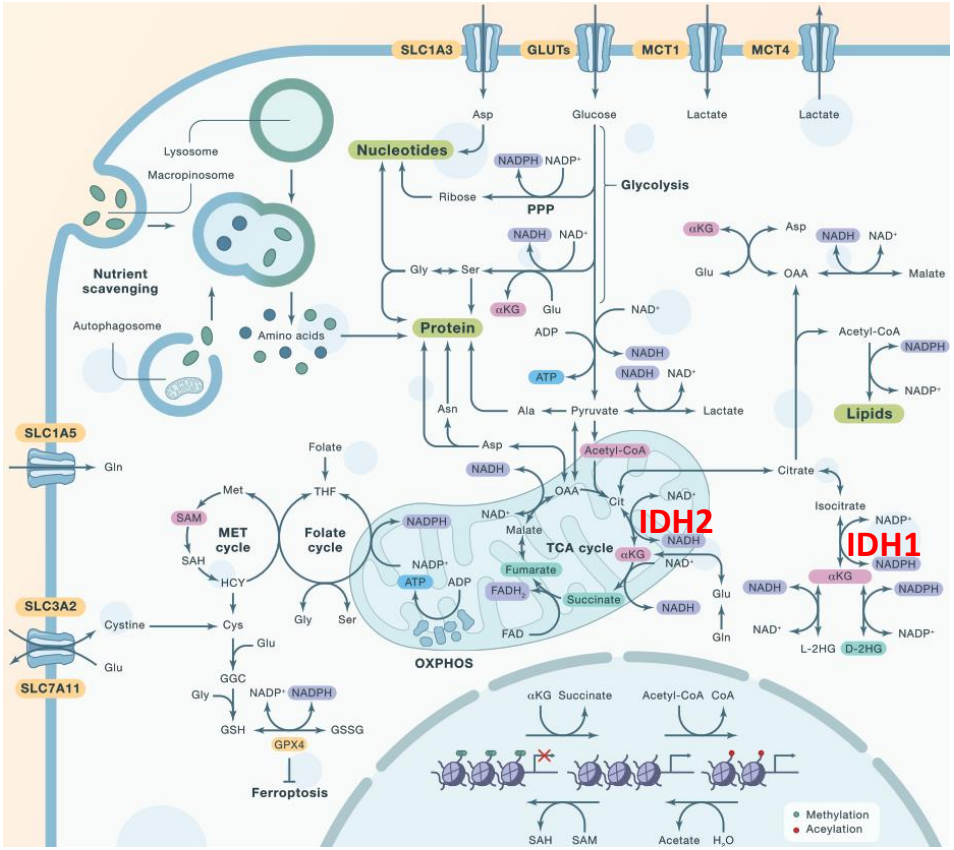
N° at risk							
NPM1-Wt	62	30	16	10	2	1	0
NPM1-Mut	53	38	31	21	11	5	1

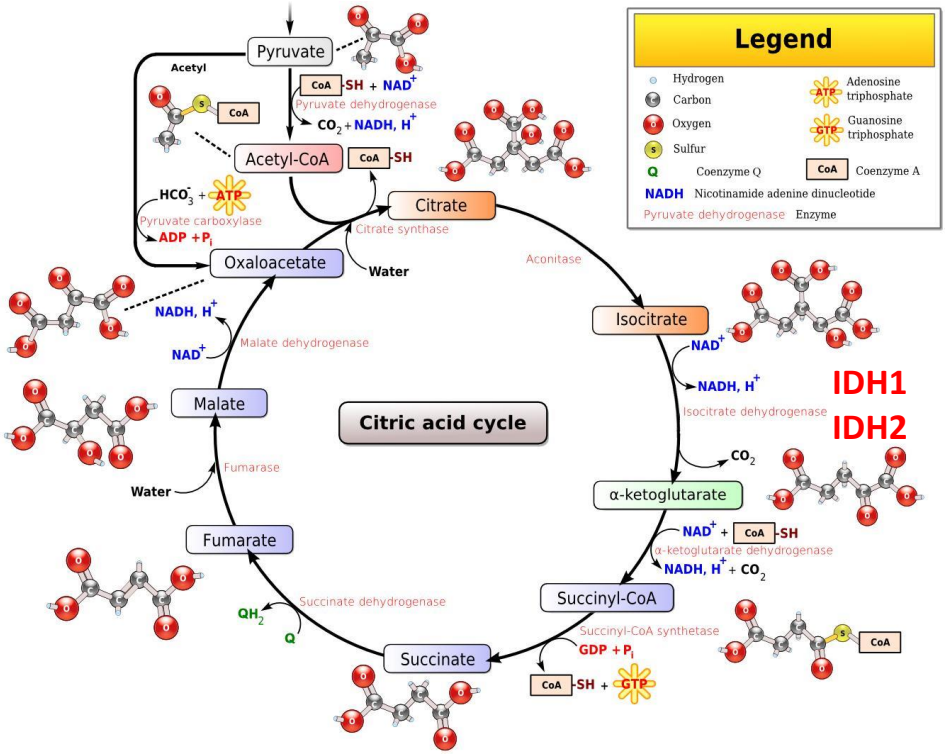
Duchmann M et al. Blood. 2021;137(20):2827-37.

Biologie des mutations IDH dans les hémopathies myéloïdes

AUTOUR DU CYCLE DE KREBS

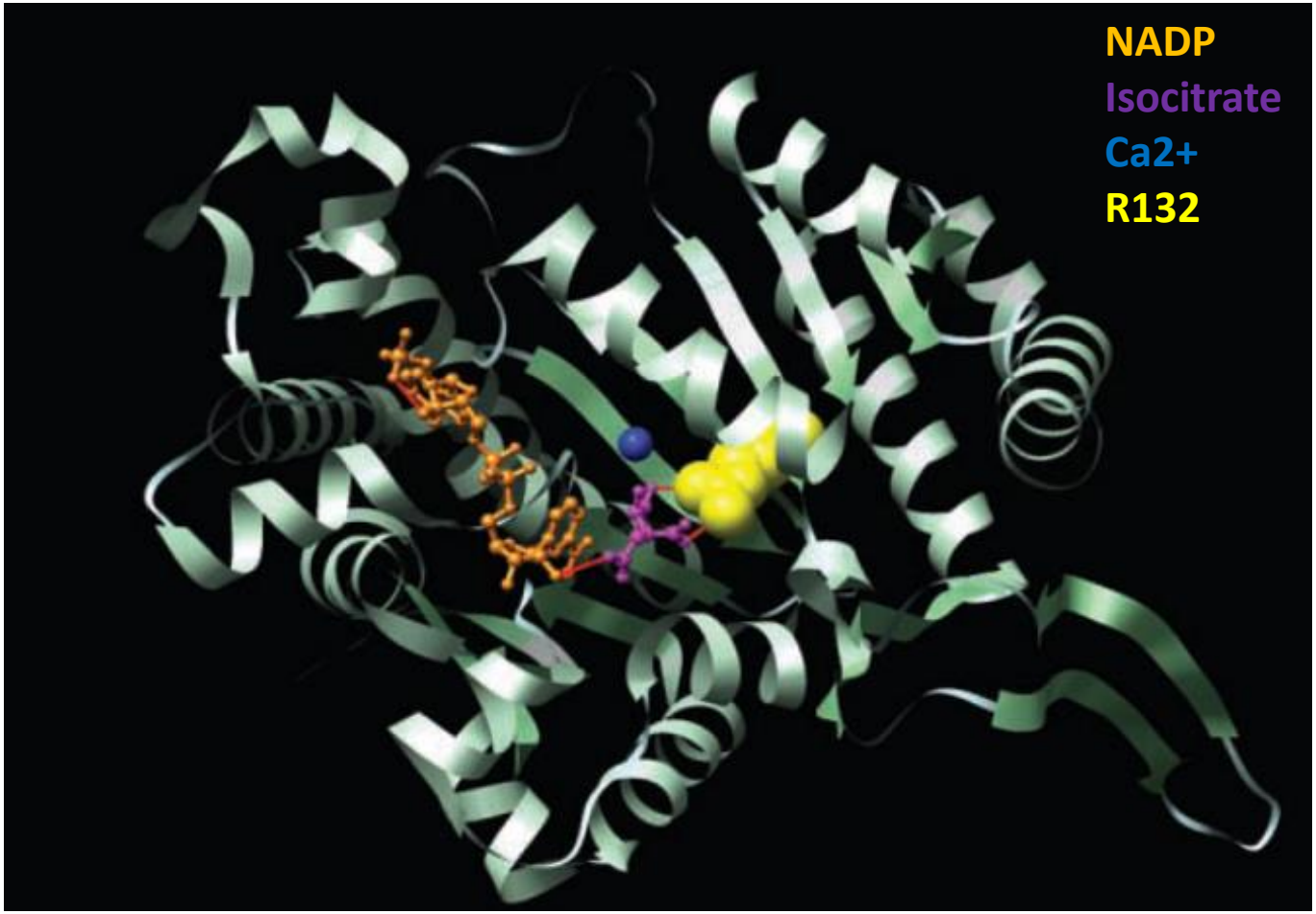
Le cycle de Krebs
Acides tricarboxyliques

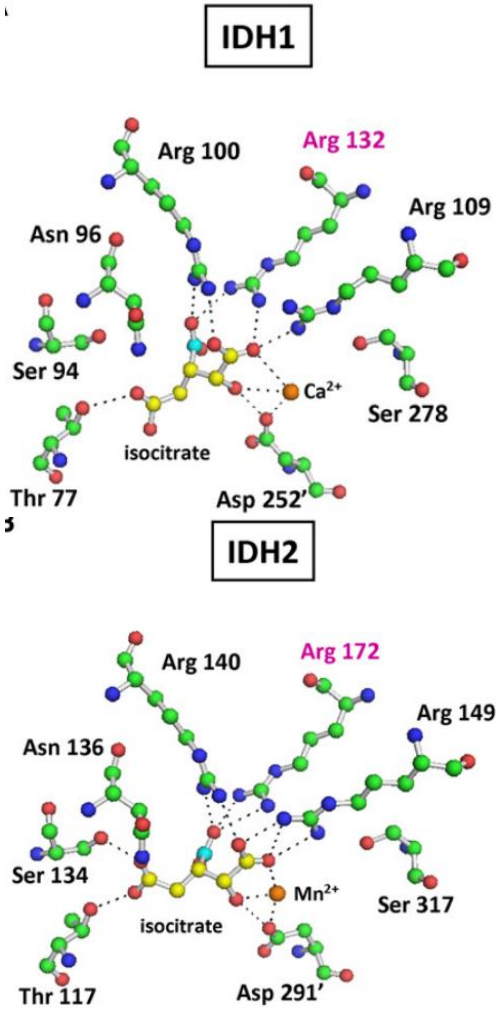




Brunner JS, Finley LWS. Mol Cell. 2021;81(18):3878- e1.

Structure IDH

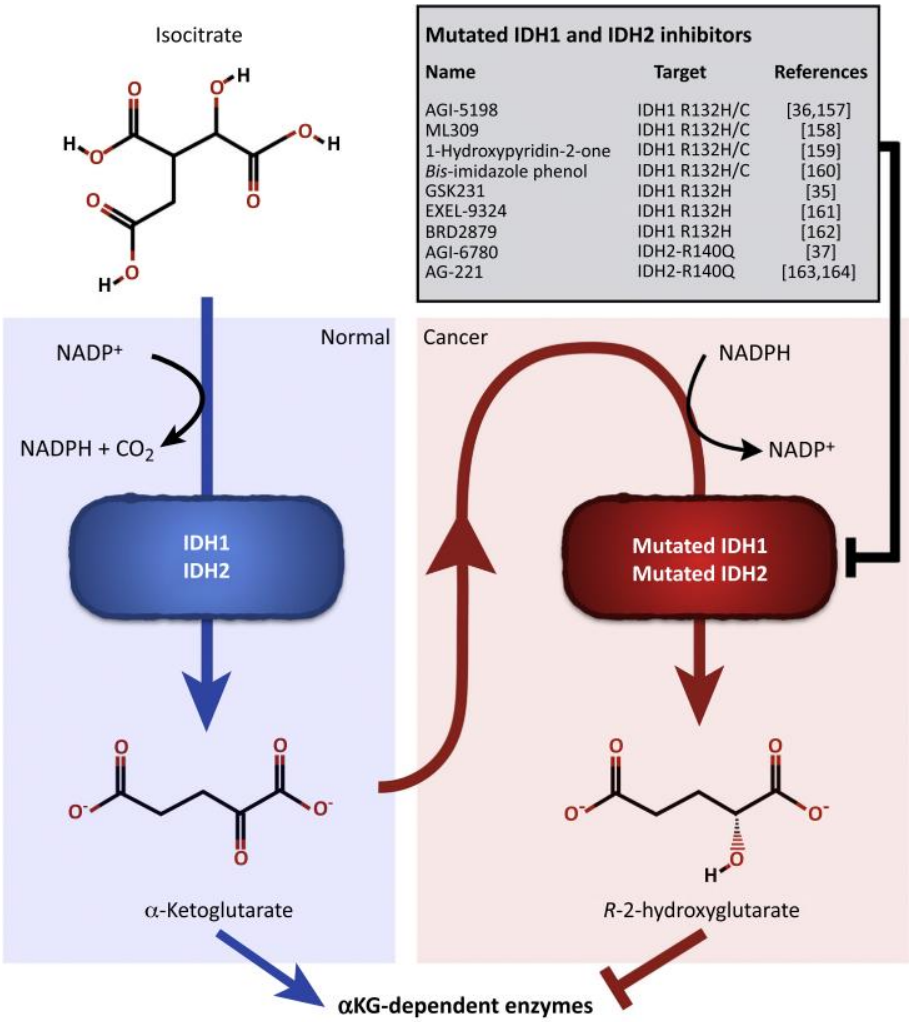


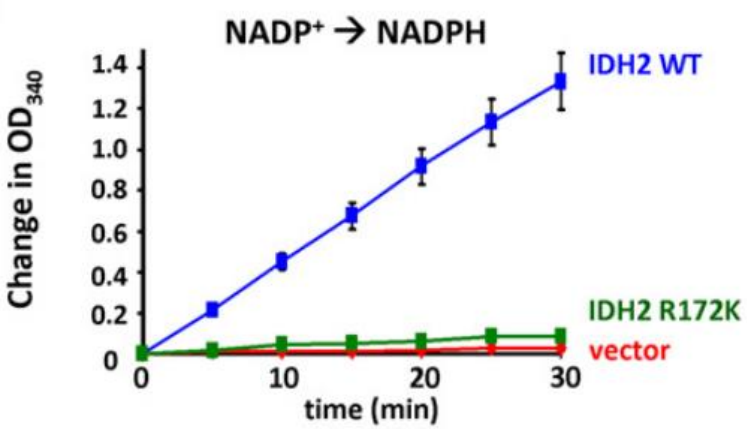


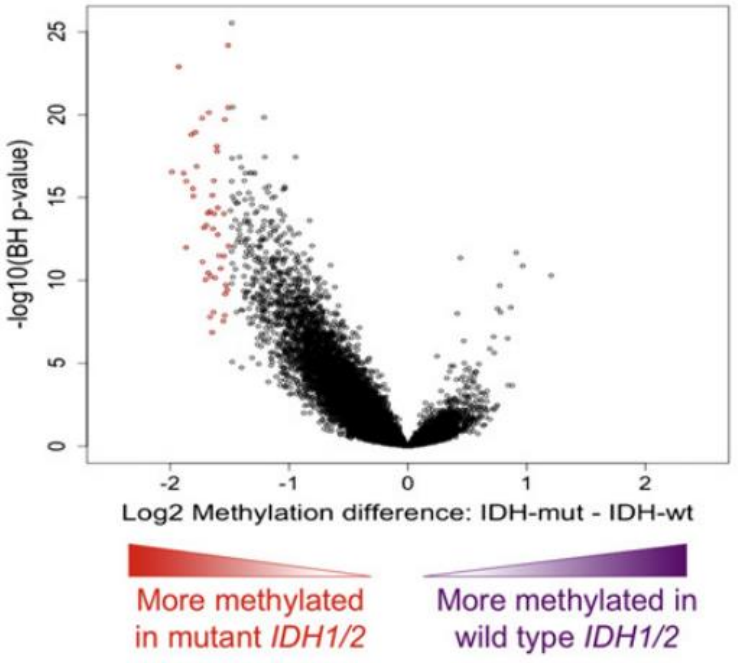
Parsons DW et al. Science. 2008;321(5897):1807-12.

Ward PS et al. Cancer Cell. 2010;17(3):225-34.

Biologie des mutations IDH







Gagné L et al. Trends Cell Biol. 2017;27(10):738-52.

Ward PS et al. Cancer Cell. 2010;17(3):225-34
Figueroa ME et al. Cancer Cell. 2010;18(6):553-67

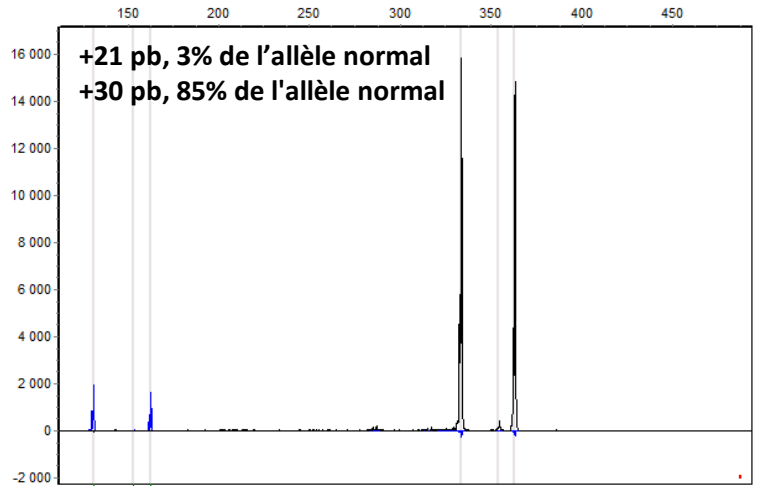
Biologie des mutations IDH dans les hémopathies myéloïdes

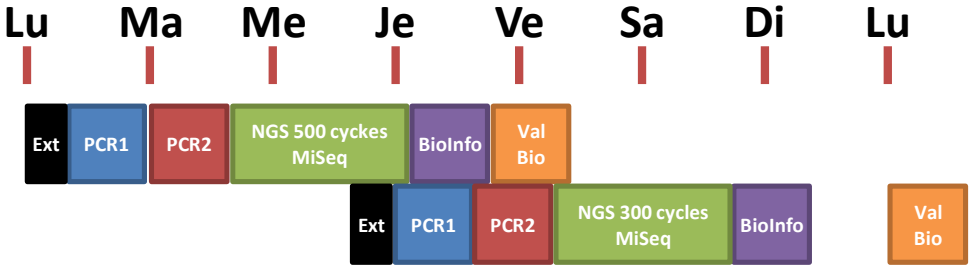
EN PRATIQUE DIAGNOSTIC

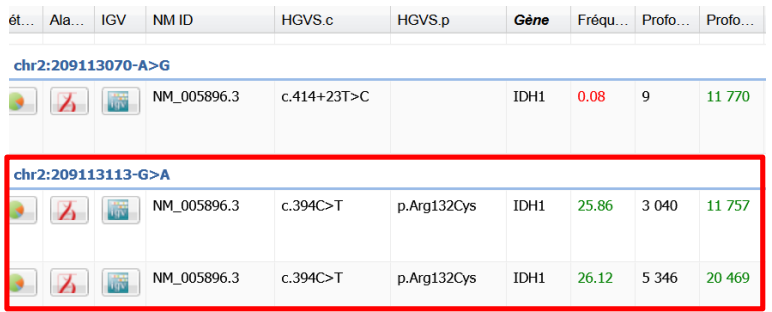
Prise en charge LAM
En pratique au CHU de Toulouse…

Toutes LAM,
Diagnostic et rechute

- 9 mutations récurrentes
- Analyse de fragment (sens. 1%)
  - FLT3 ITD (exons 13 à 15)
- NGS (sens. 0,5%)
  - PCR amplicons 8 exons
    - ASXL1 exon 12
    - DDX41 exon 15
    - DNMT3A exon 23
    - FLT3 exon 16
    - FLT3 exon 20
    - IDH1 exon 4
    - IDH2 exon 4
    - NPM1 exon 12







Prise en charge LAM
En pratique au CHU de Toulouse…

RESULTATS NGS LAM

RUN du 10/10/2023 Opérateur AD

Contrôle qualité du run : **Cluster PF** 95,29 **% > Q30 =** 85,73

	NPM1	DNMT3A	FLT3 TKD	FLT3 X16	IDH1	IDH2	ASXL1	DDX41
H2O	7	18	6	16	2	3	4	

Résultats :

	Analyse BDNGS																							
	NPM1			DNMT3A			FLT3 TKD			FLT3 X16			IDH1			IDH2			ASXL1			DDX41 X15		
	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.	Mutation	VAF (%)	Prof.
230144	NM		19097	NM		34125	NM		10705	NM		25167	NM		16816	NM		24311	NM		33164	NM		20302
231926	NM		45221	NM		37109	NM		13208	NM		36300	NM		20239	NM		36401	NM		38606	NM		11340
232004	NM		45800	NM		62086	NM		20823	NM		49938	NM		30404	NM		57036	NM		57748	NM		23729
232149	NM		5660	NM		33840	NM		7863	NM		6183	NM		14568	NM		31060	NM		33679	NM		15274
232156	NM		30036	NM		38760	NM		11679	NM		30876	NM		20979	NM		34643	NM		35133	NM		18085
232165	NM		11568	NM		30639	NM		9124	NM		21776	NM		17398	NM		27060	NM		29123	NM		28802
232180	NM		40857	NM		31997	NM		11276	NM		31030	NM		17415	NM		30798	NM		28988	NM		8401
232184	NM		16095	NM		33098	D835Y	20	8671	NM		23109	NM		17183	NM		20467	NM		28988	NM		18921
232200	NM		40080	R882H	46	65125	NM		16335	NM		56501	R132L	45	41129	NM		54948	NM		58406	NM		42433
232219	NM		20674	NM		87364	NM		16231	NM		16217	NM		34112	NM		80079	NM		80076	NM		36085
232223	NM		13925	NM		26246	NM		6888	NM		17076	NM		12887	NM		26321	NM		26882	NM		17920
232226	NM		54580	NM		28207	NM		11922	NM		32842	R132C	26	20540	NM		33210	NM		35906	NM		12105
232250	NM		17623	NM		35184	NM		8429	NM		24553	NM		16881	R140Q	3	29224	NM		30937	NM		18915
232253	NM		24374	NM		34300	NM		9549	NM		26240	NM		17870	NM		29318	NM		30208	.1550-1G>A	4,1	14462
232254	NM		64299	NM		62609	NM		23785	NM		53853	NM		33721	R140Q	33	56540	NM		57562	NM		23260
232272	NM		5816	NM		23472	NM		32434	NM		67309	NM		8251	NM		18031	NM		22060	NM		12952
													NM		16904	NM		29282	NM		28872	NM		14963
													NM		20650	NM		33841	NM		23087	NM		22383
													NM		16027	NM		26359	NM		25525	NM		14732

N° Echantillon 151276 MOELLE 04/10/2023 N° Suivi 1 NumeroExterieur 3100467146

Prescripteur _NON_PRECISE Service CH RODEZ Molis 1 2327812423

Renseignements Echantillon LAM Hb Plaquettes Molis 2

Leuco Blastes sg Molis 3

VGM Blastes mo

Num_Theque 232226 ID tube 0442108747 Type de congélation ADN L Extr à faire ☐

Remarque Date d'extractio 06/10/2023 LM Methode Extr. Auto Hamilton L

Date RT Position ADNc Qualité

PCR quali | PCR quanti | MRD Ig-TCR | MLPA/CGH | Petite Fiche | Global | Thèque

Exp	Cible de PCR qualita	Résultat PCR	Nb	Détails PCR qualitative	T	DateAnaly	Expe
☐	HALOPLEX LAM	En cours		CR 06/10/2023-08:11		17/10/2023	☐
☐	IDH1_X04	Muté		NM_005896.2(IDH1_v001):c.394C>T, NM_005896.2(IDH1_i001):p.Arg132	AD	10/10/2023	☑
☐	ASXL1_X12	Non muté			AD	10/10/2023	☑
☐	DDX41_X15	Non muté			AD	10/10/2023	☑
☐	DNMT3A_X23	Non muté			AD	10/10/2023	☑
☐	FLT3_X13_ITD	Non muté			LE	09/10/2023	☑
☐	FLT3_X16	Non muté			AD	10/10/2023	☑
☐	FLT3_X20_TKD	Non muté			AD	10/10/2023	☑
☐	IDH2_X04	Non muté			AD	10/10/2023	☑
☐	NPM1_X12	Non muté			AD	10/10/2023	☑

Enr : Aucun filtre Rechercher

Conclusion BioMol: Détection d'une mutation d'IDH1 (R132C) à un niveau intermédiaire. Absence de détection de mutations d'ASXL1 (exon 12), de DDX41 (exon 15), de DNMT3A (exon 23), de FLT3 (ITD et TKD, exons 16 et 20), d'IDH2 (exon 4) et de NPM1 (exon 12). NGS myéloïde étendu en cours.

exporter conclu. Exporter dans molis

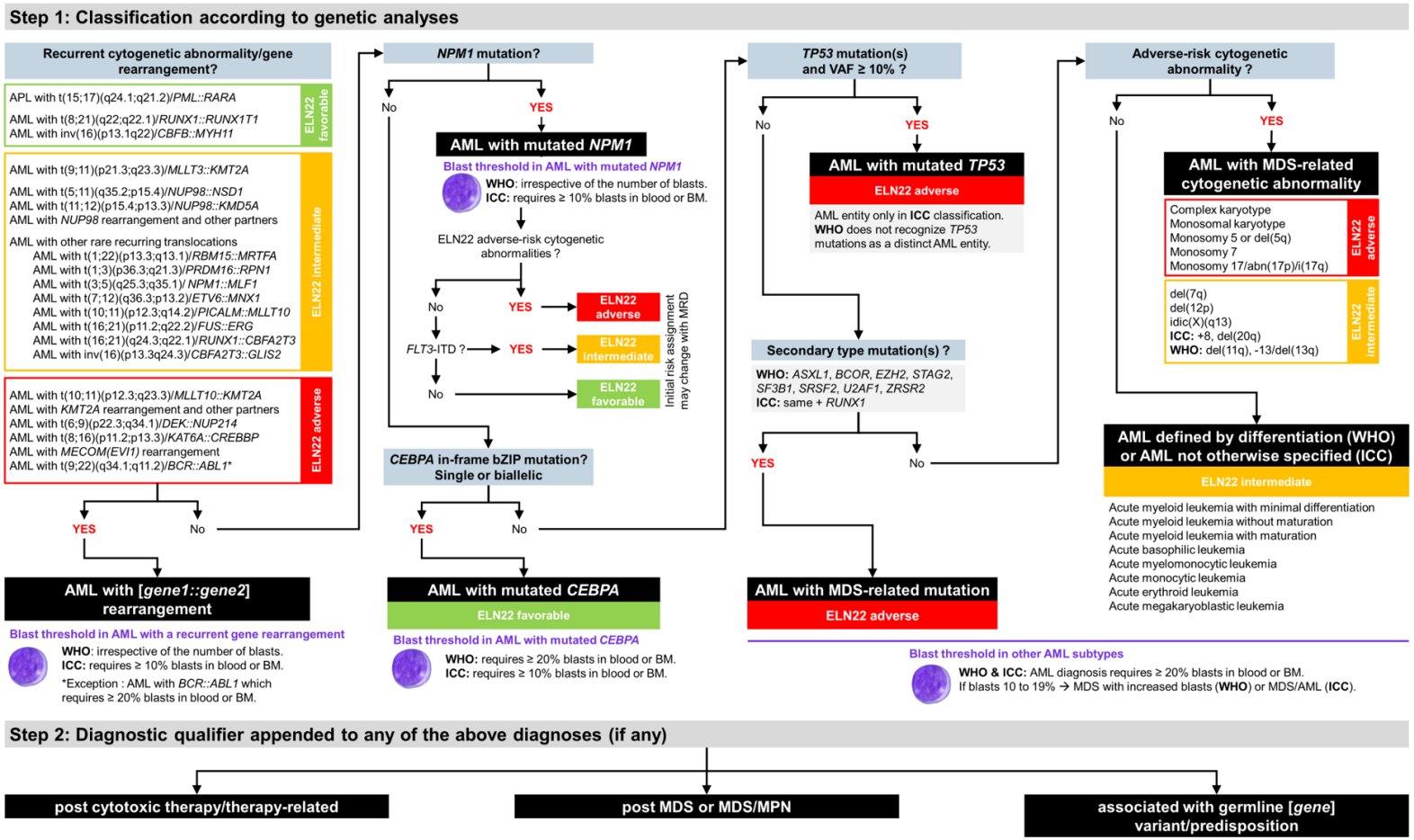
Analyses	Résultat	Unité	Valeurs de référence	Antériorités	Valideur $
Résultat					
Recherche mutation N°1:	FLT3 ITD				(DE5)
Résultat mutation N°1:	non muté				(DE5)
PCR qualitative suivie d'une analyse de fragment					
Mutations identifiées moelle	Présence				(DE5)
NM_005896.2(IDH1_v001):c.394C>T, NM_005896.2(IDH1_i001):p.Arg132Cys, fréquence allélique du variant : 26%					
Séquençage haut débit (NGS) <20kb des gènes suivants : ASXL1 (exon 12), DDX41 (exon 15), DNMT3A (exon 23), FLT3 (exons 16 et 20), IDH1 (exon 4), IDH2 (exon 4), NPM1 (exon 12).					
Conclusion					
Synthèse :	Détection d'une mutation d'IDH1 (R132C) à un niveau intermédiaire. Absence de détection de mutations d'ASXL1 (exon 12), de DDX41 (exon 15), de DNMT3A (exon 23), de FLT3 (ITD et TKD, exons 16 et 20), d'IDH2 (exon 4) et de NPM1 (exon 12).				(DE5)

Validé par (DE5) Pr Eric DELABESSE

Prise en charge LAM
En pratique au CHU de Toulouse…

LAM <75 ans
Diagnostic et rechute

Reséquençage complet de 85 gènes
Sensibilité 1%



Shallis RM et al. Lancet Haematol. 2023;10(9):e767-e776.

Remerciements

- Biologistes
  - Véronique De Mas
  - Lucie Rigolot
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  - Naïs Prade
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- Technicien.ne.s
  - Anaïs Dufour
  - Cynthia Dumas
  - Loïc Escoriza
  - Laëtitia Malard
  - Pascale Stient

Hamilton Extraction

Hamilton MixPCR1

PCRs

Hamilton MixPCR2

Agilent Magnis

MiSeq NextSeq500