Gliomaの遺伝子異常

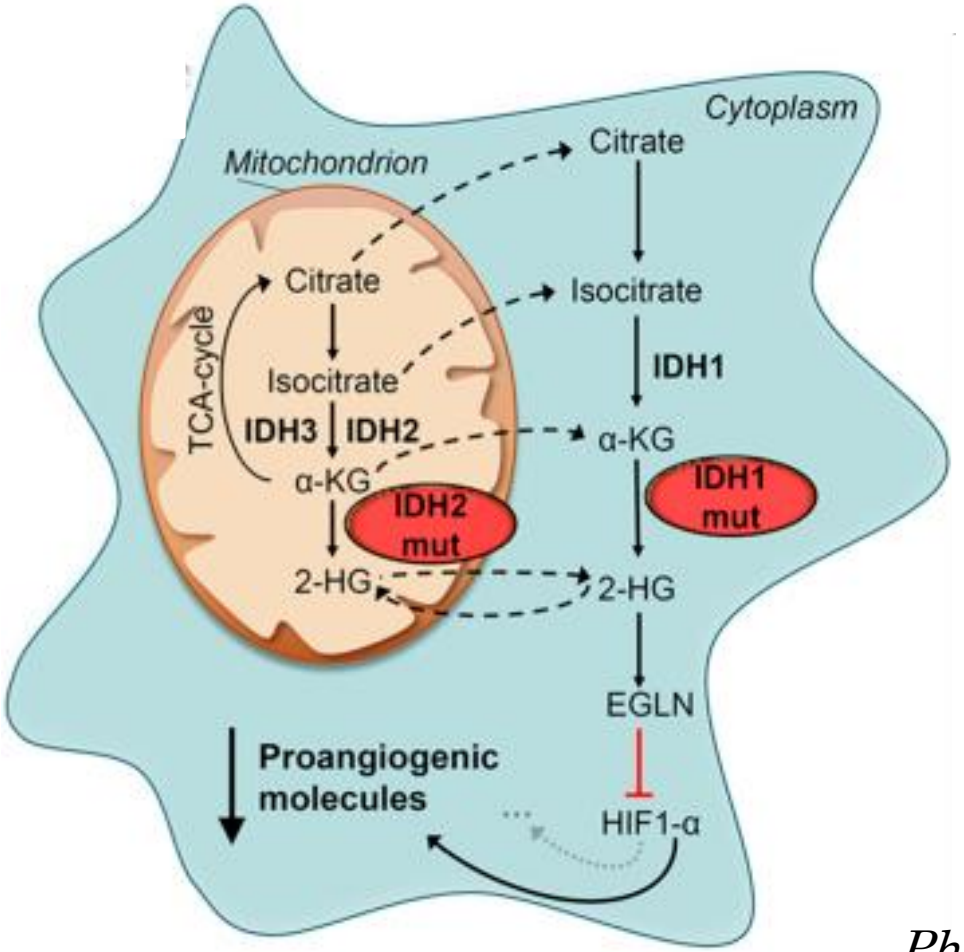
2016･2･16　抄読会　Review

梅野　哲也

主にLow grade gliomaにおいて重要な異常

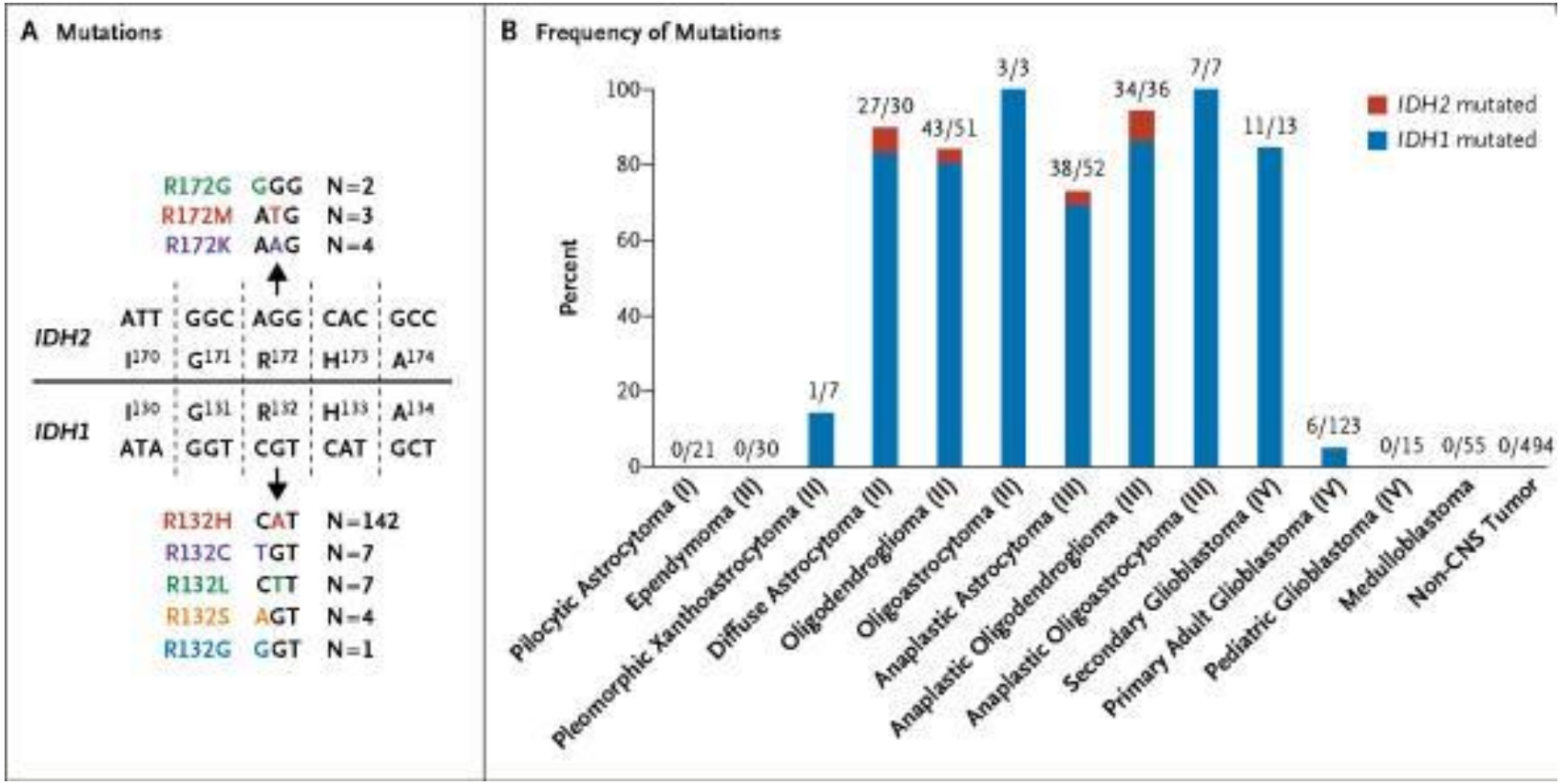
- IDH1/2
- TP53
- 1p/19q
- ATRX / TERT
- FUBPI, CIC
- BRAF

IDH1/2 mutation



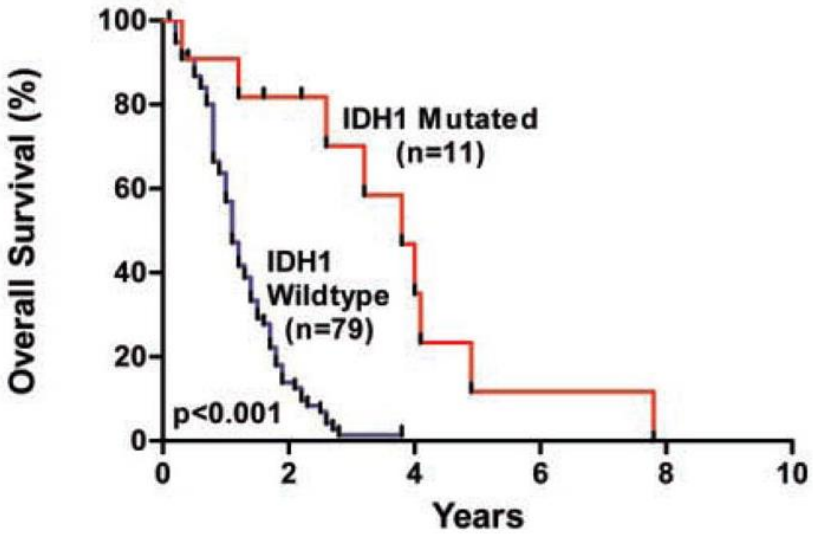
Philipp K et al. Sci Rep. 2015; 5: 16238.

IDH1/2 mutation

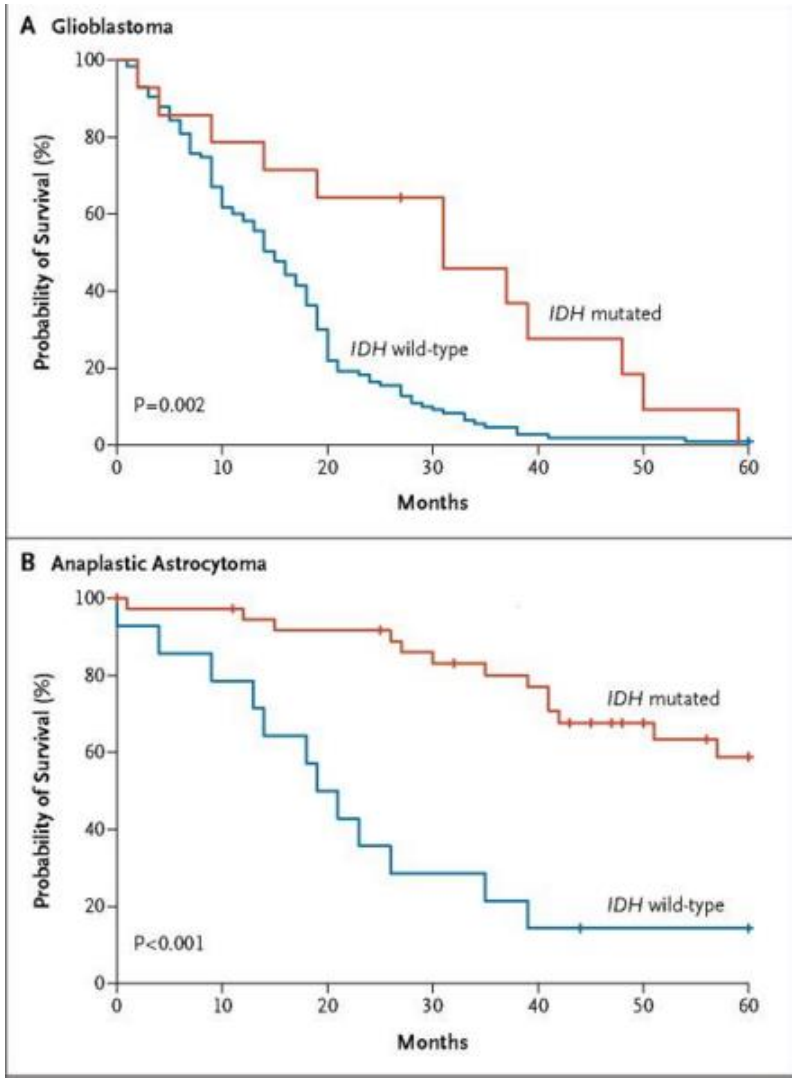


Yan H et al. NEJM 360: 765,2009

IDH1/2 mutation

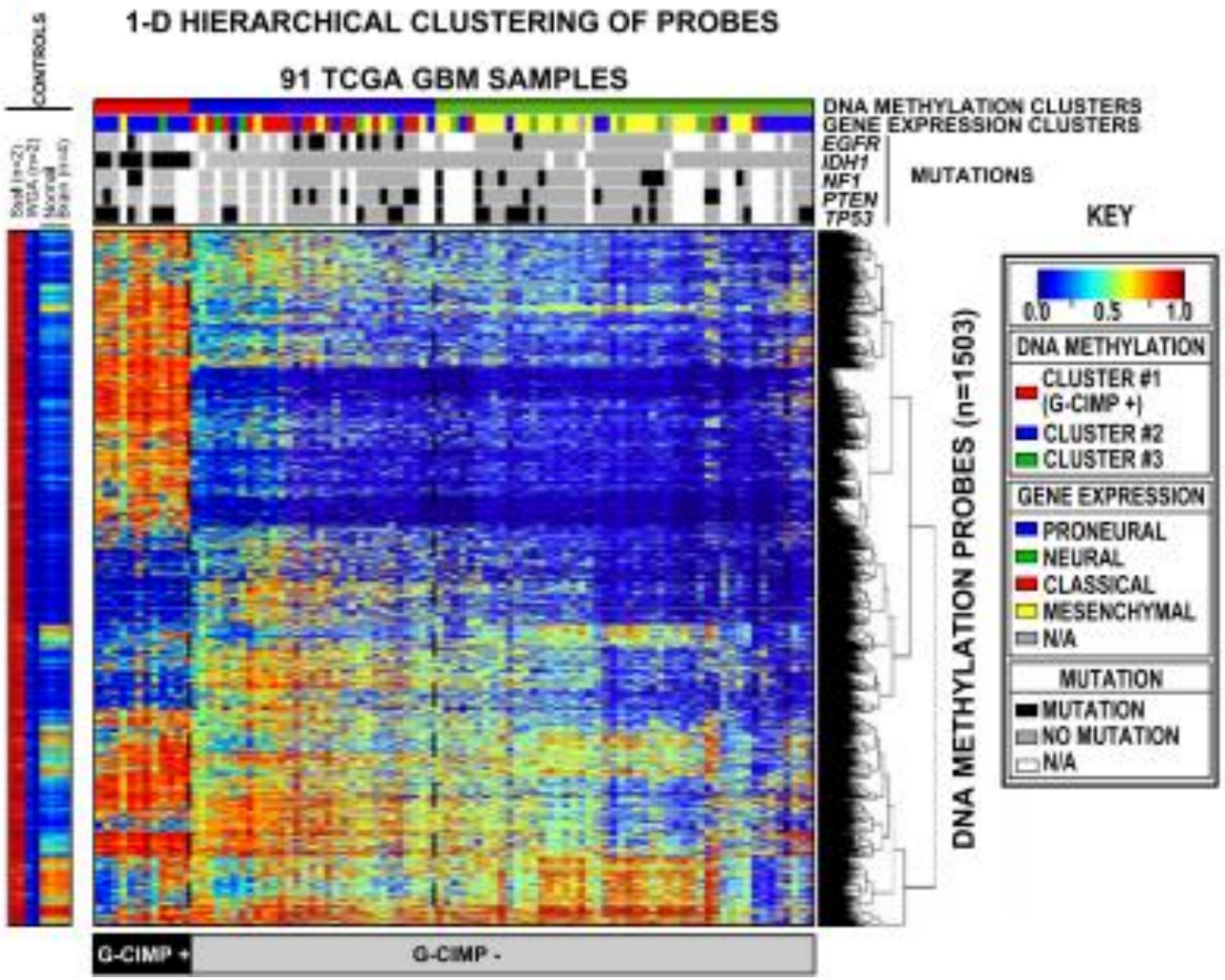


Parsons DW et al. Science 321: 1808,2008



Yan H et al. NEJM 360: 765,2009

IDH1/2　mutation

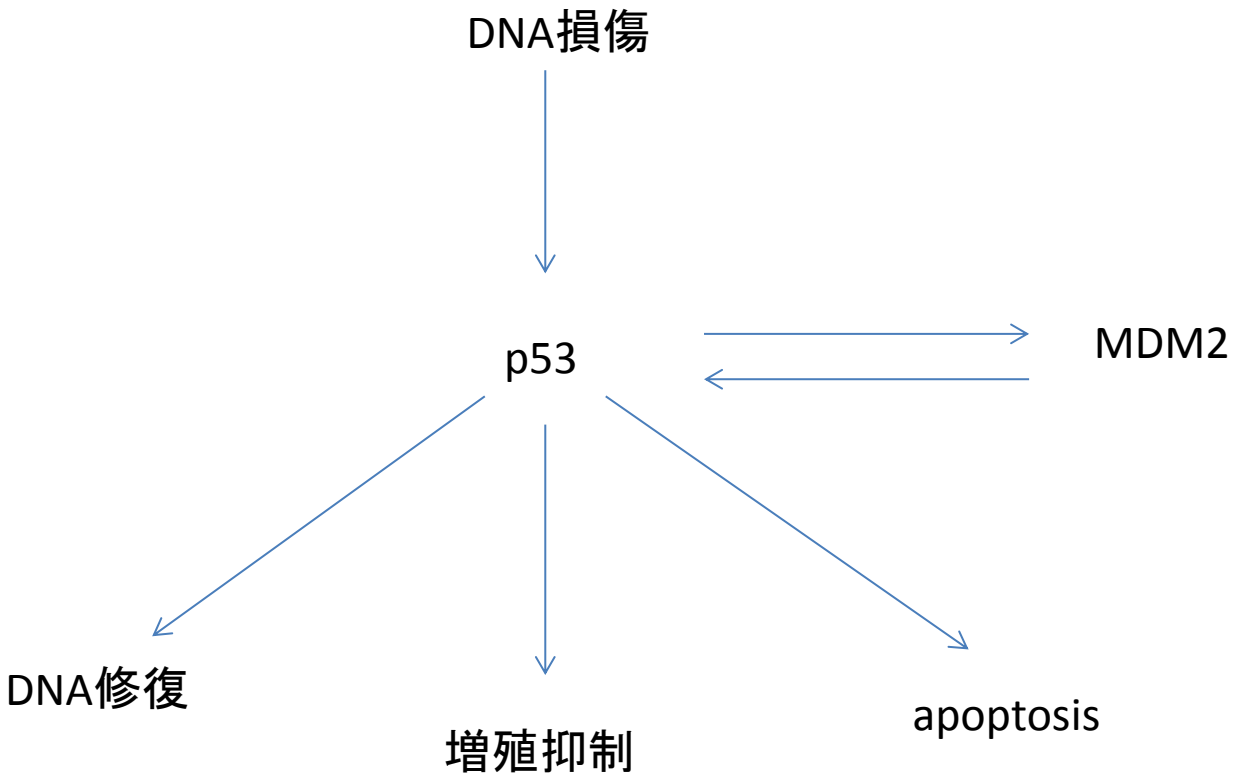


TCGAでのメチローム解析

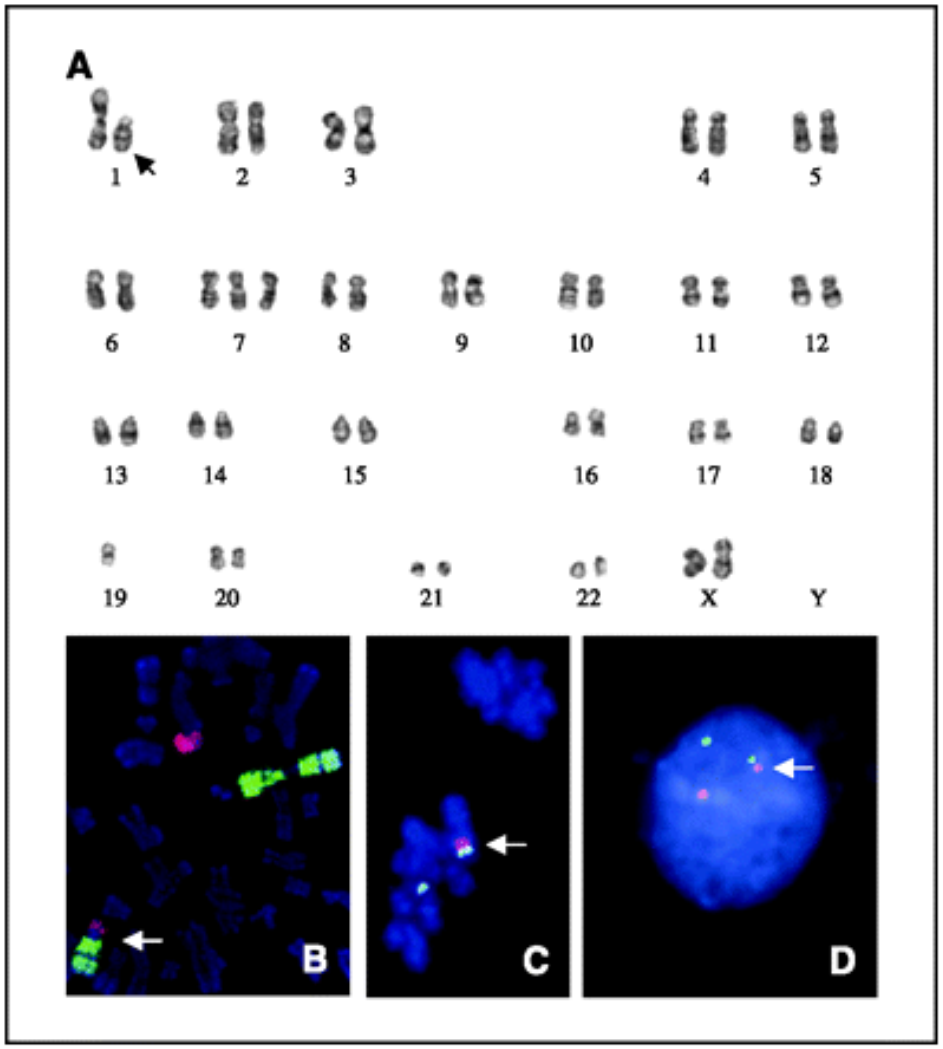
IDH1mutationとGCIMPとの相関

Noushmehr H et al. Cancer cell 2010

TP53 mutation



1p/19q codeletion

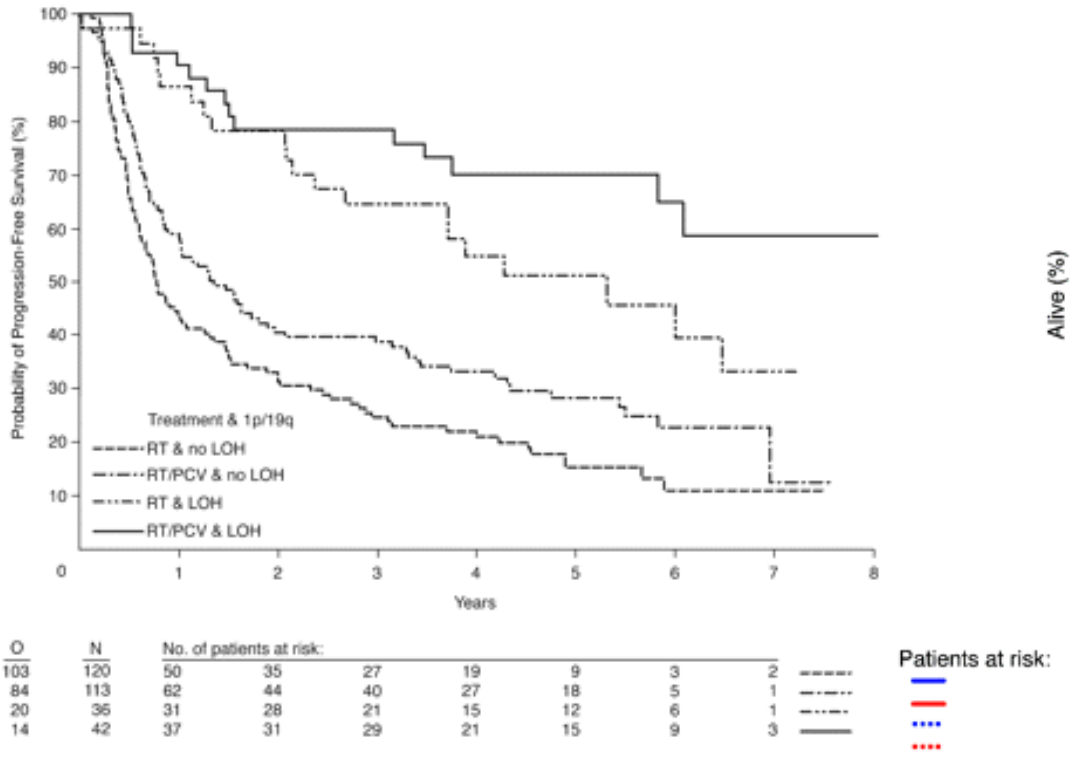


Jenkins et al. Cancer Res 2006

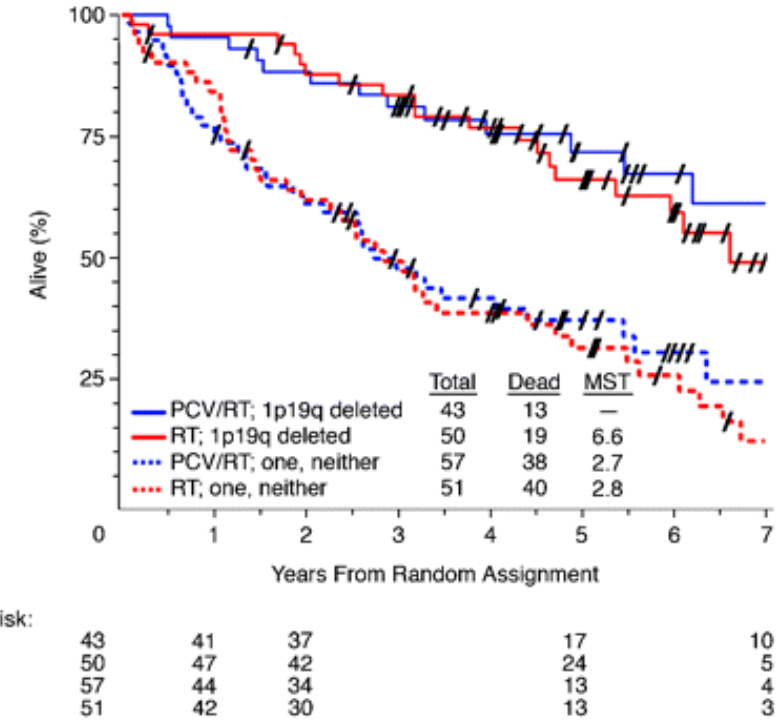
Translocation t(1;19)(q10;p10)

- Microsatellite解析
- FISH法
- MLPA法
- SNPアレイ

1p/19q codeletion



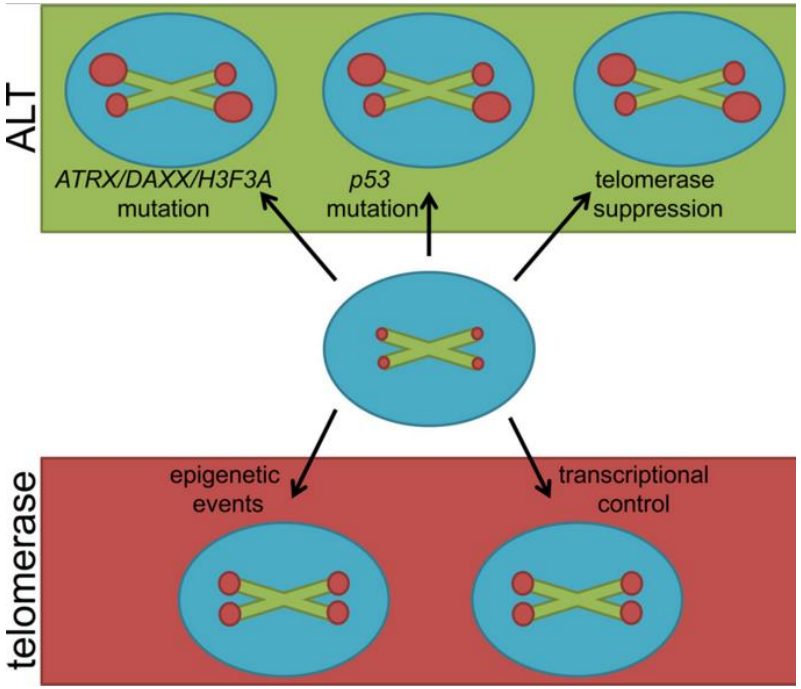
Van de Bent MJ et al. JCO 2006



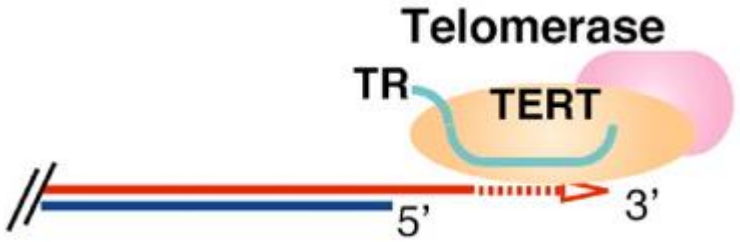
Cairncross G et al. JCO2006

ATRX mutation / TERT promotor mutation

○Teromere伸長関連変異

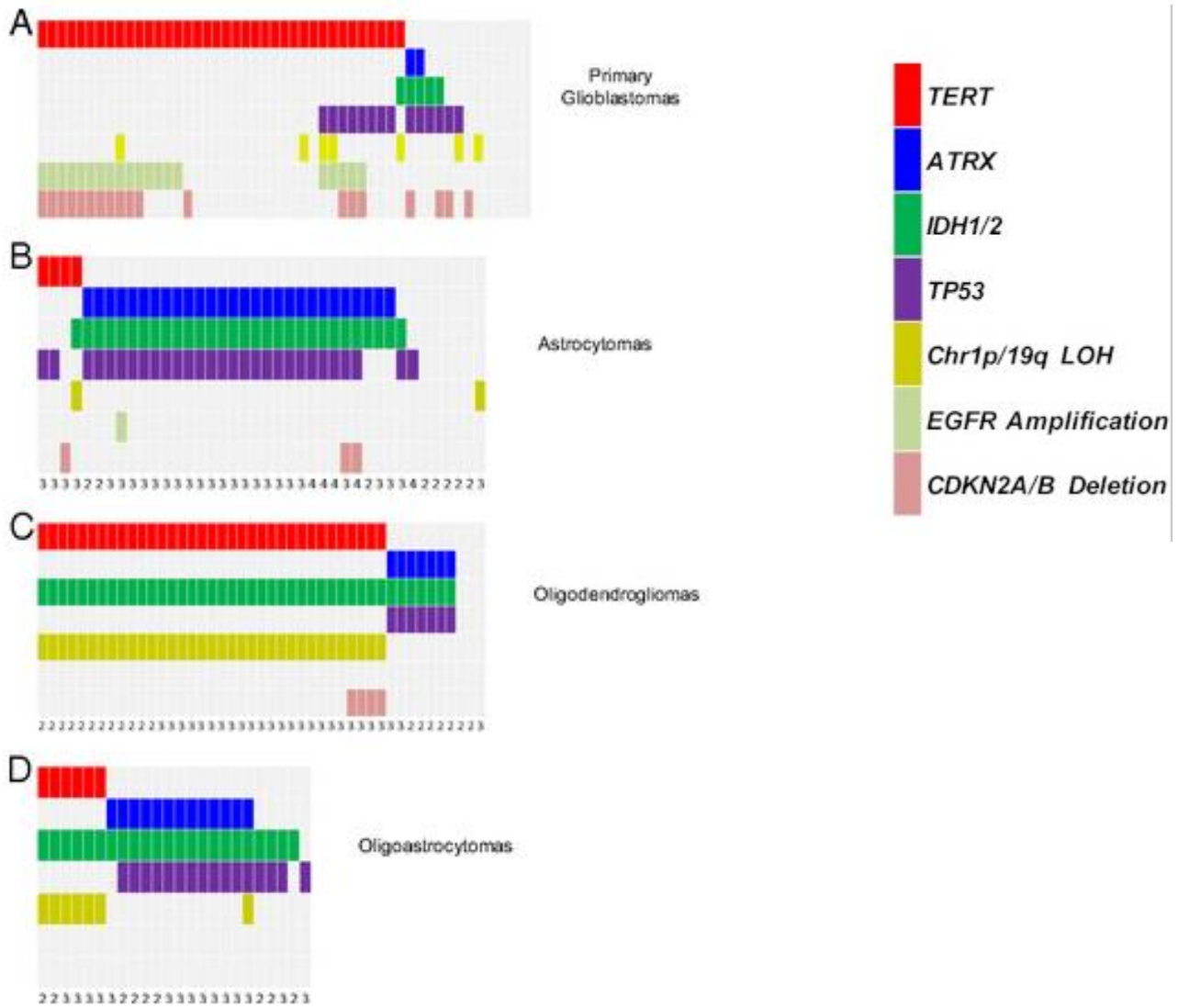


Gocha AR et al. Mutat Res 2013



Nabetani A et al. Biochem 2011

ATRX mutation / TERT promotor mutation



Mutations in FUBPI and CIC

いずれもoligodendrogliomaのexome sequence解析で新たに発見。

- FUBPI
  染色体1pに存在。mycの発現を調整。
  5/34 oligodendroglioma

- CIC
  染色体19qに存在。MAPKと関連したはたらき。
  18/26oligodendroglioma・・・69%

Bettegowda C etal. Science 2011

BRAF/KIAA1549 Fusion gene

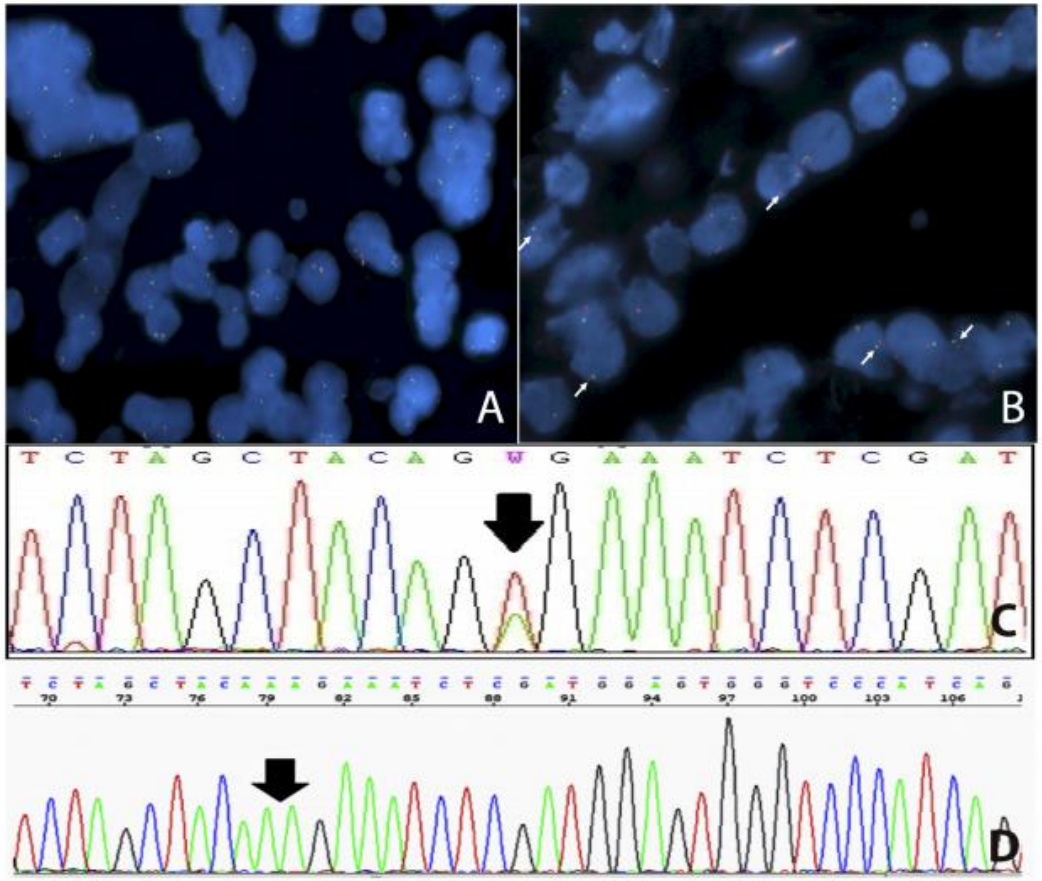


FIGURE 1. Molecular alterations in *BRAF*. **(A, B)** FISH assay for detection of *KIAA1549:BRAF* fusion showing a positive **(A)** and a negative **(B)** case (white arrows). **(C, D)** Point mutations detected by Sanger sequencing for V600E **(C)** and V600K **(D)**.

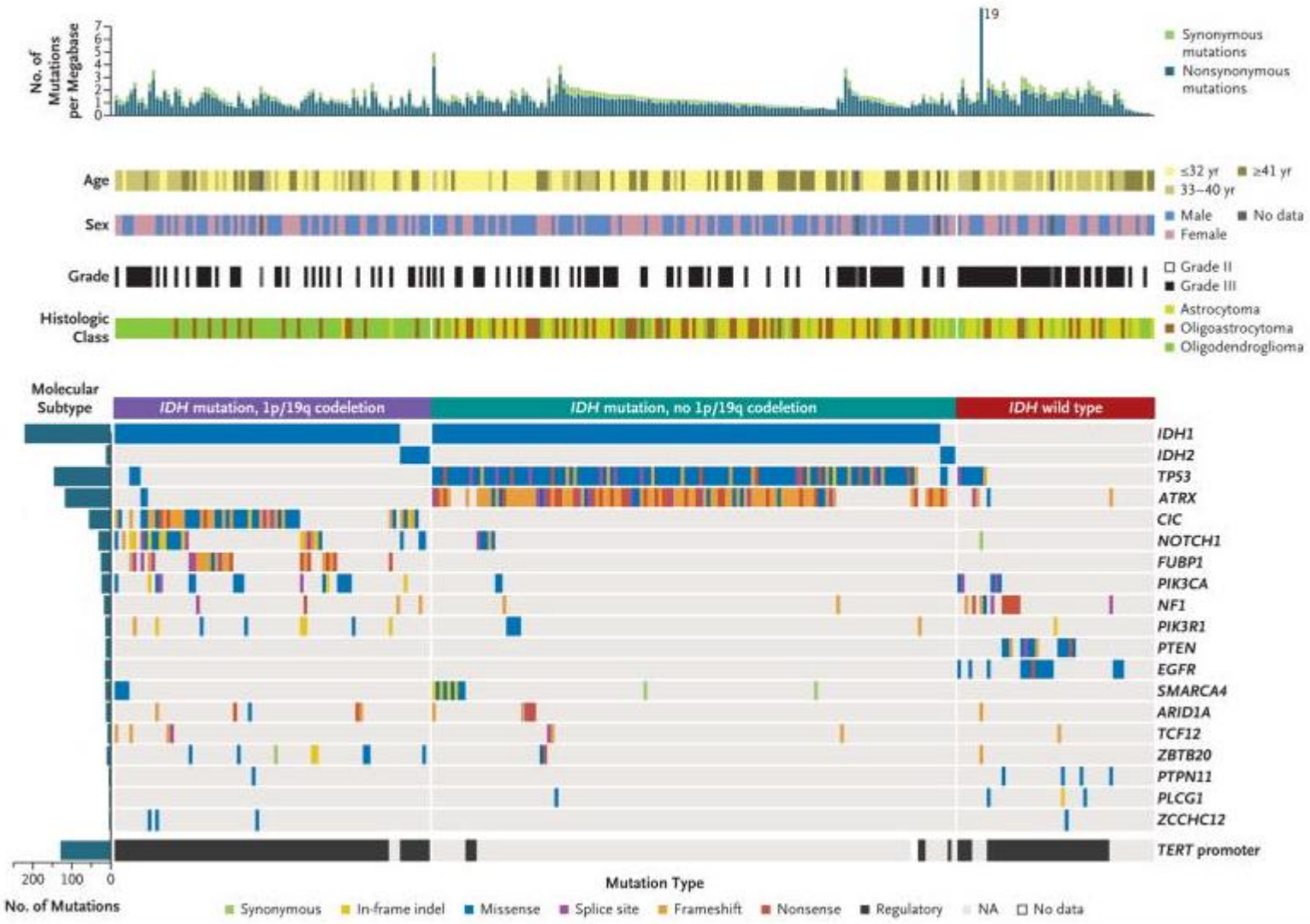
Pilocytic Aの66%
MAPK経路に関与
予後因子とはならない
PXA(6%)や
ganglioglioma(18%)にも。

Aline P et al.J Neuropathol Exp Neurol. 2015

分子診断因子とgliomaの対応

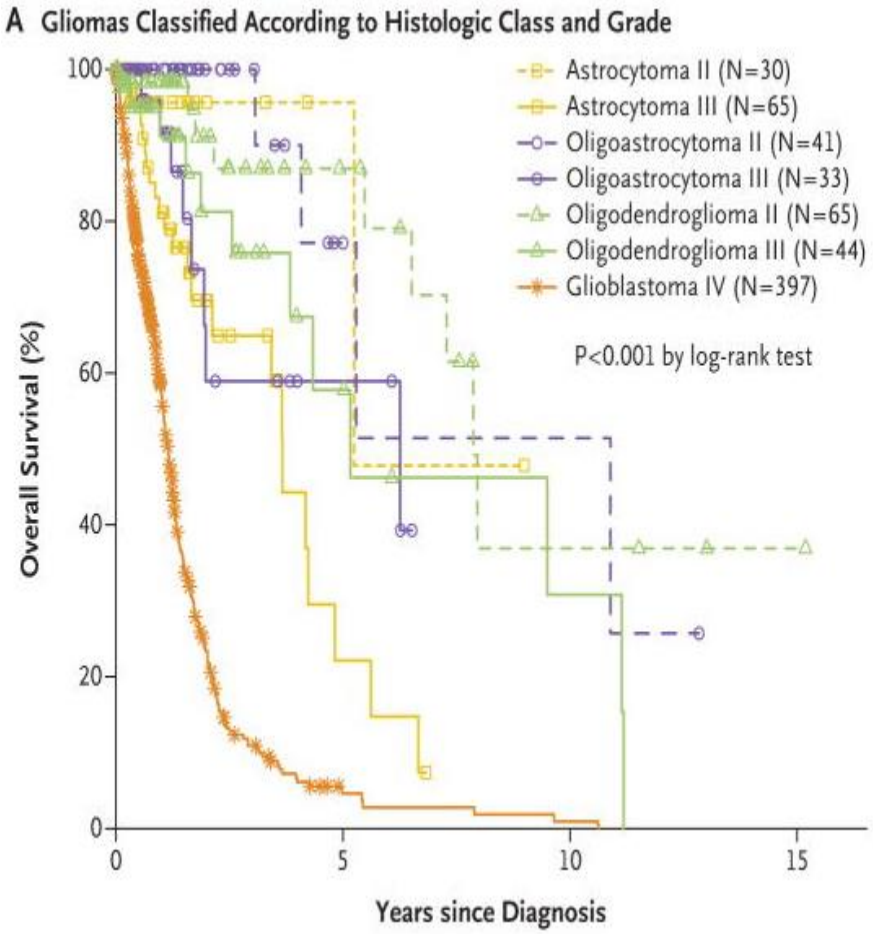
- IDH1/2 mutation : LGG, Secondary GBM
- TP53 mutation :Astrocytoma,GBM
- ATRX mutation :Astrocytic tumor
- TERT promotor mutation:Oligo,GBM
- 1p/19q codeletion :Oligo
- BRAF/KIAA fusion gene :Pilocytic A

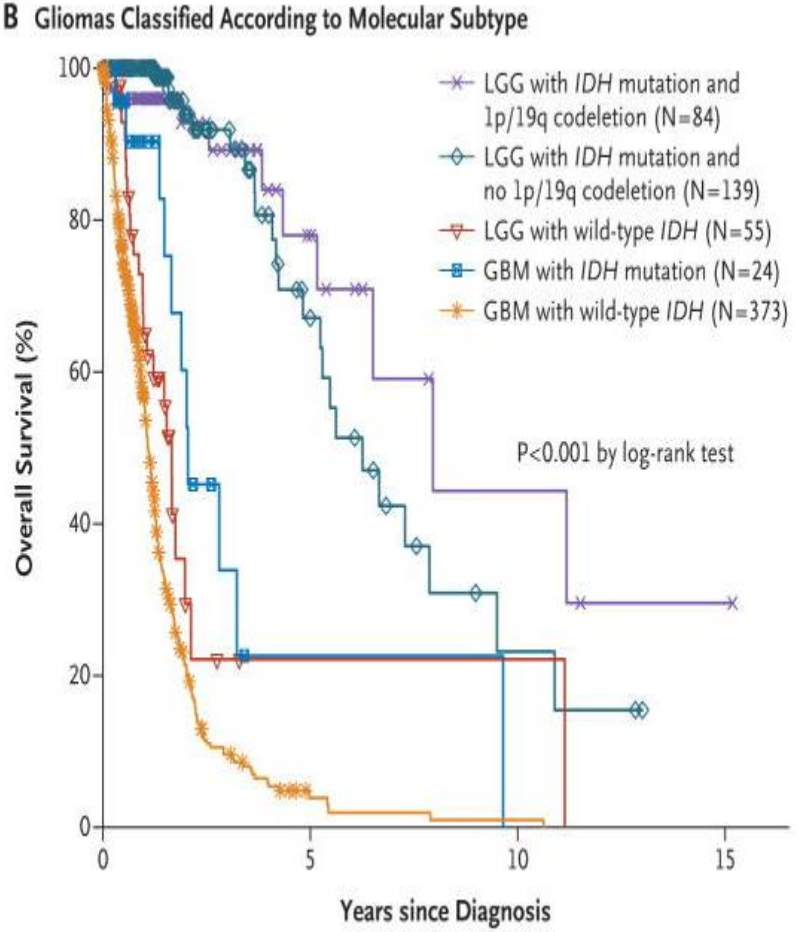
Low grade glioma：新たなWHO分類の方向性



TCGA. NEJM 2015

Low grade glioma：新たなWHO分類の方向性





TCGA. NEJM 2015

Low grade glioma：新たなWHO分類の方向性

Molecular information	Histologic classification: Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p/19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*	*Diffuse glioma* (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression*	*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p/19q-codel, ATRX intact	*Diffuse glioma (astrocytoma phenotype), 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*
IDH wild type	*Diffuse astrocytoma, IDH wild type**	*Diffuse glioma* (oligodendroglioma phenotype), IDH wild type**	*Diffuse astrocytoma, IDH wild type**
Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

Louis DN et al. Brain Pathol 2014