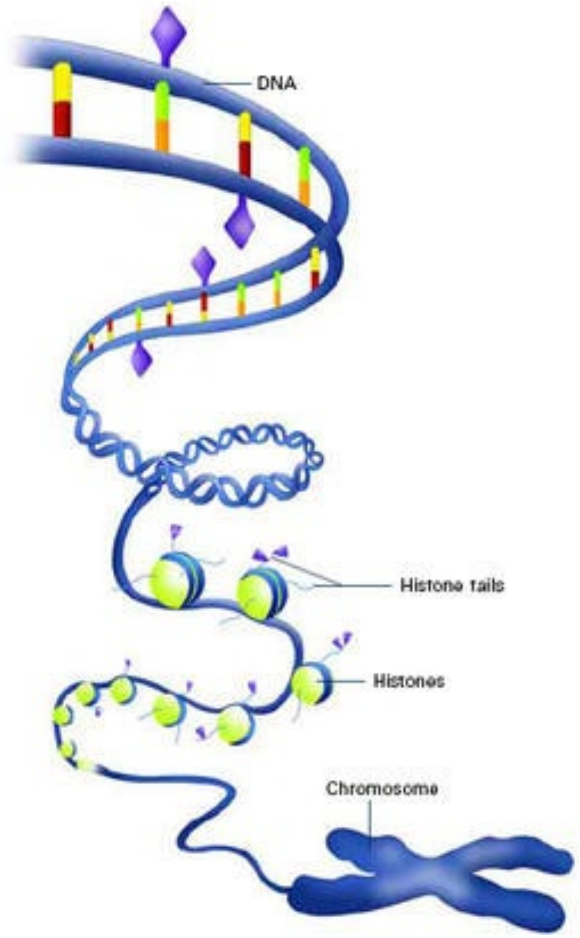
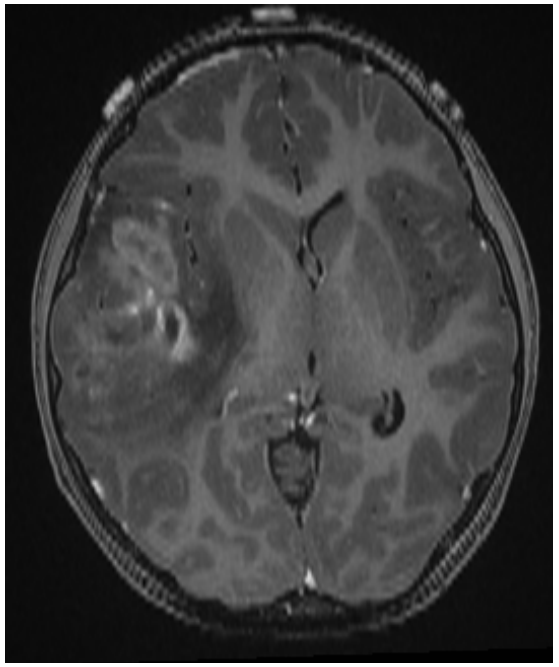
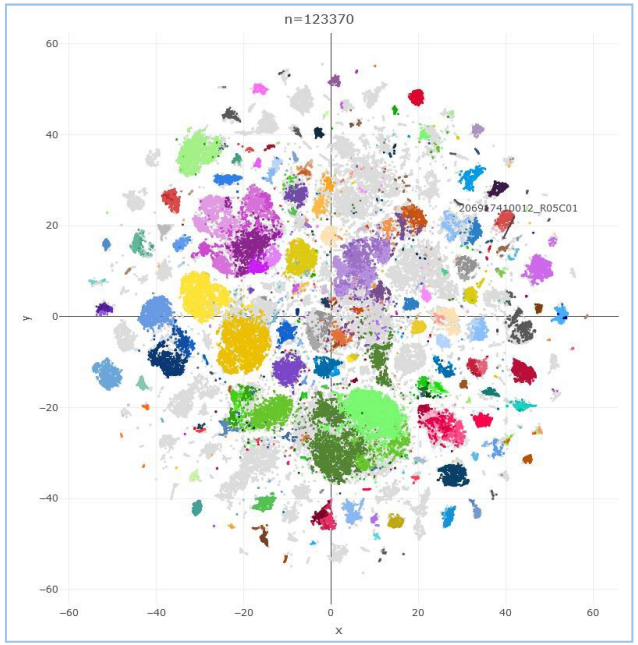
Signatures épigénétiques des gliomes radio-induits (RIG)







Pascale Varlet, GHU-Paris, site Sainte-Anne

Pas de conflit d’intérêt

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PSYCHIATRIE & NEUROSCIENCES

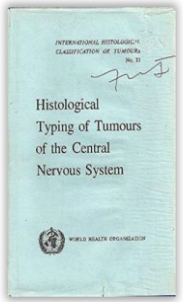
ipnp

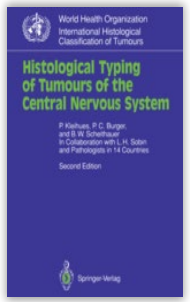
Le diagnostic des tumeurs cérébrales devient histomoléculaire à partir de 2016

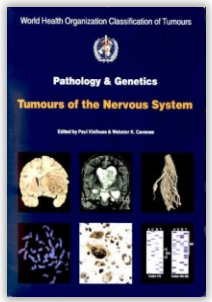
morphologie uniquement

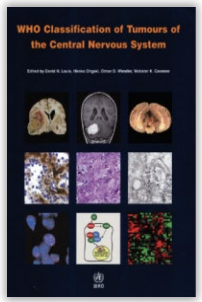
Morpho + biologie moléculaire

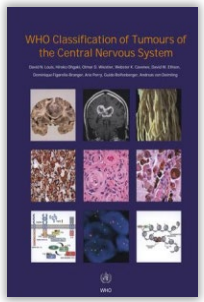
+ méthylome



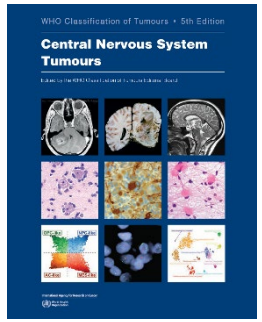








Développement de dizaines de nouveaux biomarqueurs + FISH



1979, 1ère Ed

1993, 2e Ed

2000, 3e Ed

2007, 4e Ed

2016

4e Ed. Revision.

2021

Plateforme de biologie moléculaire

Plateforme de Méthylome

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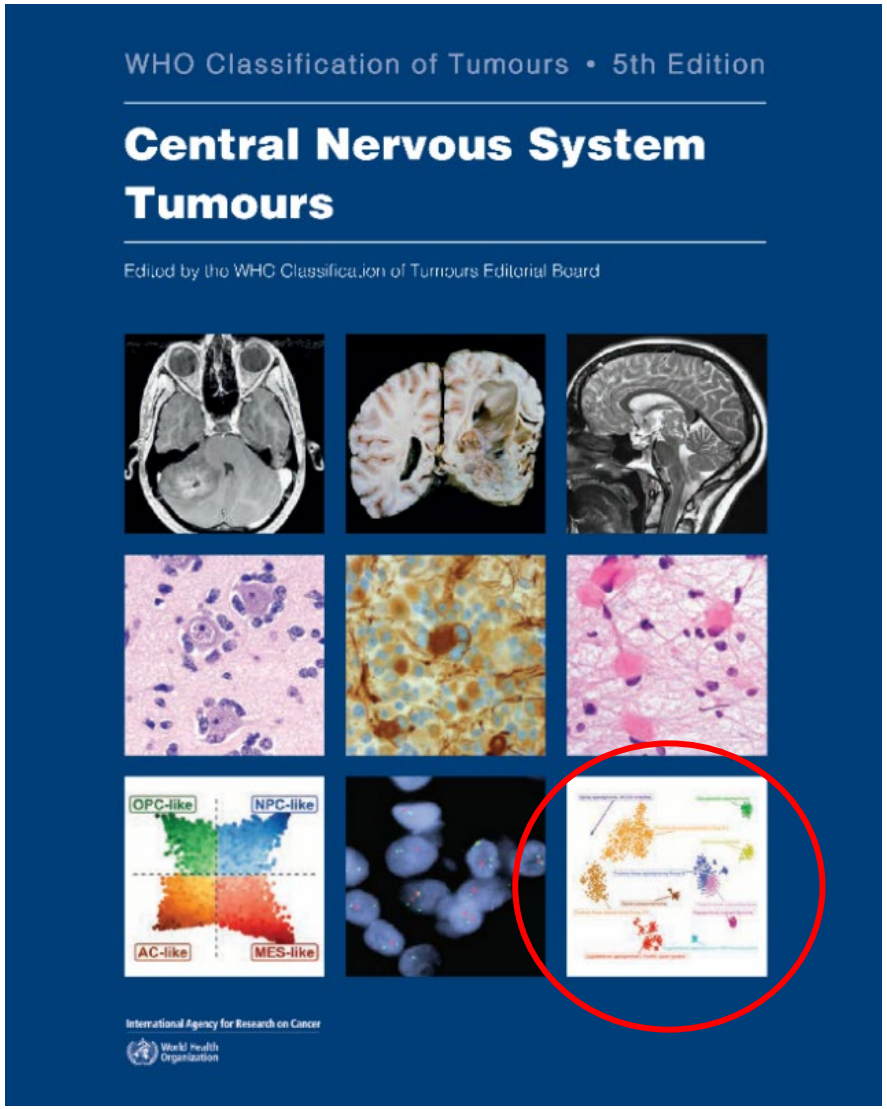
NEUROSCIENCES



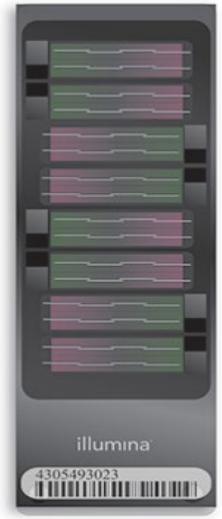
Les indications de l'utilisation du méthylome ont été officialisées et précisées dans la version OMS en 2021

International Agency for Research on Cancer
World Health Organization

Le profil de méthylation représente un critère diagnostique essentiel ou désirable pour 45 types tumoraux

Principes de la technique de méthylome

Séquençage pan-génomique de 950.000 ilots CpG répartis sur le génome

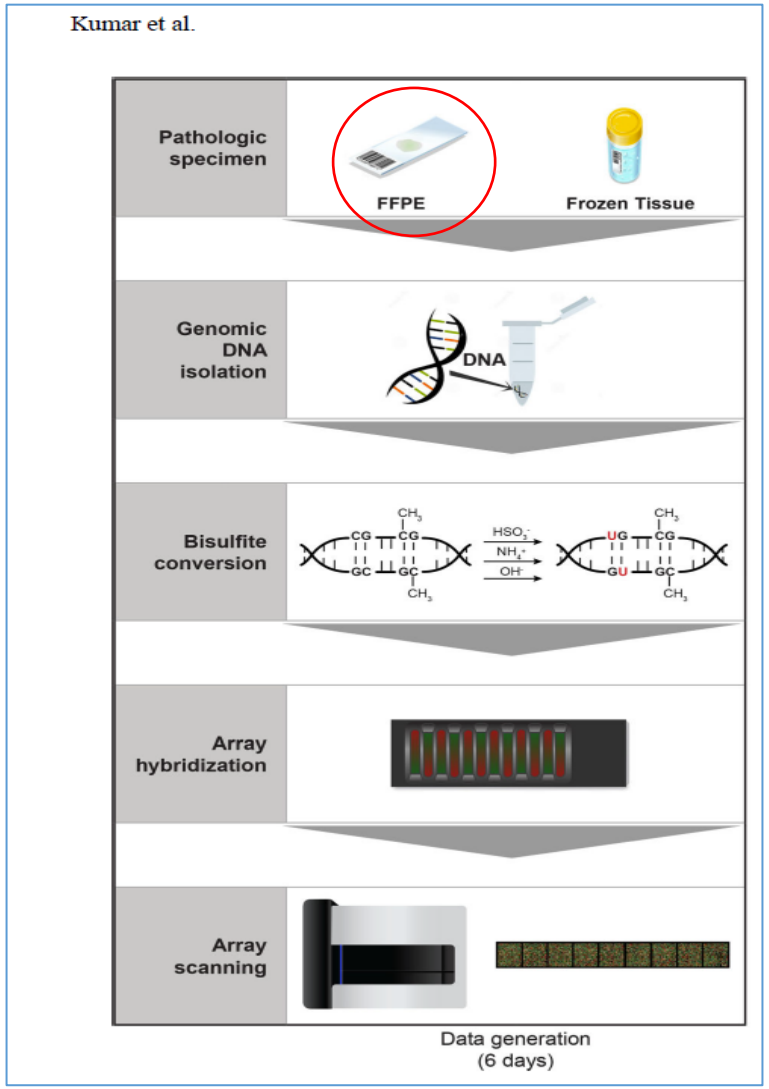


Outils d'intelligence artificielle algorithme gratuit

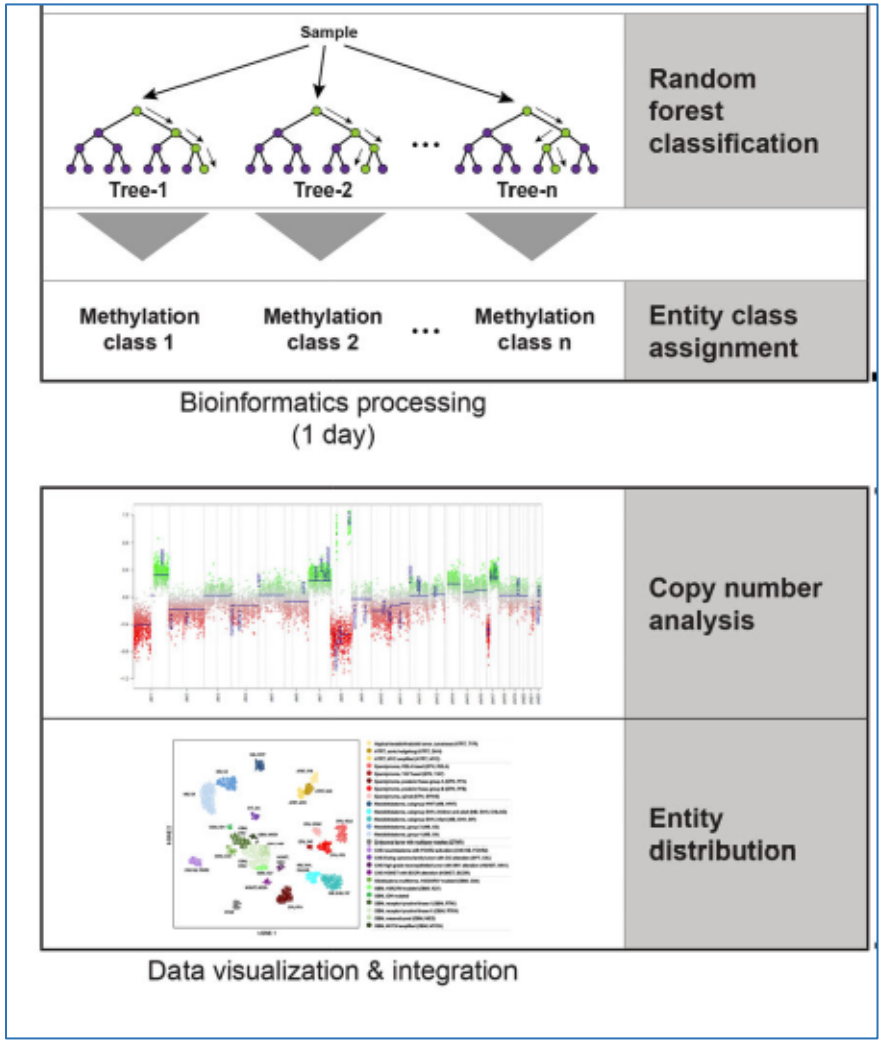
www.molecularneuropathology.org.

Sturm *et al.*, Cell 2016; Capper *et al.*, Nature 2018

Profil de méthylation de l'ADN/ IA



.idat files



ARTIFICIAL INTELLIGENCE

.idat files

SCORE

reflète

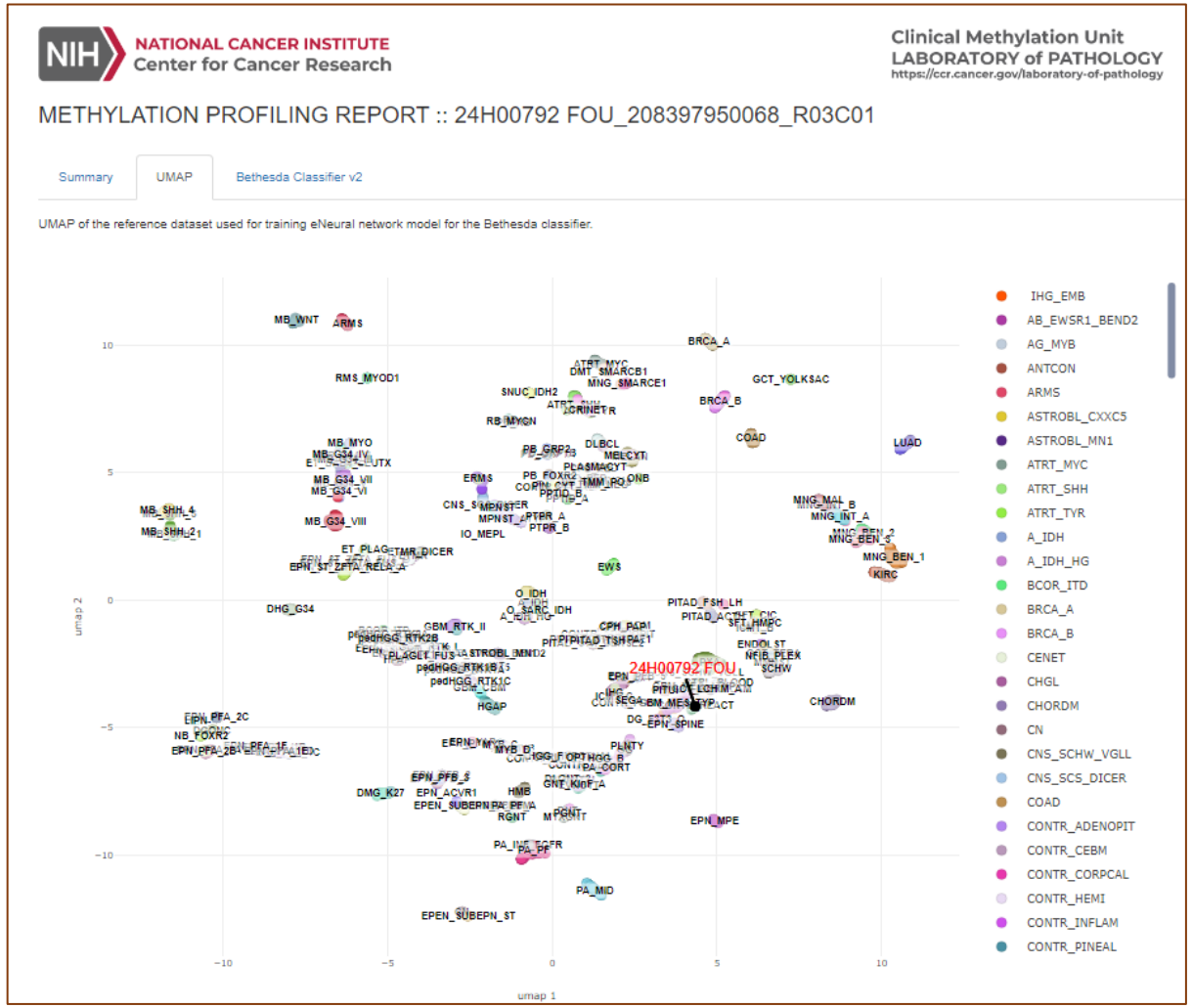
- Origine cellulaire
- Oncogenèse Intrinsèque
- CNV

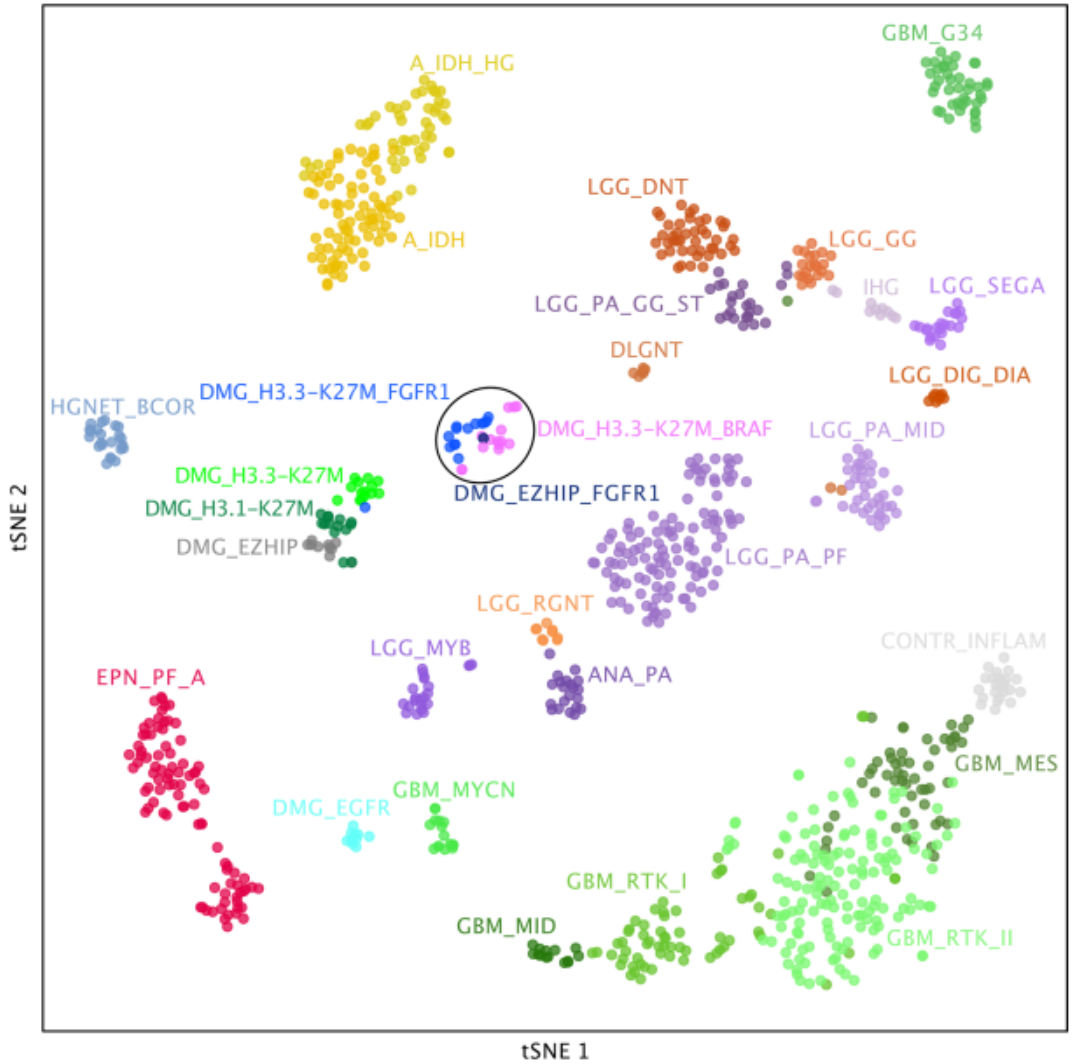
MolecularNeuropathology.org

HEIDELBERG EPIGNOSTIX

NIH NATIONAL CANCER INSTITUTE Center for Cancer Research

Methylscape Analysis



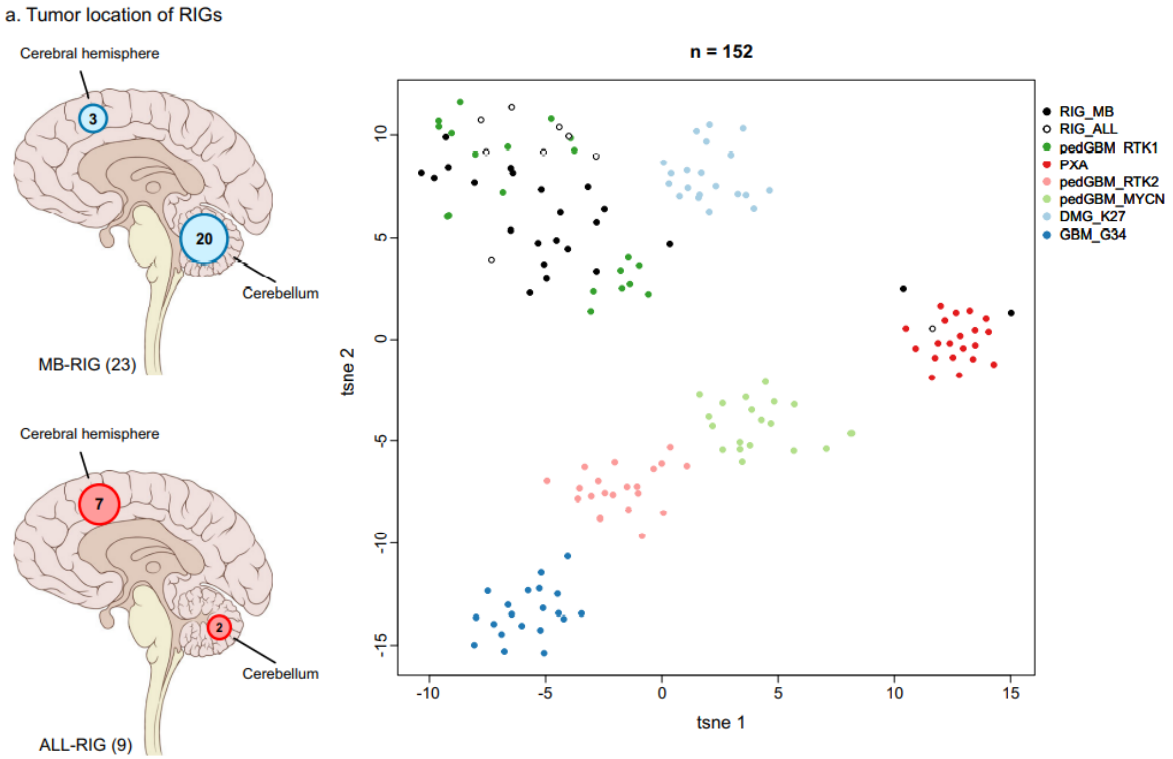


tSNE gliomes malins adulte et pédiatrique et diagnostics différentiels

nature COMMUNICATIONS

Radiation-induced gliomas represent H3-/IDH-wild type pediatric gliomas with recurrent *PDGFRA* amplification and loss of *CDKN2A/B*

Maximilian Y. Deng[1,2,18], Dominik Sturm[1,2,3,18], Elke Pfaff[1,2,3,18], Martin Sill[1,4], Damian Stichel[5,6], Gnana Prakash Balasubramanian[1,4], Stephan Tippelt[7], Christof Kramm[8], Andrew M. Donson[9], Adam L. Green[9], Chris Jones[10], Jens Schittenhelm[11], Martin Ebinger[12], Martin U. Schuhmann[13], Barbara C. Jones[1,2,3], Cornelis M. van Tilburg[1,3,14], Andrea Wittmann[1,2], Andrey Golanov[15], Marina Ryzhova[15], Jonas Ecker[1,3,14], Till Milde[1,3,14], Olaf Witt[1,3,14], Felix Sahm[1,5,6], David Reuss[5,6], David Sumerauer[16], Josef Zamecnik[17], Andrey Korshunov[5,6], Andreas von Deimling[5,6], Stefan M. Pfister[1,3,4,19] & David T. W. Jones[1,2,19]✉



2021

nature COMMUNICATIONS

Comprehensive molecular characterization of pediatric radiation-induced high-grade glioma

John DeSisto[1,13], John T. Lucas Jr.[2,13], Ke Xu[3], Andrew Donson[1], Tong Lin[4], Bridget Sanford[1], Gang Wu[3], Quynh T. Tran[5], Dale Hedges[2], Chih-Yang Hsu[2], Gregory T. Armstrong[6,7], Michael Arnold[8], Smita Bhatia[7,9], Patrick Flannery[1], Rakeb Lemma[1], Lakotah Hardie[10], Ulrich Schüller[11], Sujatha Venkataraman[1], Lindsey M. Hoffman[1,10], Kathleen Dorris[1,10], Jean M. Mulcahy Levy[1,10], Todd C. Hankinson[1,10], Michael Handler[1,10], Arthur K. Liu[10], Nicholas Foreman[1,10], Rajeev Vibhakar[1,10], Kenneth Jones[1], Sariah Allen[5], Jinghui Zhang[3], Suzanne J. Baker[12], Thomas E. Merchant[2], Brent A. Orr[5,14]✉ & Adam L. Green[1,10,14]✉

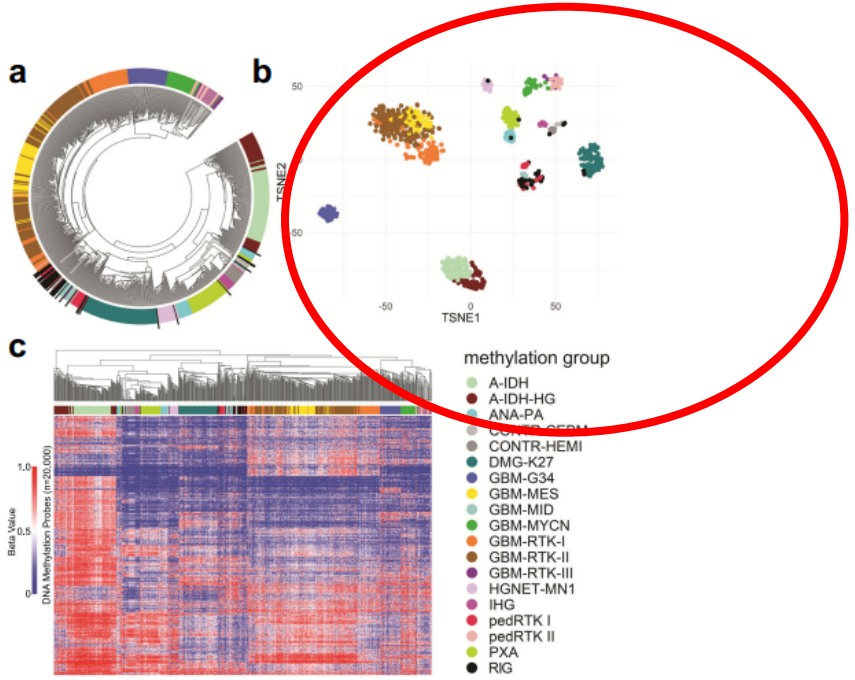
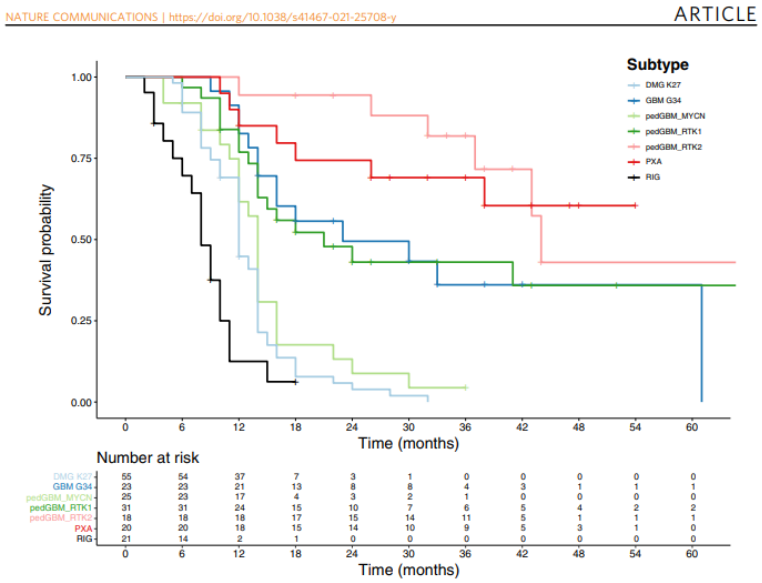
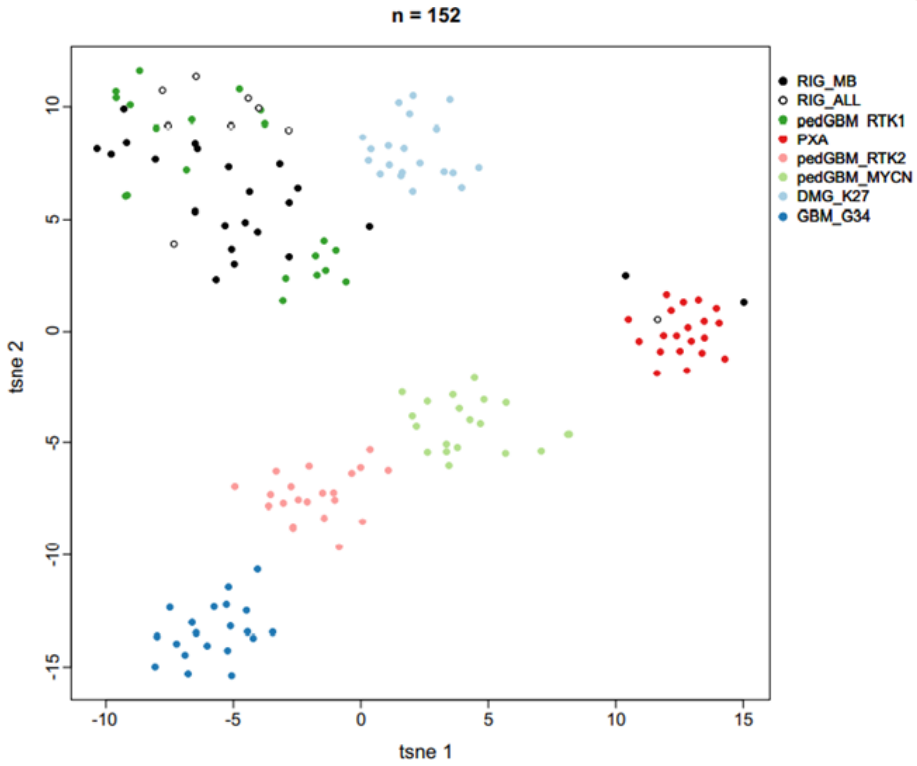


Fig. 2 Methylation group-based classification of RIG. a Circular dendrogram indicating the location of RIG (black bars) relative to reference CNS tumors. **b** Localization of RIGs relative to other CNS cancers in t-SNE space (legend shown below). **c** Dendrogram and heatmap of RIG cases clustered against reference CNS tumors (legend to right). A-IDH astrocytoma, subclass IDH-mutant, A-IDH-HG high-grade astrocytoma, subclass IDH-mutant, ANA PA anaplastic pilocytic astrocytoma, CONTR-CEBM control cerebellum, CONTR-HEMI control cerebral cortex, DMG-K27 diffuse midline glioma, H3K27M-mutant, GBM-G34 glioblastoma, subclass H3.3 p.G34R-mutant, GBM-MES glioblastoma, subclass mesenchymal, GBM-MID glioblastoma, IDH-wild type, subclass midline, GBM-MYCN glioblastoma, subclass MYCN-amplified, GBM-RTK-I, adult glioblastoma, subclass RTK I, GBM-RTK-II adult glioblastoma, subclass RTK II, GBM-RTK-III adult glioblastoma, subclass RTK III, HGNET-MN1 high-grade neuroepithelial tumor with MN1 alteration, IHG infantile high-grade glioma, pedRTK I pediatric glioblastoma, subclass RTK I, pedRTK II pediatric glioblastoma, subclass RTK II, PXA pleomorphic xanthoastrocytoma, RIG radiation-induced high-grade glioma, t-SNE t-distributed stochastic neighbor embedding.

Les gliomes radio-induits pédiatriques

- 3% des enfants survivants de KC pédiatriques (MB, LAL)
- Morphologie identique gliomes malins *de novo*
- Latence de 5 ans (MB) à 8 ans (LAL)
- En zones irradiées
- Moléculairement moins hétérogènes que les gliomes *de novo*
- Mauvais pronostic (médiane 9 mois)

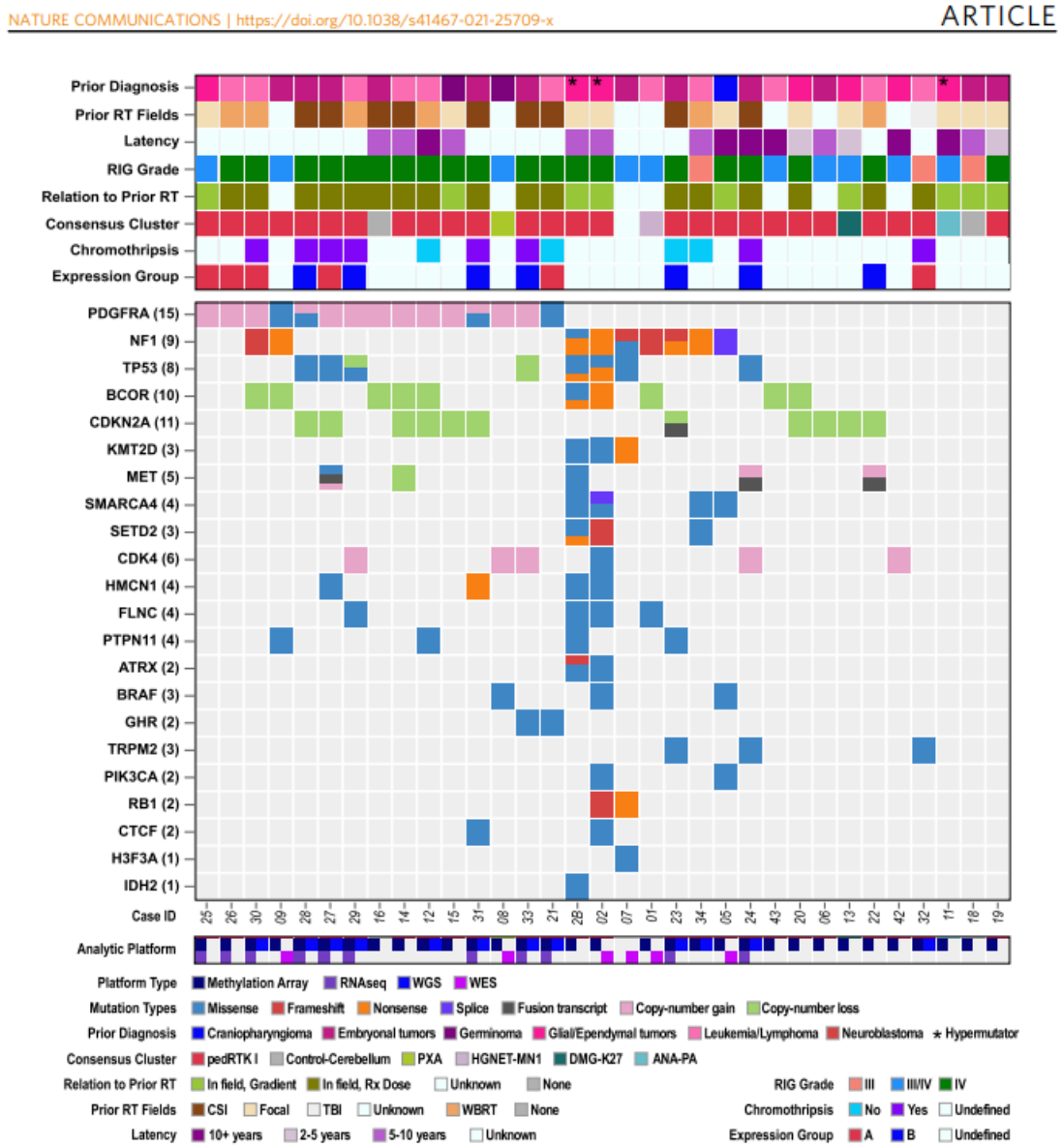




- ✓ Cluster de méthylation = **ped HGG RTK1**
- ✓ Distinct des gliomes de l'adulte et des autres gliomes de l'enfant
- ✓ Probable cellule d'origine similaire
- ✓ Caractérisée par activation aberrante de la voie des MAPKinase/ERK (ampli PDGFRαα) et perte du contrôle du cycle (CDKN2A/B)

Caractéristiques moléculaires des gliomes radio-induits pédiatriques

- ✓ Perte 1p, 113 et 14 et gain du 1q (50%)
- ✓ Amplification PDGFRα (53%)
- ✓ Délétion homozygote CDKN2A/B
- ✓ Gain CDK4
- ✓ Chromotripsis
- ✓ Pas de mutation driver H3 ou IDH1/2
- ✓ Transcriptome: stem-like



Gliomes radio-induits: expositions ou prédispositions ?

nature COMMUNICATIONS

Comprehensive molecular characterization of pediatric radiation-induced high-grade glioma

John DeSisto[1,13], John T. Lucas Jr.[2,13], Ke Xu[3], Andrew Donson[1], Tong Lin[4], Bridget Sanford[1], Gang Wu[3], Quynh T. Tran[5], Dale Hedges[2], Chih-Yang Hsu[2], Gregory T. Armstrong[6,7], Michael Arnold[8], Smita Bhatia[7,9], Patrick Flannery[1], Rakeb Lemma[1], Lakotah Hardie[10], Ulrich Schüller[11], Sujatha Venkataraman[1], Lindsey M. Hoffman[1,10], Kathleen Dorris[1,10], Jean M. Mulcahy Levy[1,10], Todd C. Hankinson[1,10], Michael Handler[1,10], Arthur K. Liu[10], Nicholas Foreman[1,10], Rajeev Vibhakar[1,10], Kenneth Jones[1], Sariah Allen[5], Jinghui Zhang[3], Suzanne J. Baker[12], Thomas E. Merchant[2], Brent A. Orr[5,14]✉ & Adam L. Green[1,10,14]✉

N=32

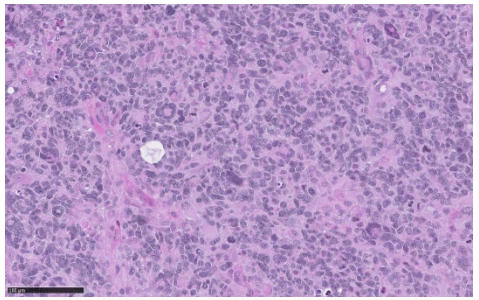
1 seul contexte de Li-Fraumeni

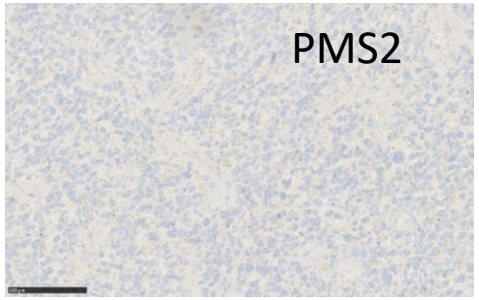
Neuro-Oncology Advances

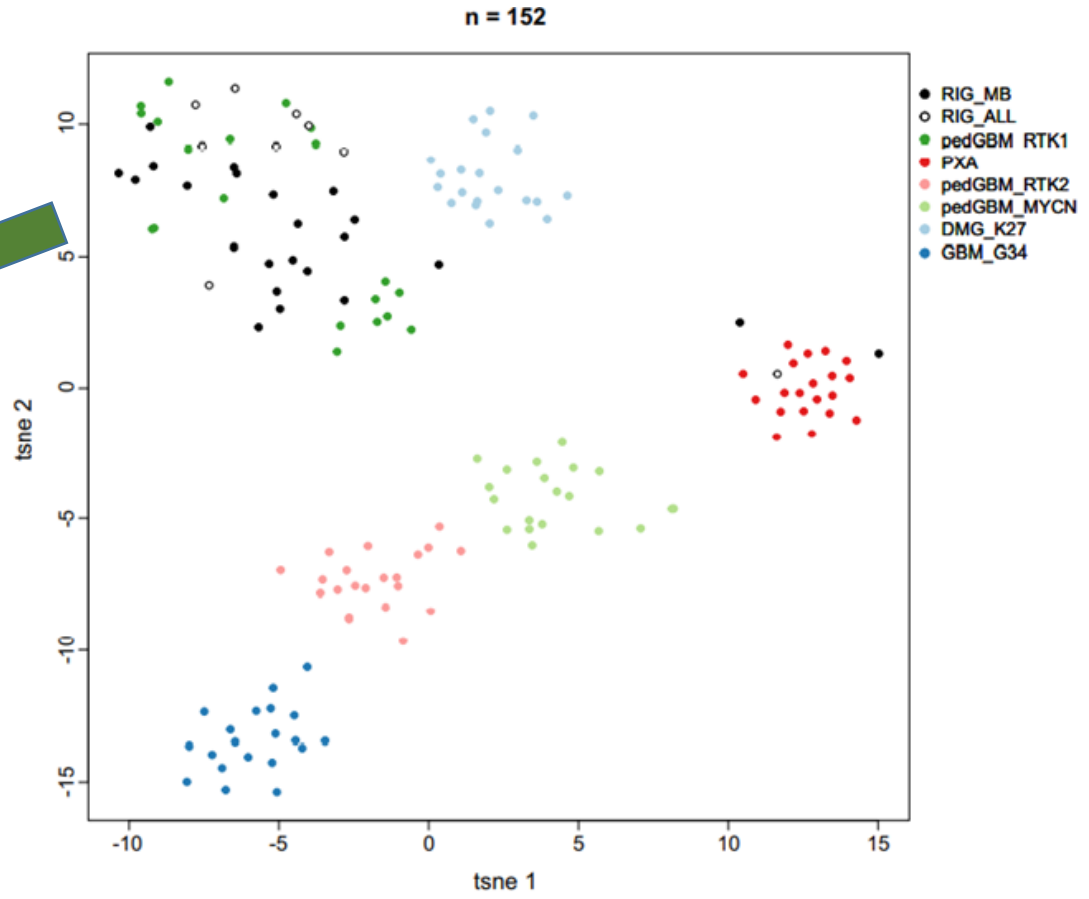
XX(XX), 1–13, 2019 | doi:10.1093/noajnl/vdz033 | Advance Access date 30 November 2019

Constitutional mismatch repair deficiency–associated brain tumors: report from the European C4CMMRD consortium

Léa Guerrini-Rousseau, Pascale Varlet, Chrystelle Colas, Felipe Andreiuolo, Franck Bourdeaut, Karin Dahan, Christine Devalck, Cécile Faure-Conter, Maurizio Genuardi, Yael Goldberg, Michaela Kuhlen, Salma Moalla, Enrico Opocher, Vanessa Perez-Alonso, Astrid Sehested, Irene Slavc, Sheila Unger, Katharina Wimmer, Jacques Grill,† and Laurence Brugières†



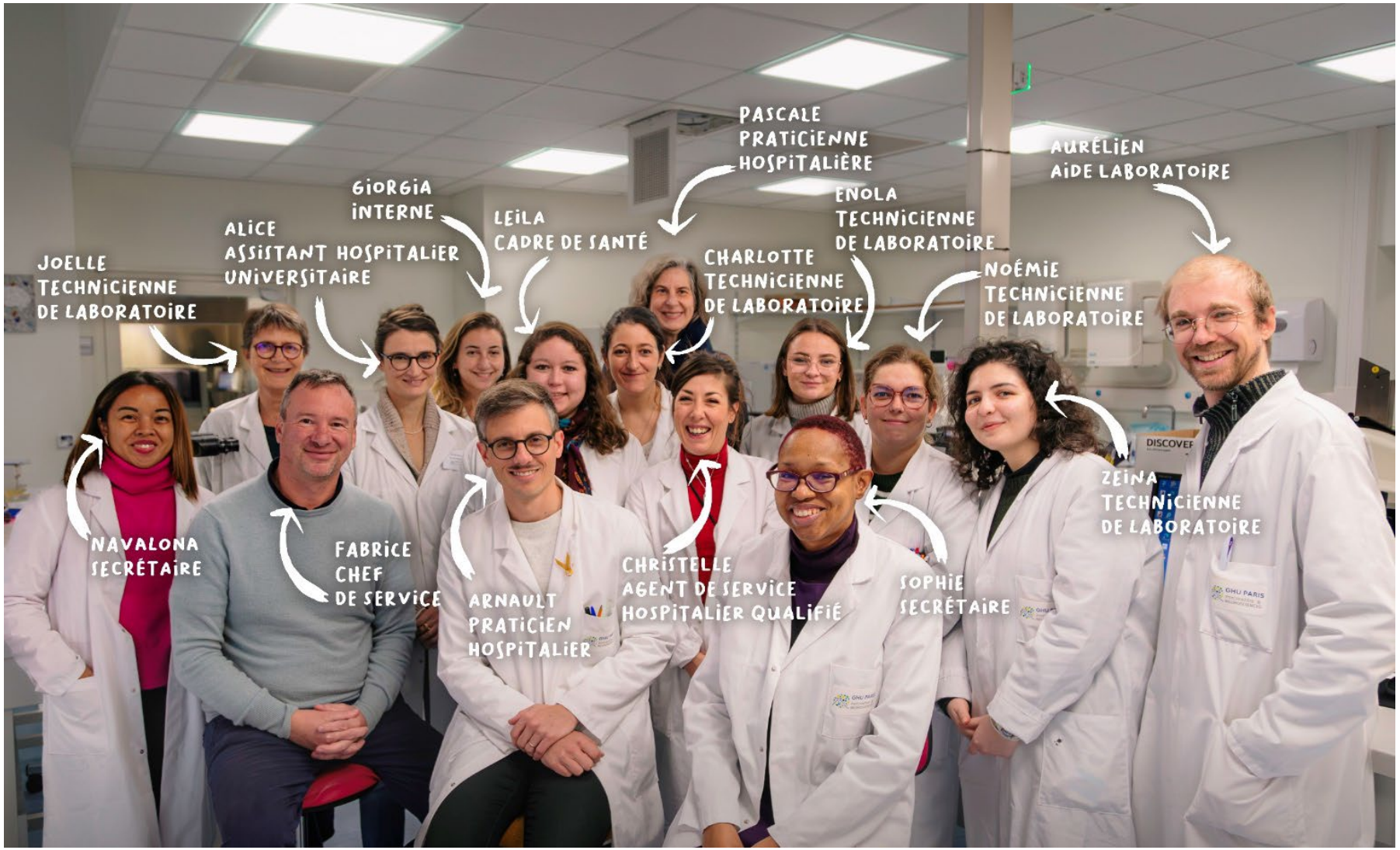




CONCLUSION:
Signatures épigénétiques des gliomes radio-induits

- Données récentes, pas incluses OMS 2021
- **Nouveau type tumoral émergent**: contexte clinique, caractéristiques moleculaires récurrentes, cluster de méthylation unique malgré un aspect morphologique et radiologiques non spécifiques
- Cluster pedHGG RTK1 commun avec CMMRD, Lynch et Li-Fraumeni

⟶ cellule d'origine sensible aux cassures double-brins?



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Few data on histological and radiological features of diffuse pedHGG, RTK2 A/B

Gliomas, glioneuronal tumours, and neuronal tumours

Adult-type diffuse gliomas
- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas
- Diffuse astrocytoma, MYB- or MYBL1-altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumour of the young
- Diffuse low-grade glioma, MAPK pathway-altered

Paediatric-type diffuse high-grade gliomas
- Diffuse midline glioma, H3 K27-altered
- Diffuse hemispheric glioma, H3 G34-mutant
- Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma

International Agency for Research on Cancer
World Health Organization 2021

Acta Neuropathol (2017) 134:507–516
DOI 10.1007/s00401-017-1710-1

ORIGINAL PAPER

H3-/IDH-wild type pediatric glioblastoma is comprised of molecularly and prognostically distinct subtypes with associated oncogenic drivers

Andrey Korshunov[1,2,3] · Daniel Schrimpf[1,2] · Marina Ryzhova[4] · Dominik Sturm[5,6] · Lukas Chavez[5] · Volker Hovestadt[7] · Tanvi Sharma[5] · Antje Habel[1,2] · Anna Burford[8] · Chris Jones[8] · Olga Zheludkova[9] · Ella Kumirova[10] · Christof M. Kramm[11] · Andrey Golanov[4] · David Capper[1,2,3] · Andreas von Deimling[1,2,3] · Stefan M. Pfister[3,5,6] · David T. W. Jones[3,5]

3 distinct molecular subtypes recognized by their DNA methylation profiles:

1. pedHGG-MYCN(*MYCN* amplification/LFS, co-amplification *MYCN-ID2*)
2. pedHGG-RTK1 (CMMRD, Lynch, RIG, *PDGFRA* amplification)
3. pedHGG-RTK2 (*EGFR* ampli. *hTERT with 2 subclasses A and B)*

the rarest being RTK2A> RTK2B

#18439

Diagnostic criteria for diffuse paediatric-type high-grade glioma (pHGG), H3-wildtype and IDH-wildtype

Essential:	
A diffuse glioma with mitotic activity occurring in a child or young adult	
AND	
Absence of mutations in *IDH1* or *IDH2*	
AND	
Absence of mutations in H3 genes	
AND	
	Methylation profile aligned with pHGG RTK1, pHGG RTK2, or pHGG MYCN
	OR
	Key molecular features: *PDGFRA* alteration, *EGFR* alteration, or *MYCN* amplification
Desirable:	
Microvascular proliferation	
Necrosis, typically palisading	
H3 p.K28me3 (K27me3) retained	

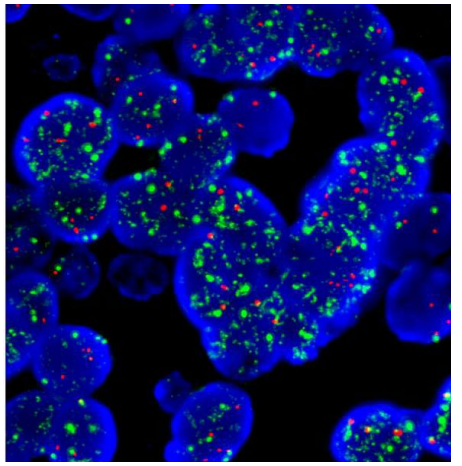
International Agency for Research on Cancer

World Health Organization

Au moins 3 sous-types:
pRTK1
pRTK2a/b
HGG MYCN

Toutes localisations

Diffuse paediatric-type HGG, H3-WT and IDH-WT



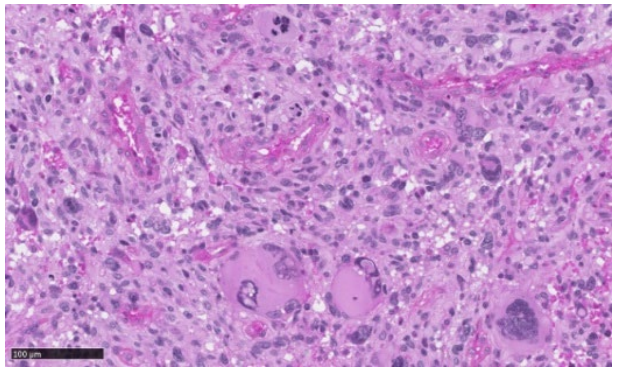
- Diagnostic d'exclusion
- Toutes localisations et âges
- Grade 4

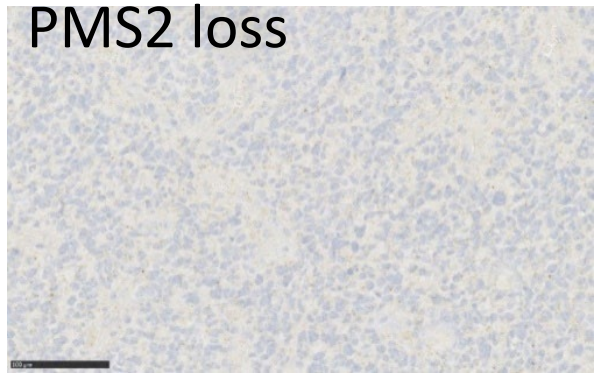
- Gliome radio-induit (driver PDGFR amplification)
- Dans le contexte de constitutional mismatch repair deficiency (CMMRD)

Ped RTK1

- PedRTK2 enriched with EGFR amplification

- Ped HGG with MYCN amplification enriched with MYCN/ID2 co-amplification



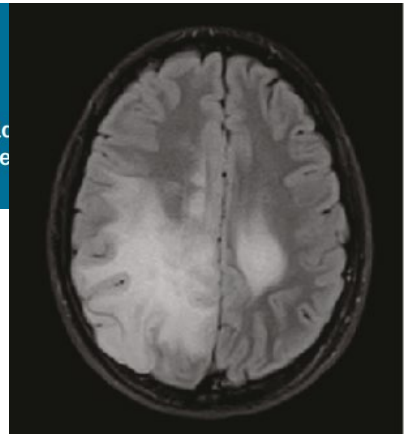


Search for CMMRD or Li-Fraumeni

Molecular pediatric GC-associated characteristics

Neuro-Oncology
26(9), 1723–1737, 2024 | https://doi.org/10.1093/neuonc/noae080 | Advance Access date 8 May 2024

Gliomatosis cerebri in children: A poor prognostic phenotype of diffuse gliomas with a distinct molecular profile

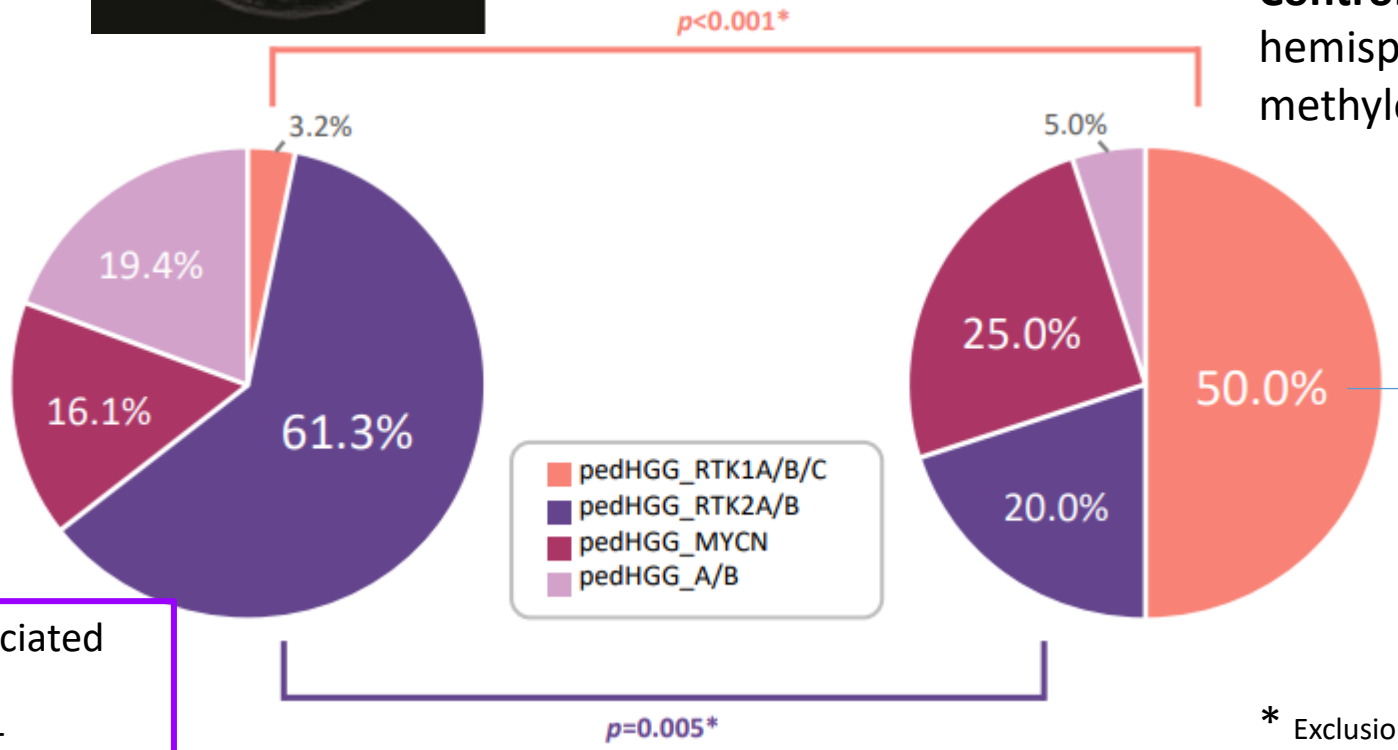


European ped **GC cohort**
n=104 methyloma = 49
850K V12.5

nature medicine
2022
Article
https://doi.org/10.1038/s41

Multiomic neuropathology improves diagnostic accuracy in pediatric neuro-oncology

Dominik Sturm[1,2,3], David Capper[4,5], Felipe Andreiuolo[6,7,8], Marco Gessi[6], Christian Kölsche[9], Annekathrin Reinhardt[10], Philipp Sievers[10], Annika K. Wefers[11], Azadeh Ebrahimi[6,10,12], Abigail K. Suwala[10,12,13], Gerrit H. Gielen[6], Martin Sill[1,14], Daniel Schrimpf[10], Damian Stichel[10,12], Volker Hovestadt[15,16], Bjarne Daenekas[4,15,16], Agata Rode[1,2], Stefan Hamelmann[10,12], Christopher Previti[1,14], Natalie Jäger[1,14], Ivo Buchhalter[17], Mirjam Blattner-Johnson[1,2], Barbara C. Jones[1,2,3], Monika Warmuth-Metz[18,19], Brigitte Bison[19,20], Kerstin Grund[21], Christian Sutter[21], Steffen Hirsch[1,14,21], Nicola Dikow[21], Martin Hasselblatt[22], Ulrich Schüller[11,23,24], Arend Koch[4], Nicolas U. Gerber[25], Christine L. White[26,27,28], Molly K. Buntine[26,27], Kathryn Kinross[29], Elizabeth M. Algar[26,27,30], Jordan R. Hansford[31], Nicholas G. Gottardo[32,33,34], Martin U. Schuhmann[35], Ulrich W. Thomale[36], Pablo Hernáiz Driever[37], Astrid Gnekow[38], Olaf Witt[1,3,39], Hermann L. Müller[40], Gabriele Calaminus[41], Gudrun Fleischhack[42], Uwe Kordes[23], Martin Mynarek[23,43], Stefan Rutkowski[23], Michael C. Frühwald[38], Christof M. Kramm[44], Andreas von Deimling[10,12], Torsten Pietsch[6,45], Felix Sahm[1,10,12,45], Stefan M. Pfister[1,3,14,45] & David. T. W. Jones[1,2,45]



Control population-based pediatric hemispheric diffuse gliomas methyloma-defined n=80*

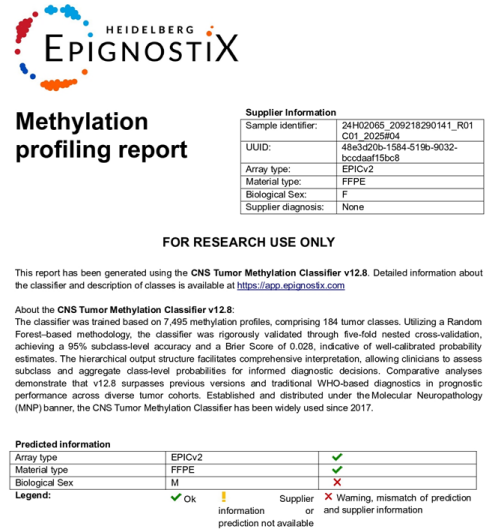
→ essentially radiation-associated gliomas

ped GC are significantly associated with pedHGG RTK2 A>B
pedHGG RTK1 almost absent

* Exclusion infant-type HGG, isolated midline location, non-diffuse gliomas, calibrated score < 0,9 V11.b4

Plusieurs classifieurs en 2024

- Différents types d'algorithmes (RF, neural network)
- Différents set de référence
- Différents types de données (450K, EPIC V1 ou V2, nanopore,


HEIDELBERG EPIGNOSTIX

Methylation profiling report

Supplier Information

Sample identifier:	24H02065_209218290141_R01C01_2025#04
UUID:	48e3d20b-1584-519b-9032-bccdaaf15bc8
Array type:	EPICv2
Material type:	FFPE
Biological Sex:	F
Supplier diagnosis:	None

FOR RESEARCH USE ONLY

This report has been generated using the **CNS Tumor Methylation Classifier v12.8**. Detailed information about the classifier and description of classes is available at https://app.epignostix.com

About the **CNS Tumor Methylation Classifier v12.8**:
The classifier was trained based on 7,495 methylation profiles, comprising 184 tumor classes. Utilizing a Random Forest-based methodology, the classifier was rigorously validated through five-fold nested cross-validation, achieving a 95% subclass-level accuracy and a Brier Score of 0.028, indicative of well-calibrated probability estimates. The hierarchical output structure facilitates comprehensive interpretation, allowing clinicians to assess subclass and aggregate class-level probabilities for informed diagnostic decisions. Comparative analyses demonstrate that v12.8 surpasses previous versions and traditional WHO-based diagnostics in prognostic performance across diverse tumor cohorts. Established and distributed under the Molecular Neuropathology (MNP) banner, the CNS Tumor Methylation Classifier has been widely used since 2017.

Predicted information

Array type	EPICv2	✓
Material type	FFPE	✓
Biological Sex	M	✗

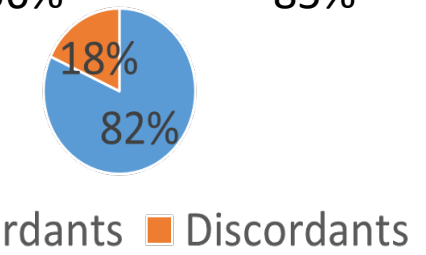
Legend: ✓ Ok ! Supplier information or prediction not available ✗ Warning, mismatch of prediction and supplier information

  - Standardisation/ études comparatives/ accessibilité
  - Traçabilité des données utilisées +++ (set de référence, algorithme, type de matériel)

NIH NATIONAL CANCER INSTITUTE Center for Cancer Research

n=946

- Score > 0,9 56% 85%



Les gliomes malins dans le cadre d'un syndrome CMMRD= pRTK1

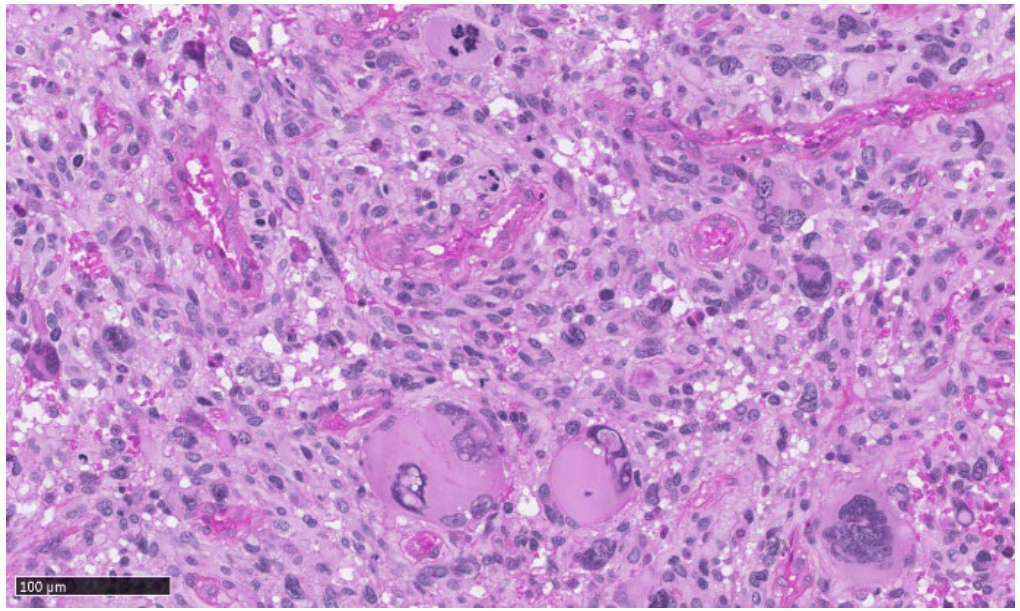
C4MMRD European consortium, 10 pays
79 patients avec perte bi-allélique gènes MMR
49 patients avec une tumeur cérébrale
Moyenne 9,3 ans
26 cas relus et classés selon OMS 2016

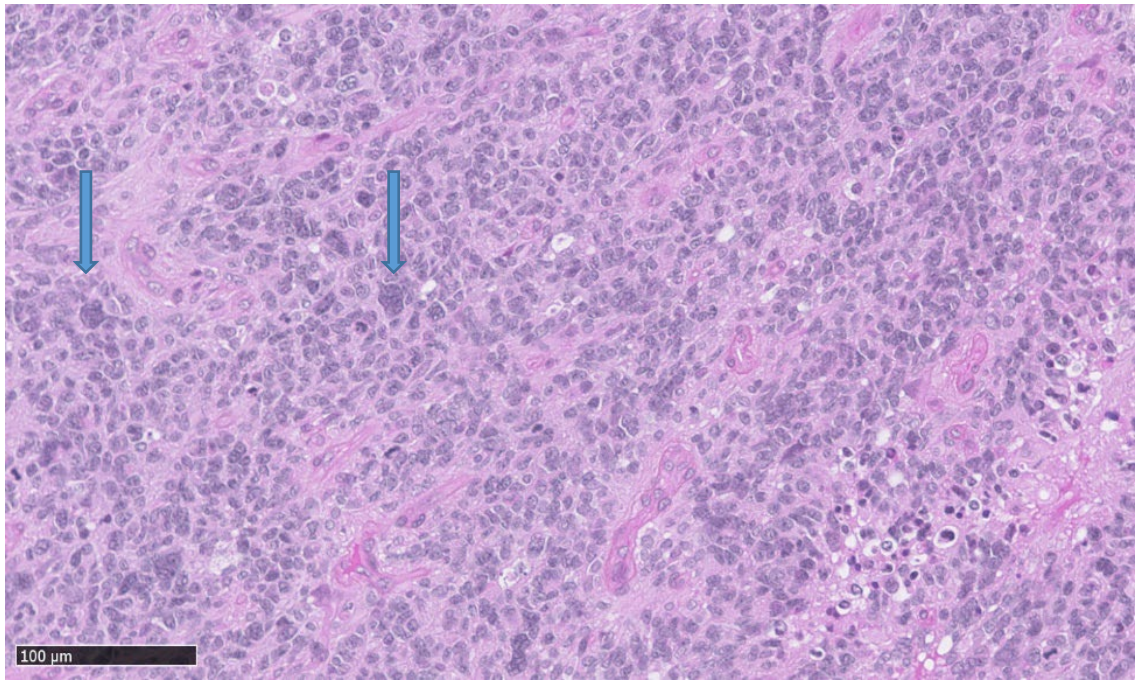
Neuro-Oncology Advances
XX(XX), 1–13, 2019 | doi:10.1093/noajnl/vdz033 | Advance Access date 30 November 2019

Constitutional mismatch repair deficiency–associated brain tumors: report from the European C4CMMRD consortium

Léa Guerrini-Rousseau, Pascale Varlet, Chrystelle Colas, Felipe Andreiuolo, Franck Bourdeaut, Karin Dahan, Christine Devalck, Cécile Faure-Conter, Maurizio Genuardi, Yael Goldberg, Michaela Kuhlen, Salma Moalla, Enrico Opocher, Vanessa Perez-Alonso, Astrid Sehested, Irene Slavc, Sheila Unger, Katharina Wimmer, Jacques Grill,† and Laurence Brugières†

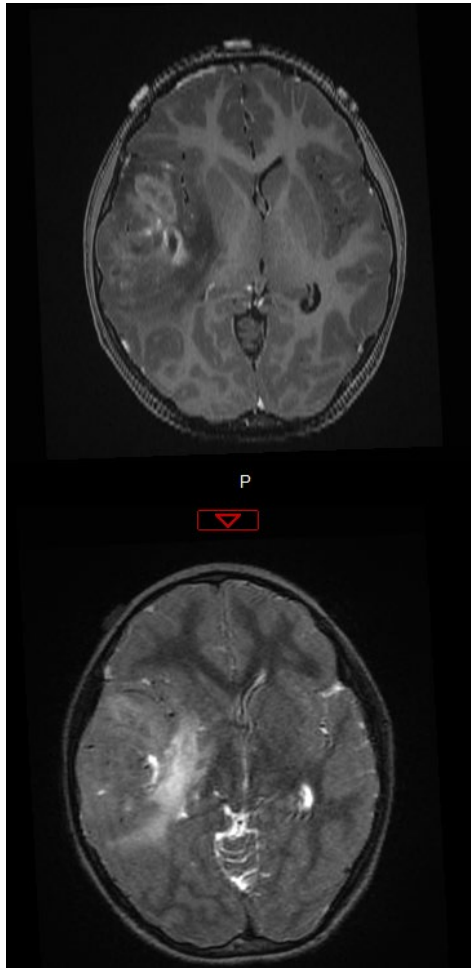
21 GBM-IDH WT dont 5 à cellules géantes et 11 avec quelques cellules géantes, 3 A3 et 2 PXA 3.



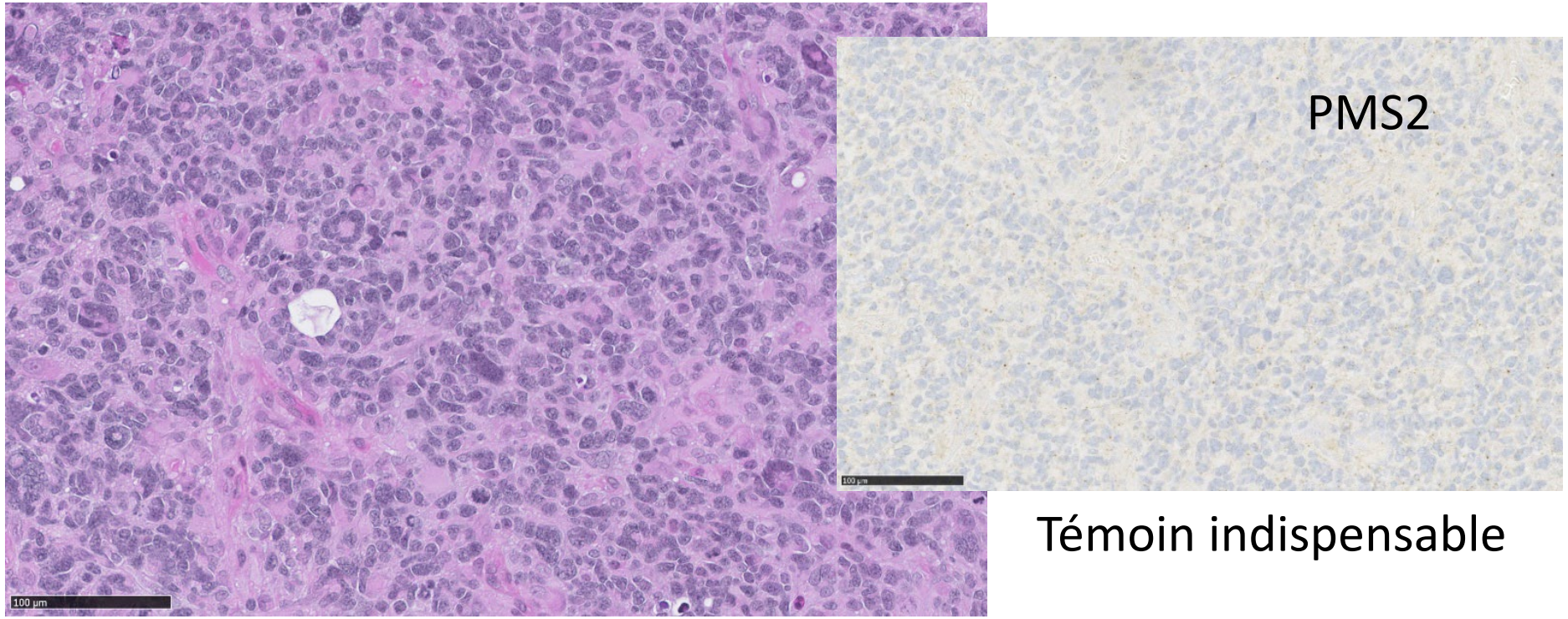


Les gliomes malins dans le cadre d'un syndrome CMMRD

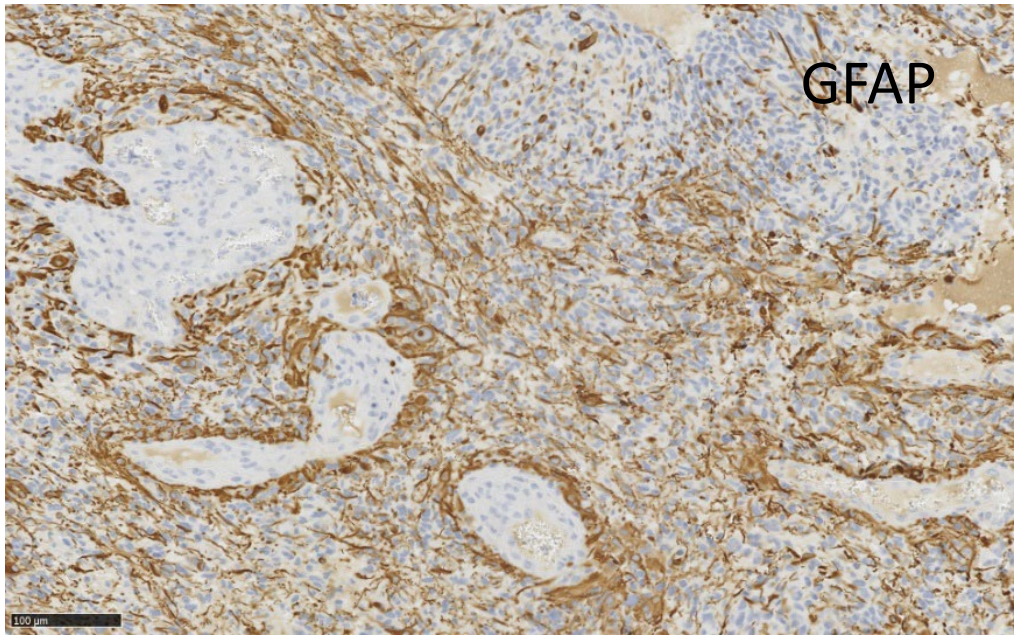
Bonne concordance des données de perte d'expression avec les données moléculaires

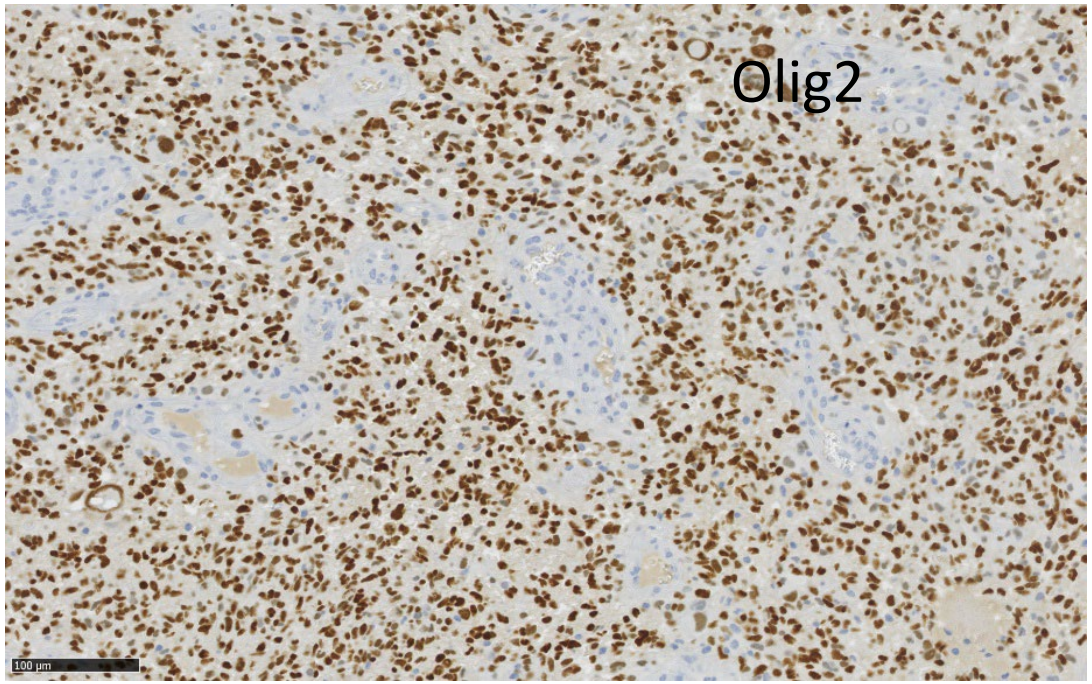


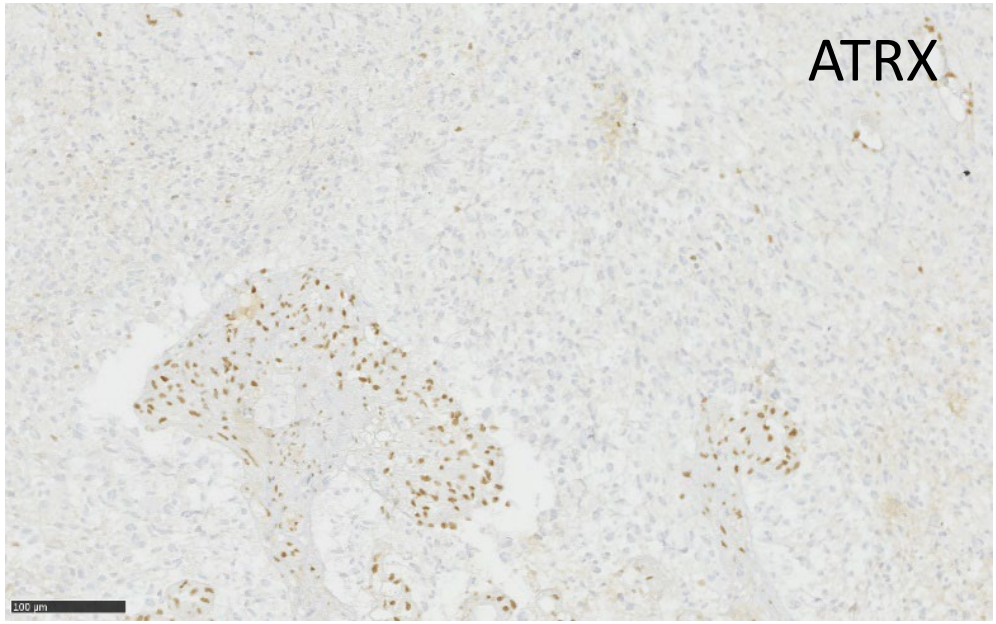
Le plus fréquent: **perte PMS2** puis MSH2, MSH6



Témoin indispensable







Tester CMMRD si gliome malin non-IDH, non-histone surtout si cellules géantes

Demander renseignements cliniques: ATCD familiaux, personnels (lymphome), consanguinité ou taches café-au-lait