

Vooruitgang in moleculaire diagnostiek in primaire hersentumoren: behoefte aan centralisatie?

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disclosures

- no

moleculaire diagnostiek

- Relateren aan de WHO classificatie van 2016

Towards an integrated morphological and molecular WHO diagnosis of central nervous system tumors: a paradigm shift

Elisabeth J. Rushing^a and Pieter Wesseling^{b,c}

Purpose of review

It is now fully clear that information on the molecular underpinnings of tumors of the central nervous system (CNS) can be used for a more robust characterization of at least selected neoplasms. During a meeting organized in Haarlem, The Netherlands, in May 2014, about 30 neuropathologists discussed how exactly molecular information could be incorporated in the routine classification of CNS tumors.

Recent findings

This article highlights recent developments in the WHO CNS tumor classification and the role of molecular information.

Summary

The evolving paradigm shift represents a major leap forward in the diagnosis of CNS tumors that will contribute substantially to optimizing interobserver reproducibility and clinico-pathological predictions.

some tests used in clinical practice for the detection of molecular features, may provide false positive or false negative results.

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Keywords

brain tumor, grading, molecular

Glial and Mixed Neuronal-Glial Tumors
in the **WHO 2007 (in black and blue)** and **WHO 2016 (in black and red)** Classification

Diffuse astrocytic and oligodendroglial tumors

- Diffuse astrocytoma, *IDH* mutant
- Gemistocytic astrocytoma, *IDH* mutant
- Fibrillary astrocytoma**
- Protoplasmic astrocytoma**
- Diffuse astrocytoma, *IDH* wild-type
- Diffuse astrocytoma, NOS

- Anaplastic astrocytoma, *IDH* mutant
- Anaplastic astrocytoma, *IDH* wild-type
- Anaplastic astrocytoma, NOS

- Glioblastoma, *IDH* wild-type
 - Giant cell glioblastoma
 - Gliosarcoma
 - Epitheloid glioblastoma**
- Glioblastoma, *IDH* mutant
- Glioblastoma, NOS
- Gliomatosis cerebri**

- Diffuse midline glioma, H3-K27M mutant

- Oligodendrogloma, *IDH* mutant and 1p/19q codeleted
- Oligodendrogloma, NOS

- Anaplastic oligodendrogloma, *IDH* mutant and 1p/19q codeleted
- Anaplastic oligodendrogloma, NOS

- Oligoastrocytoma, NOS
- Anaplastic oligoastrocytoma, NOS

Other astrocytic tumors

- Pilocytic astrocytoma
- Pilomyxoid astrocytoma
- Subependymal giant cell astrocytoma
- Pleomorphic xanthoastrocytoma
- Anaplastic pleomorphic xanthoastrocytoma

Ependymal tumors

- Subependymoma
- Myxopapillary ependymoma
- Ependymoma
 - Cellular ependymoma**
 - Papillary ependymoma
 - Clear cell ependymoma
 - Tanycytic ependymoma
- Ependymoma, *RELA* fusion-positive
- Anaplastic ependymoma

Other gliomas

- Chordoid glioma of the third ventricle
- Angiocentric glioma
- Astroblastoma

Mixed neuronal-glial tumors

- Ganglioglioma
- Anaplastic ganglioglioma
- Desmoplastic infantile astrocytoma and ganglioglioma
- Papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor
- Diffuse leptomeningeal glioneuronal tumor

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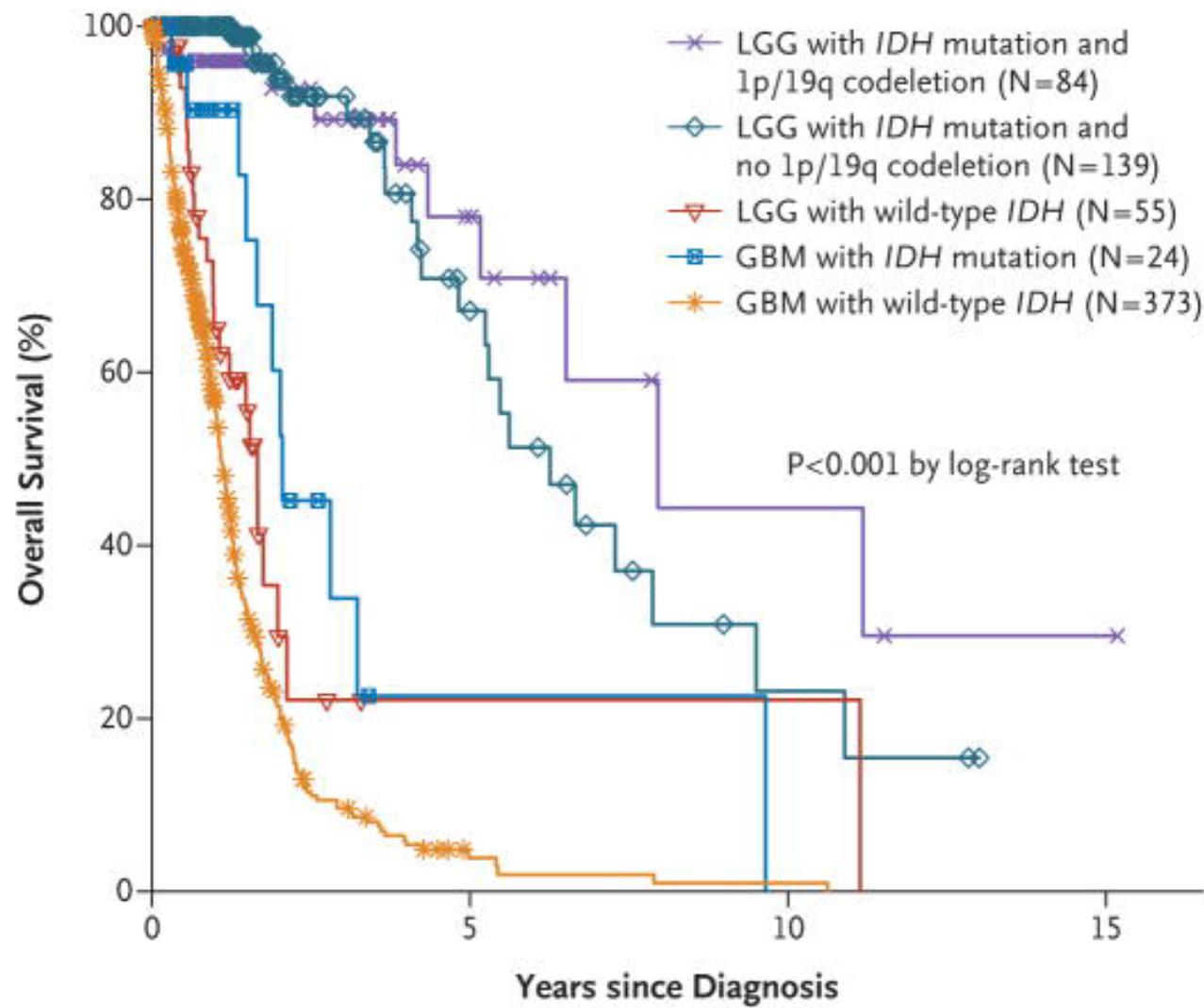
Other gliomas

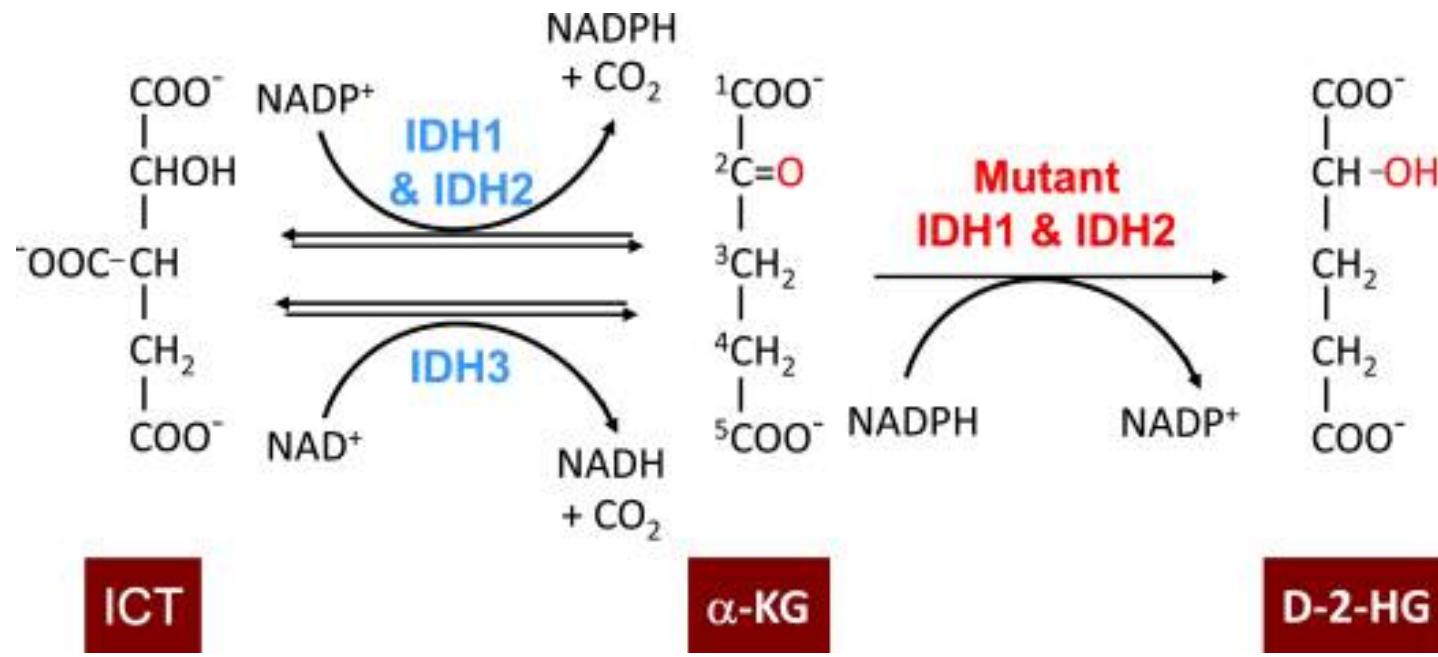
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Mixed neuronal-glial tumors

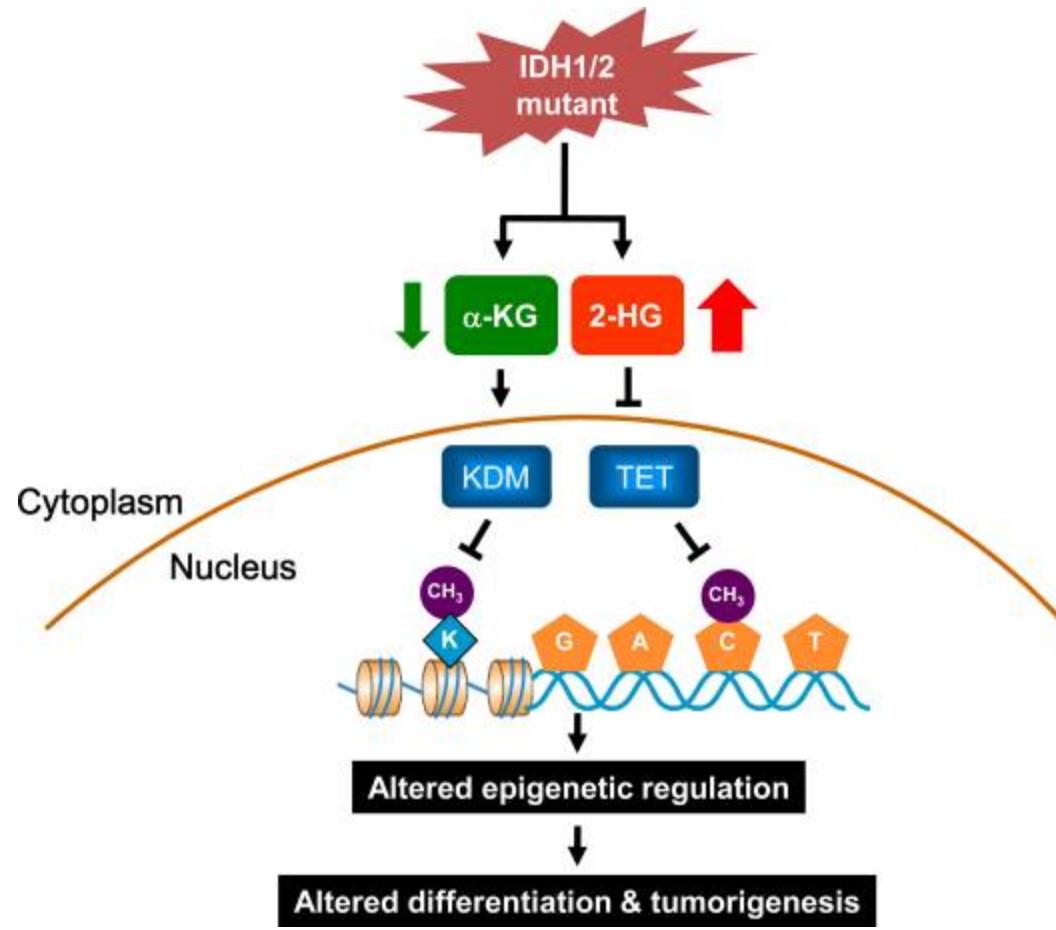
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B Gliomas Classified According to Molecular Subtype





Clin Cancer Res. 2012 Oct 15; 18(20): 5562–5571.



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IDH1/2 mutated astrocytomas

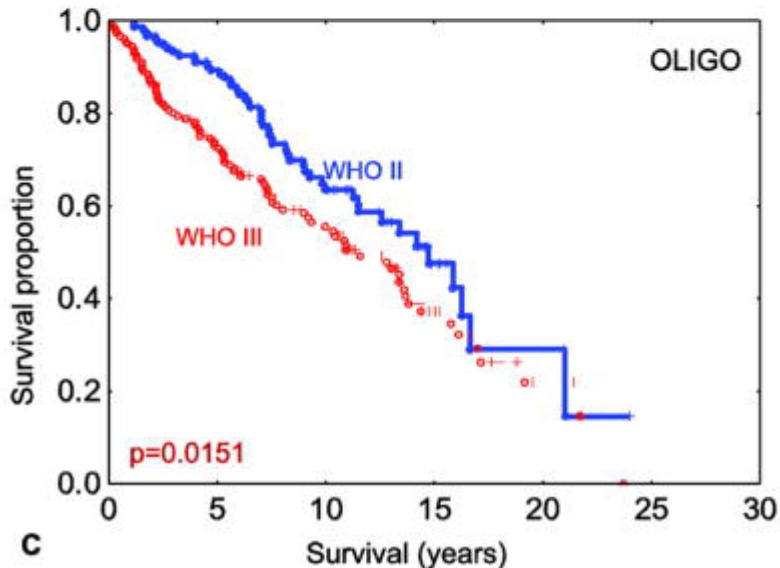
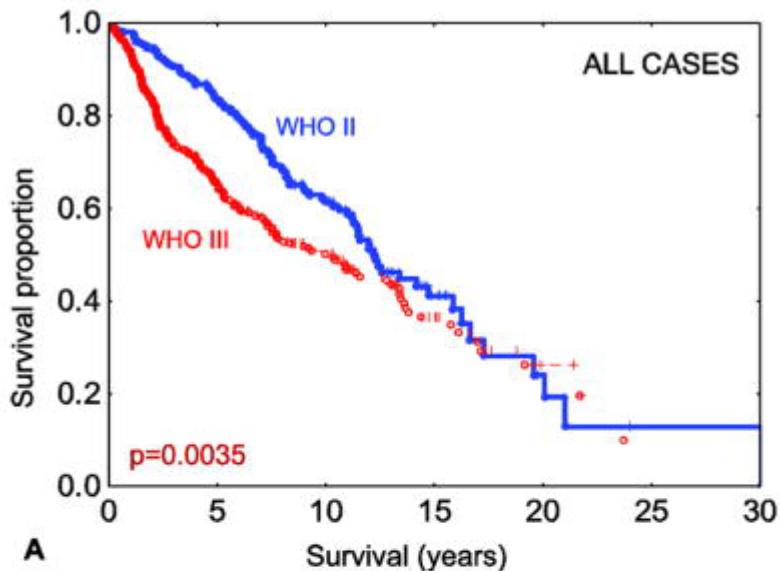
- Dedifferentiatie mogelijk van AII>AIII>GBM

IDH1/2 mutaties in gliomen

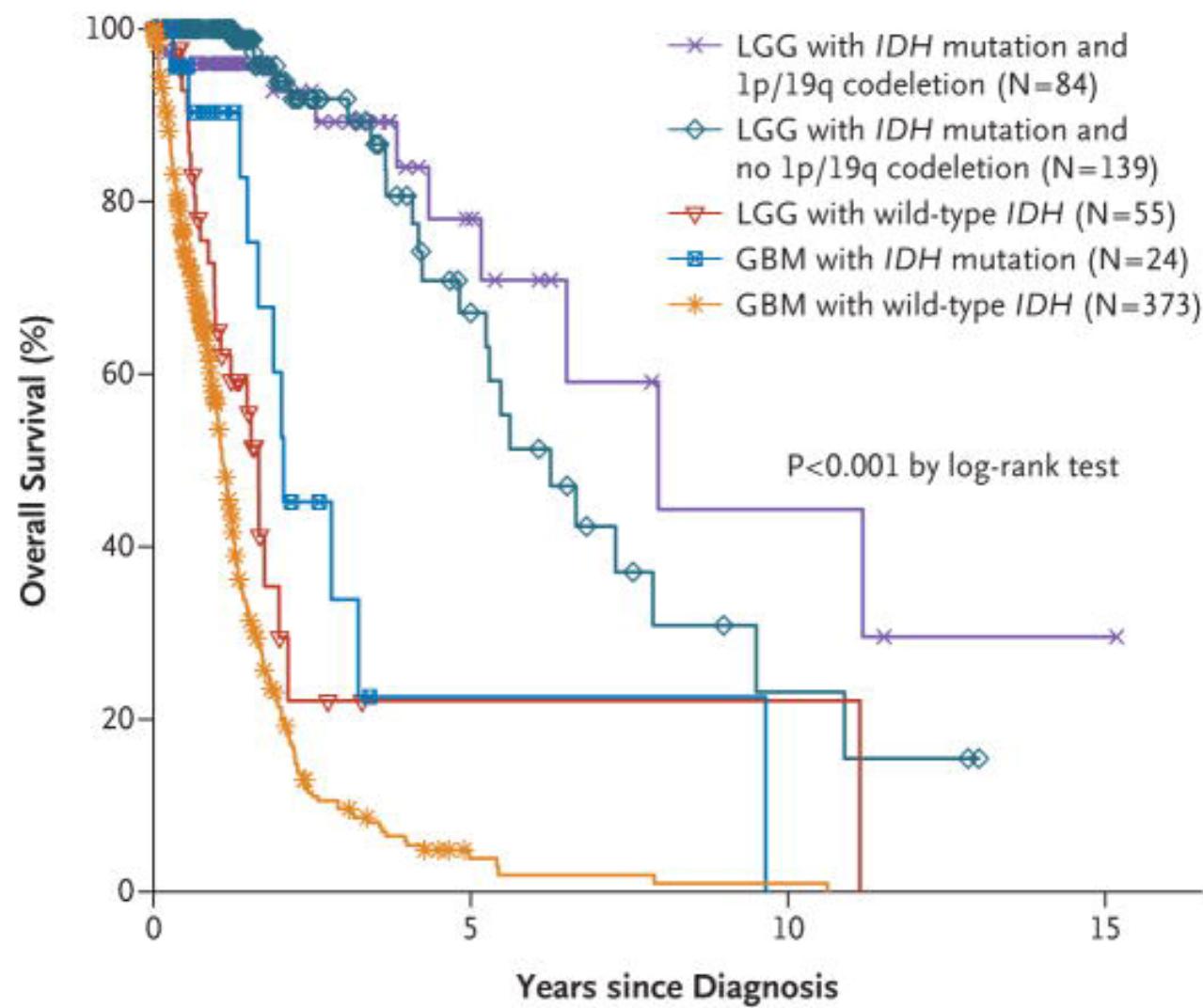
Testen:

- IHC voor de meest frequente mutatie R132H (hiermee opsporen van ca. 90%) van alle IDH1/2 mutatie)
- In 10 % andere mutaties: sequentieanalyse op IDH1/2

Grading in IDH mutated gliomas: Significance!?

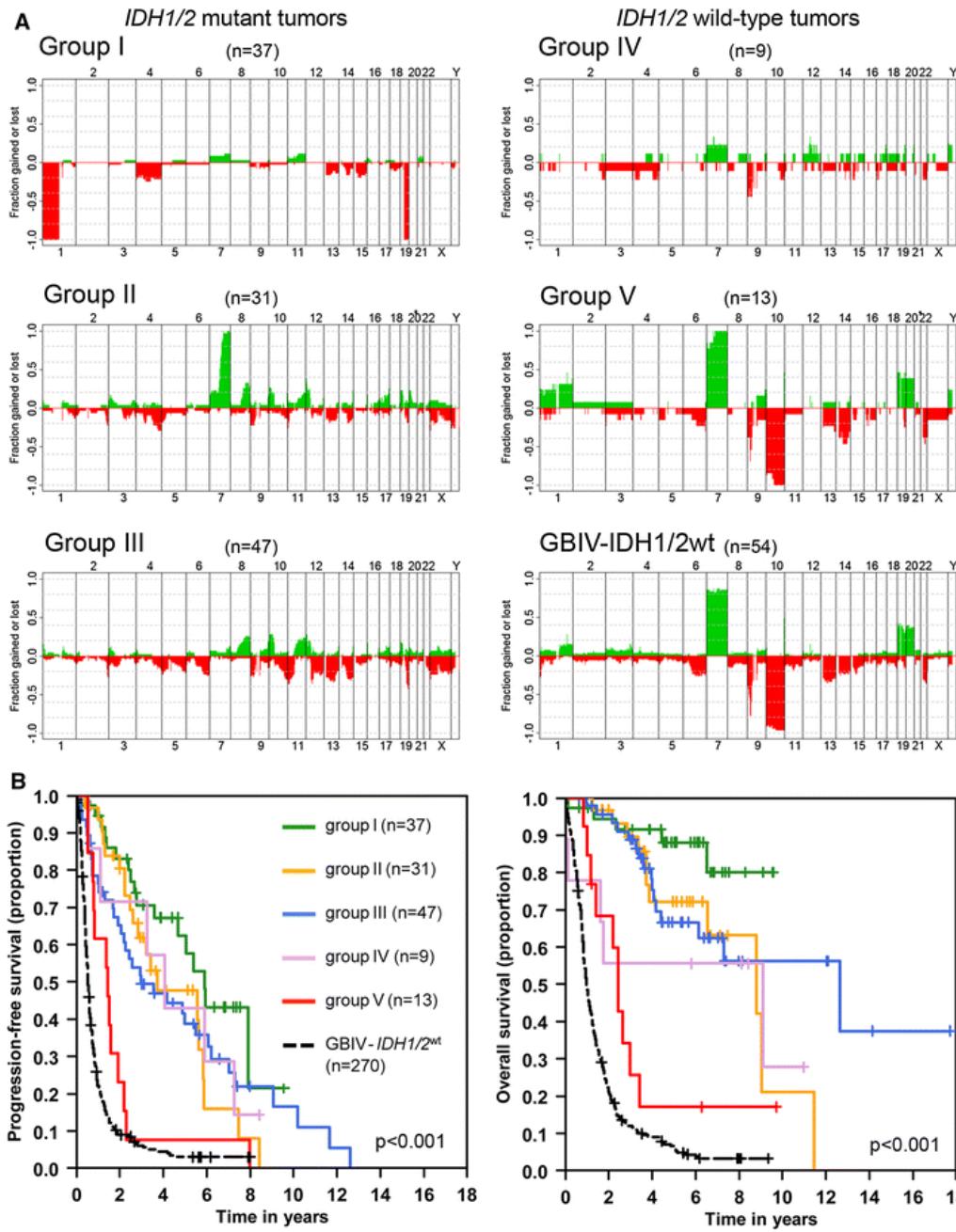


B Gliomas Classified According to Molecular Subtype



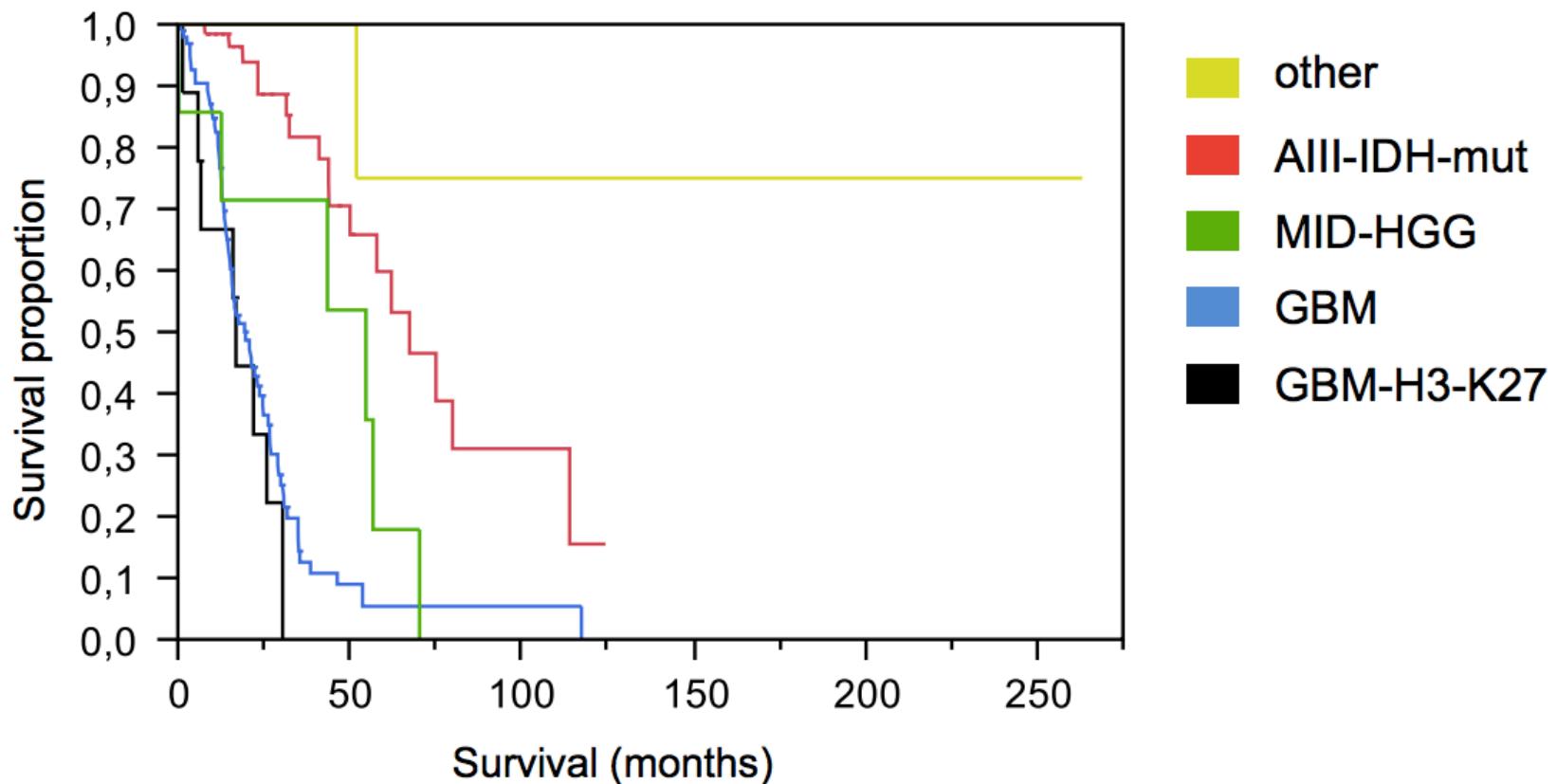
IDH1/2 wt gliomas

- Heterogene groep
- 1. diffuse gliomen (astrocytomen)
- 2. variant gliomen (pilocytair A. etc)
- >>>clou is het uitbreidingspatroon (diffuus vs circumschrift)



Weller, M., Weber, R.G.,
Willscher, E. et al. Acta
Neuropathol (2015) 129: 679

Adult *IDH* wild type astrocytomas biologically and clinically resolve into other tumor entities



Acta Neuropathologica



Acta Neuropathol. 2015; 130(6): 815–827.

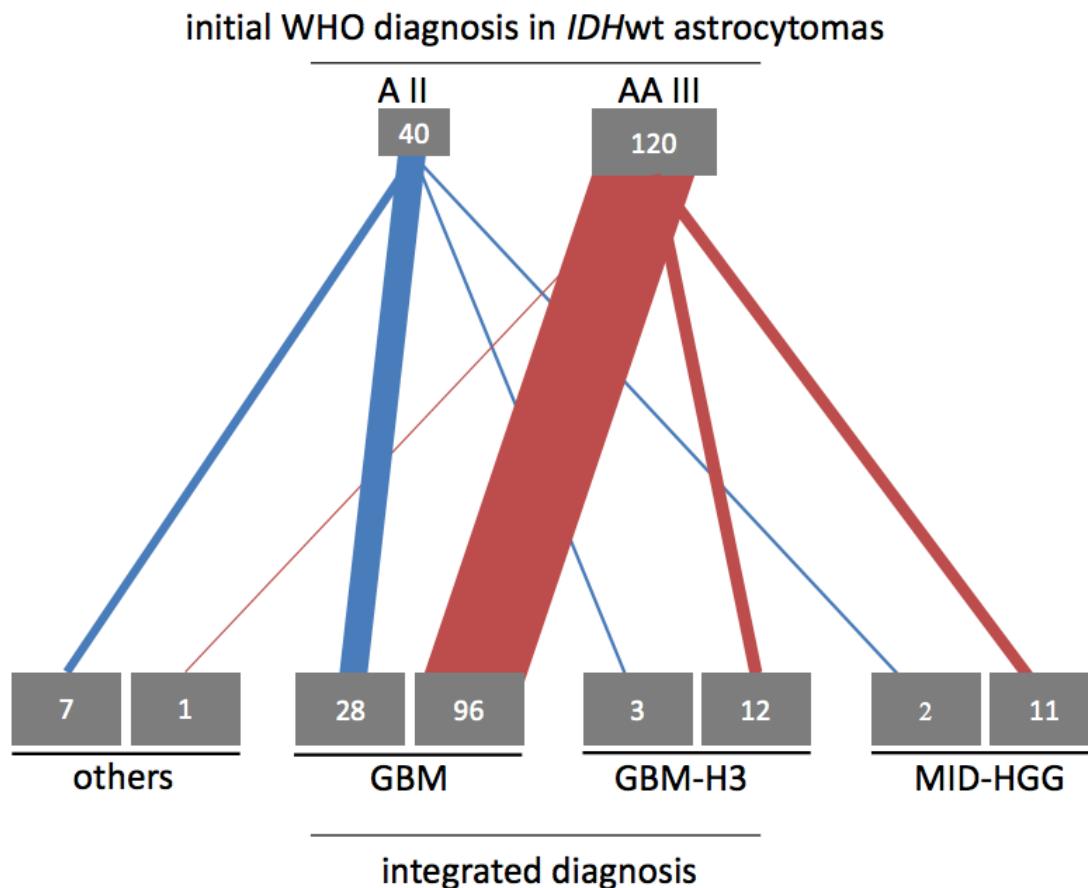
Published online 2015 Sep 23. doi: [10.1007/s00401-015-1478-0](https://doi.org/10.1007/s00401-015-1478-0)

PMCID: PMC4654747

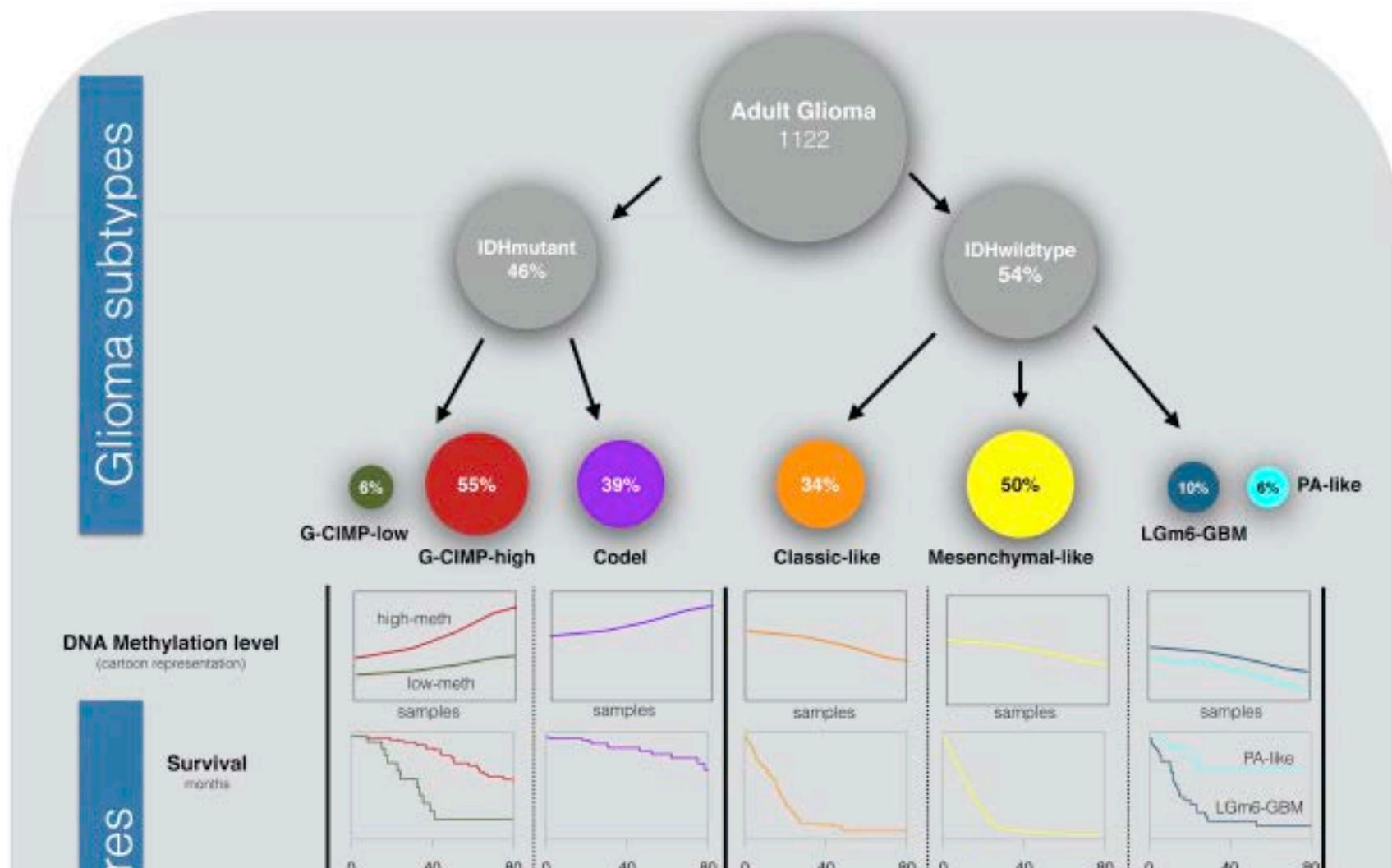
Histone *H3F3A* and *HIST1H3B* K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes

David Castel,[#] Cathy Philippe,[#] Raphaël Calmon, Ludivine Le Dret,
Nathalène Truffaux, Nathalie Boddaert, Mélanie Pagès, Kathryn R. Taylor,
Patrick Saulnier, Ludovic Lacroix, Alan Mackay, Chris Jones, Christian
Sainte-Rose, Thomas Blauwblomme, Felipe Andreiuolo, Stephanie Puget,
Jacques Grill, Pascale Varlet, and Marie-Anne Debily

Adult *IDH* wild type astrocytomas biologically and clinically resolve into other tumor entities



Multidimensional molecular profiling



Dilemma in IDH1/2 wt diffuus gliomen, histologisch non GBM

- Sampling error: diffuus deel gebiopteerd zonder vatproliferatie, zonder necrose >>> relateren aan radiologie: is dit radiologisch een GBM?
- Vroeg gebiopteerd (primair) GBM nog zonder de klassieke radiologie

IDH1/2 wt gliomen

Differentiaal diagnose non GBM

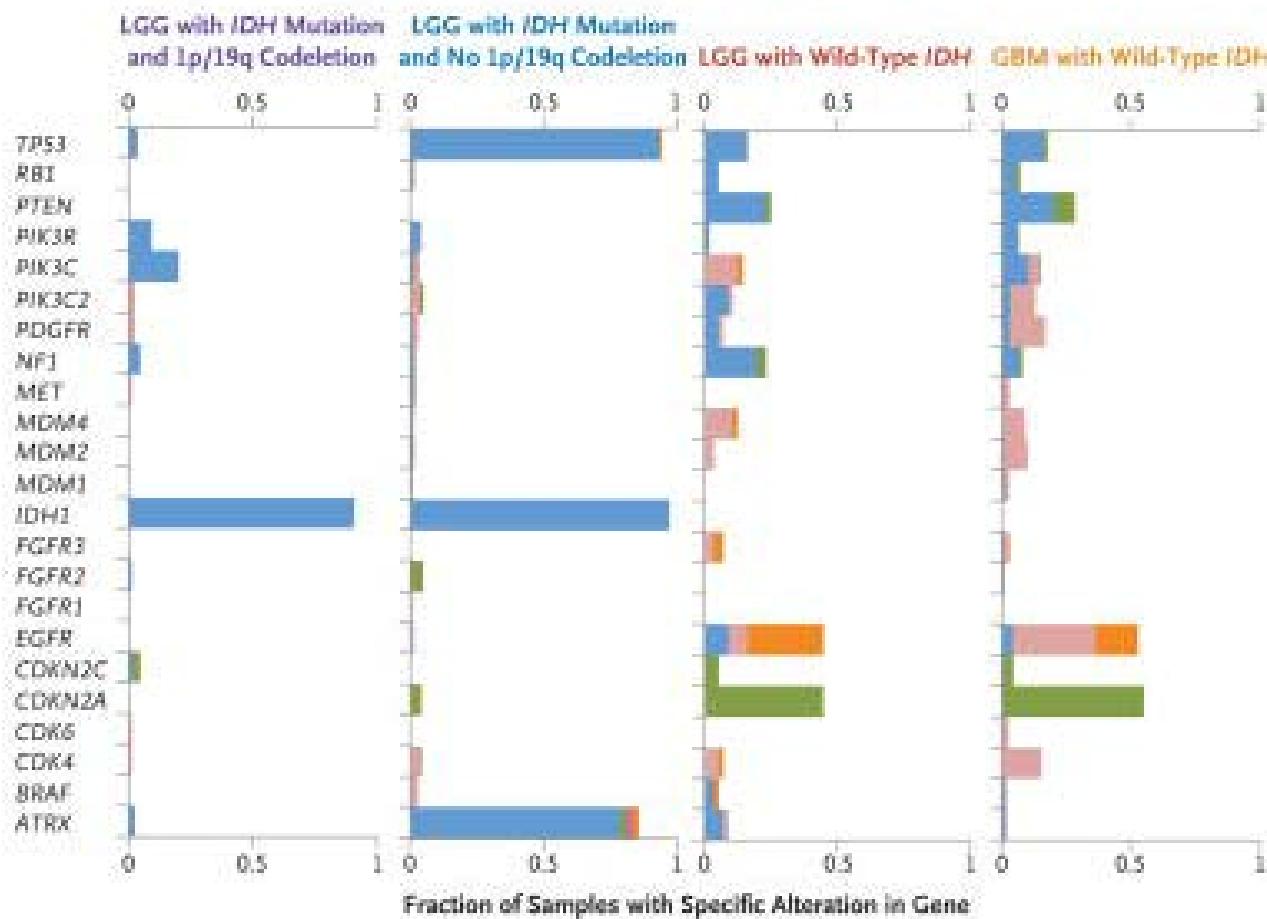
- Variant gliomen
- Pilocytair astrocytoom: BRAF-KIAA fusiegen
- Pleomorf xanthoastrocytoom: BRAF V600E mutatie (cave, echter ook beschreven in diffuse astrocytomen!)

Moleculaire kenmerken van primaire GBM (IDH1/2 wt)

- Chromosomale afw, PTEN p53 etc.

B

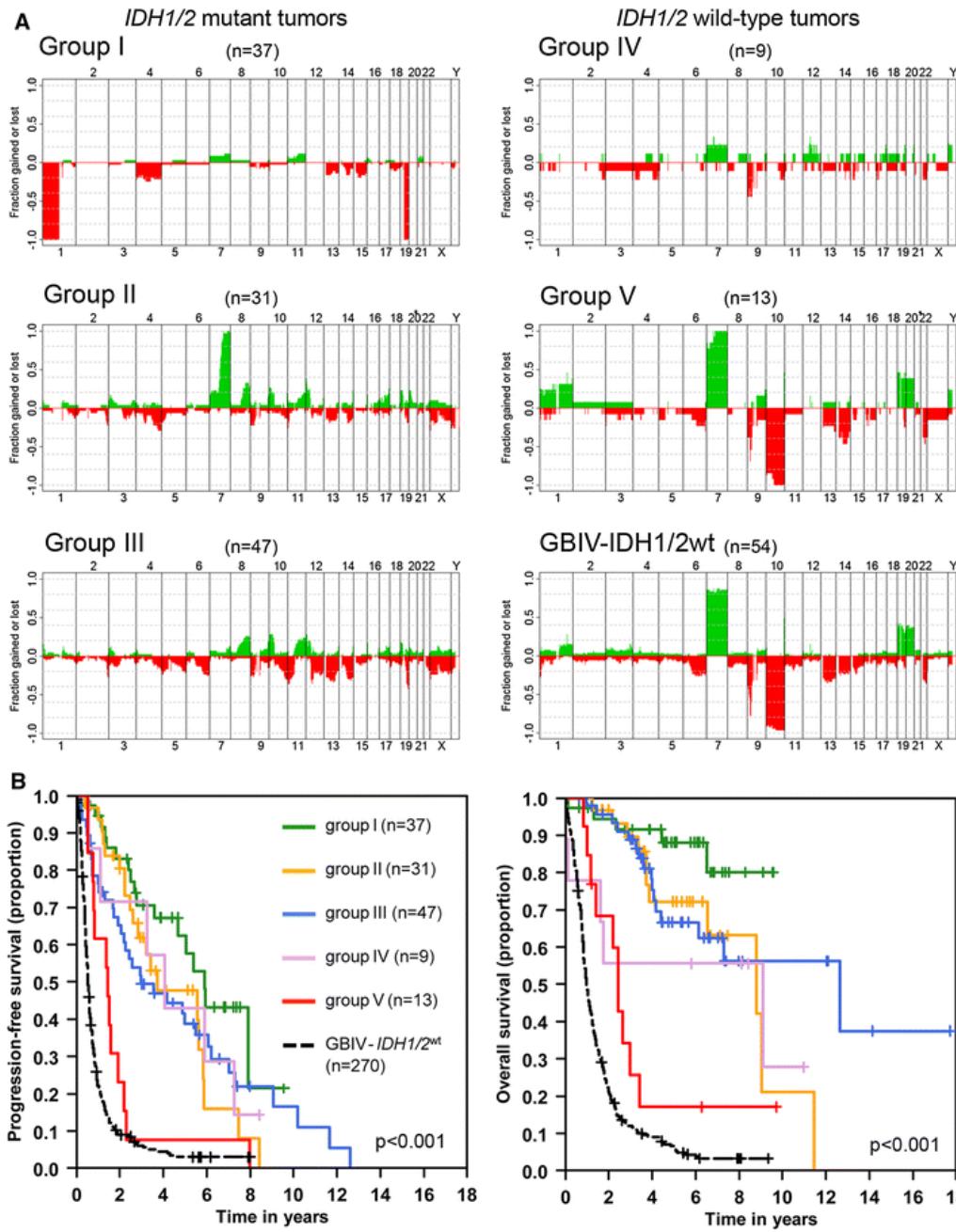
■ SNV or indel ■ Amplification ■ Deletion ■ SV ■ Fusion ■ Two or more aberrations



Adult *IDH* wild type astrocytomas biologically and clinically resolve into other tumor entities

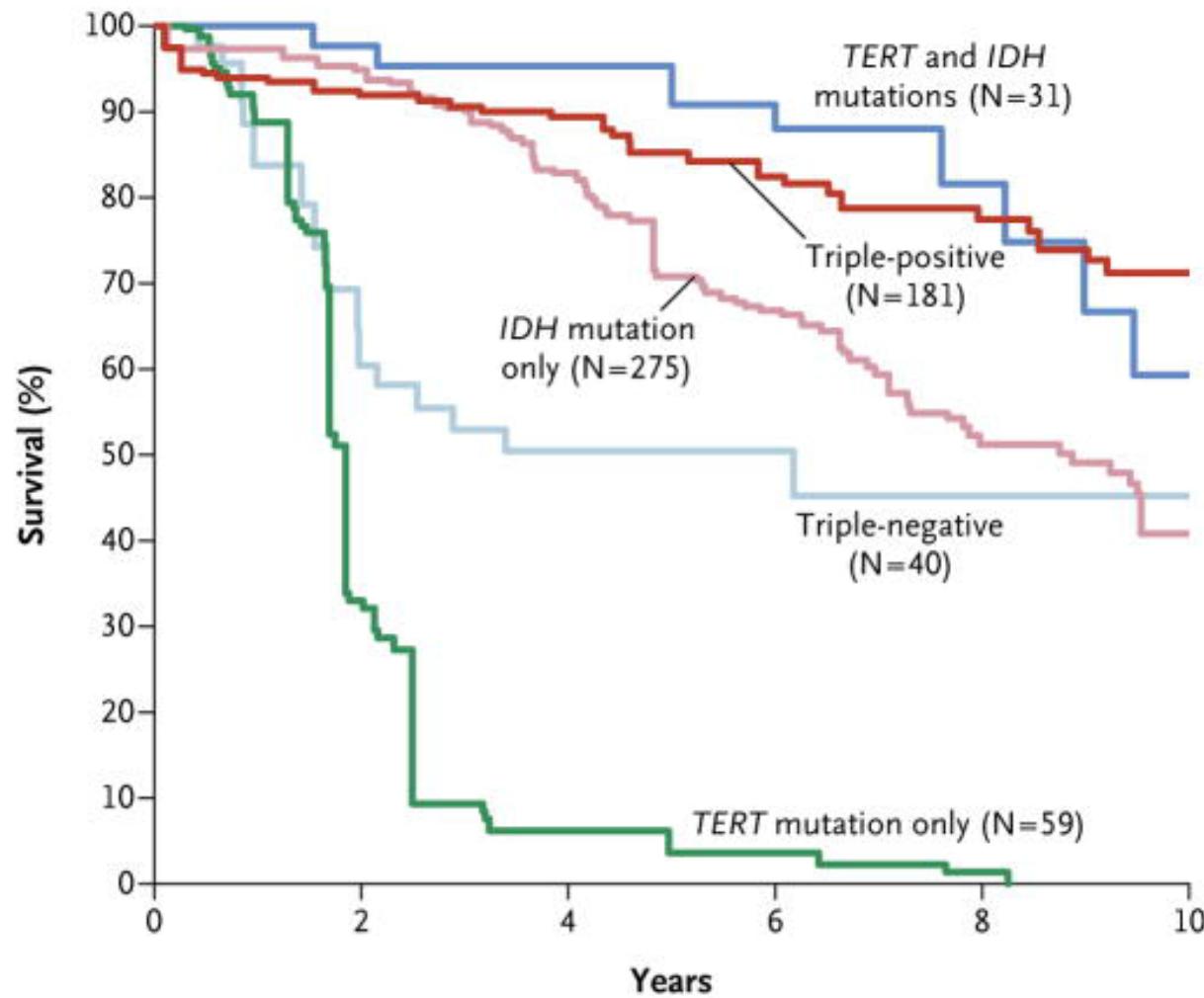
Table 1 Overview of 160 *IDH*wt astrocytomas divided into four distinct molecular groups

Designation	GBM	GBM-H3	MID-HGG	Others
<i>n/ (%)</i>	124 (78 %)	15 (9 %)	13 (9 %)	8 (7 %)
Methylation profile	GBM (121)	H3	Distinct	Variant
<i>H3F3A</i> -mutant	0	15	0	0
<i>TERT</i> -mutant	84/108 (78 %)	0	0	0
ATRX loss (IHC)	2/82 (2 %)	8/11 (73 %)	2/10 (20 %)	0/6 (0 %)
7p gain/10q loss	83/124 (67 %)	0	0	0
<i>EGFR</i> amp	54/124 (44 %)	0	0	0
10q-/13q-/14q-	21/124 (17 %)	1 (7 %)	0	0
OS median (months)	19.4	16.9	54.7	Not reached
AA III (<i>n</i> = 120)	96 (80 %)	12 (10 %)	10 (8 %)	1 (1 %)
A II (<i>n</i> = 40)	28 (70 %)	3 (7 %)	4 (10 %)	7 (17 %)
Age median	54	51.5	54	49

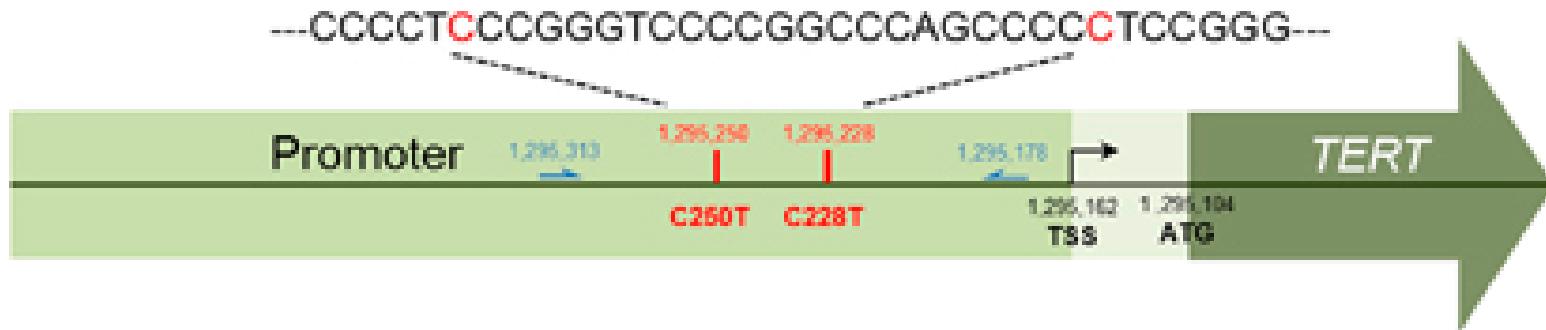


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A Grades II and III

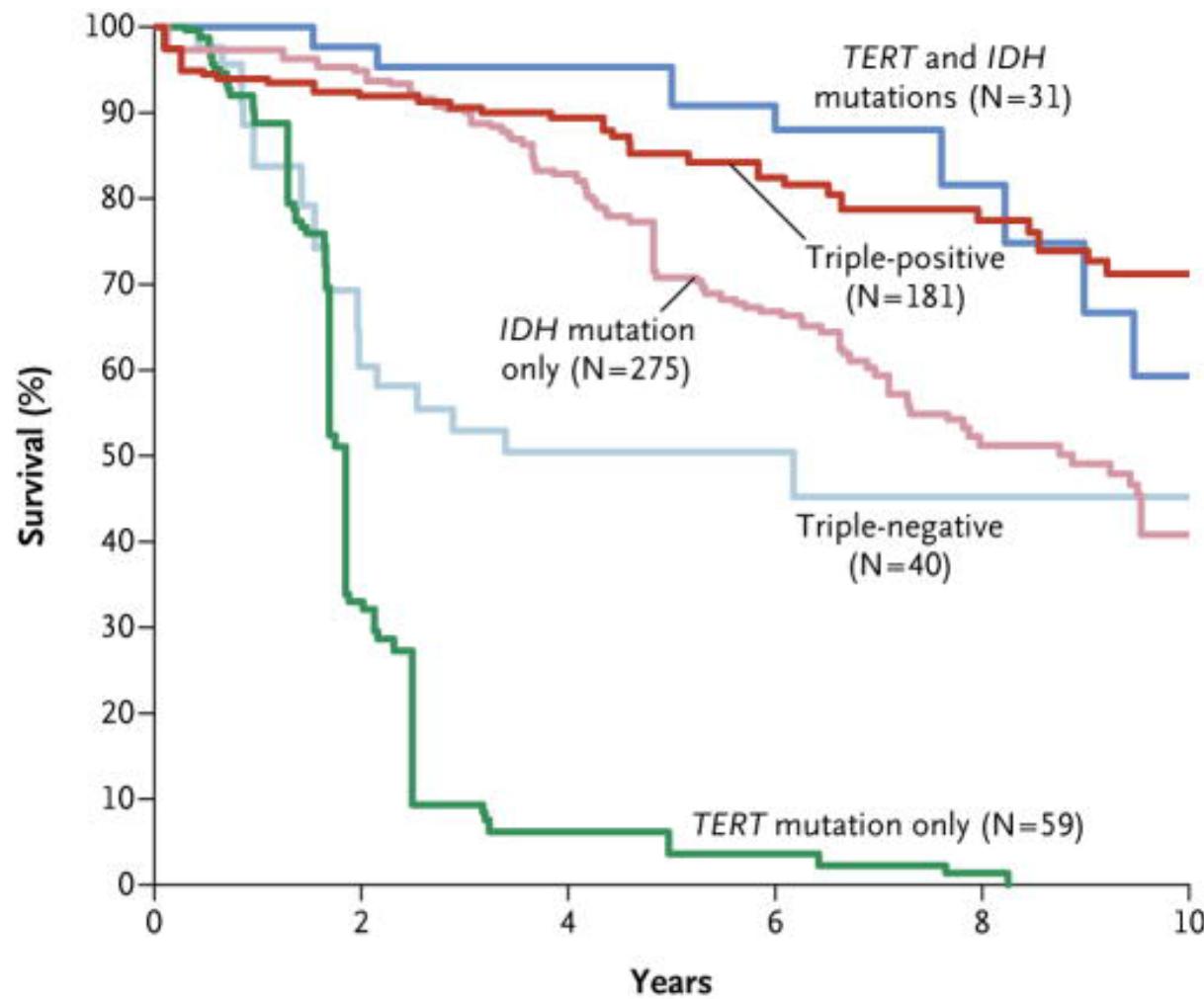


telomerase reverse transcriptase

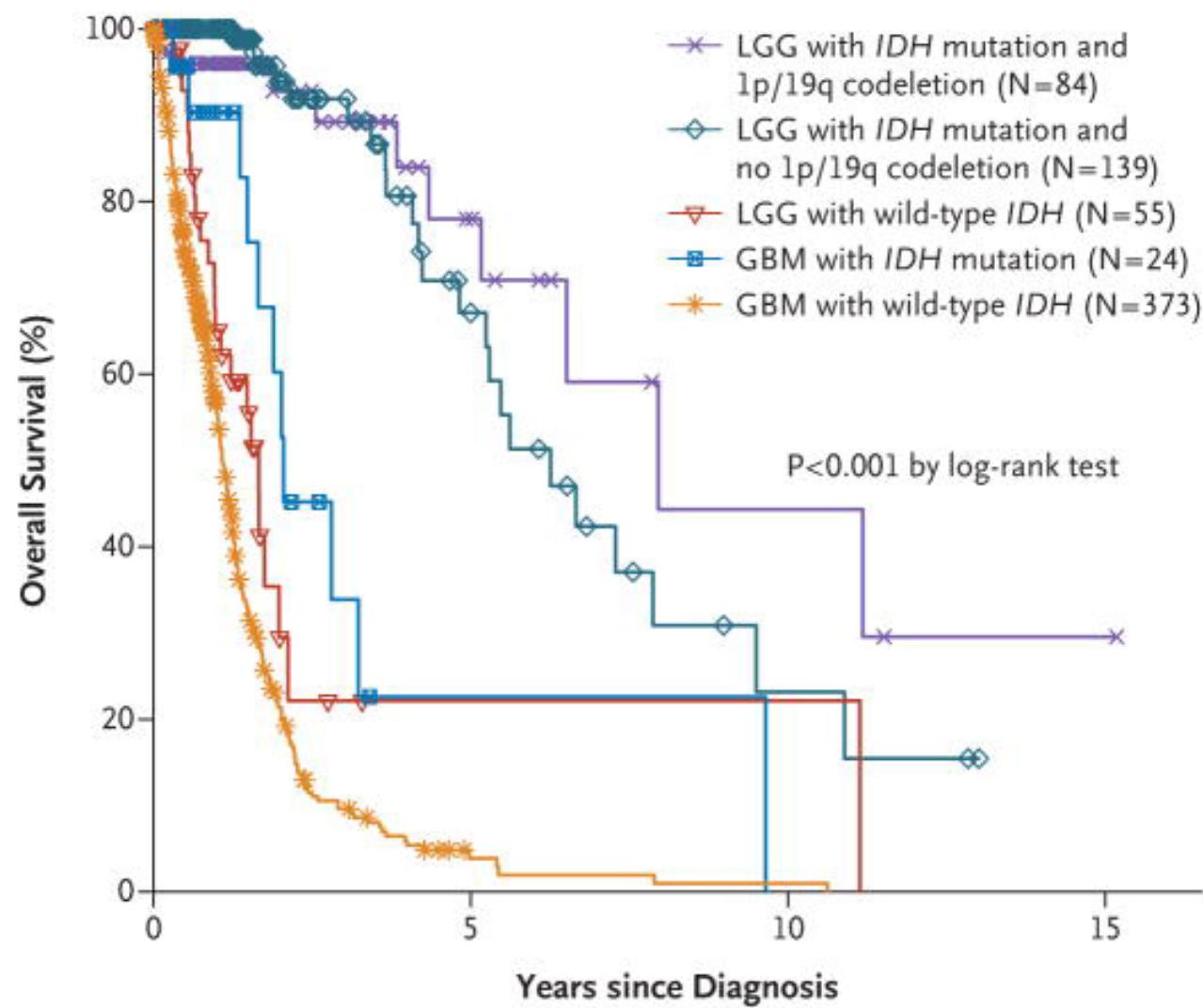


Modern Pathology (2015) **28**, 177–186; doi:10.1038/modpathol.2014.94

A Grades II and III



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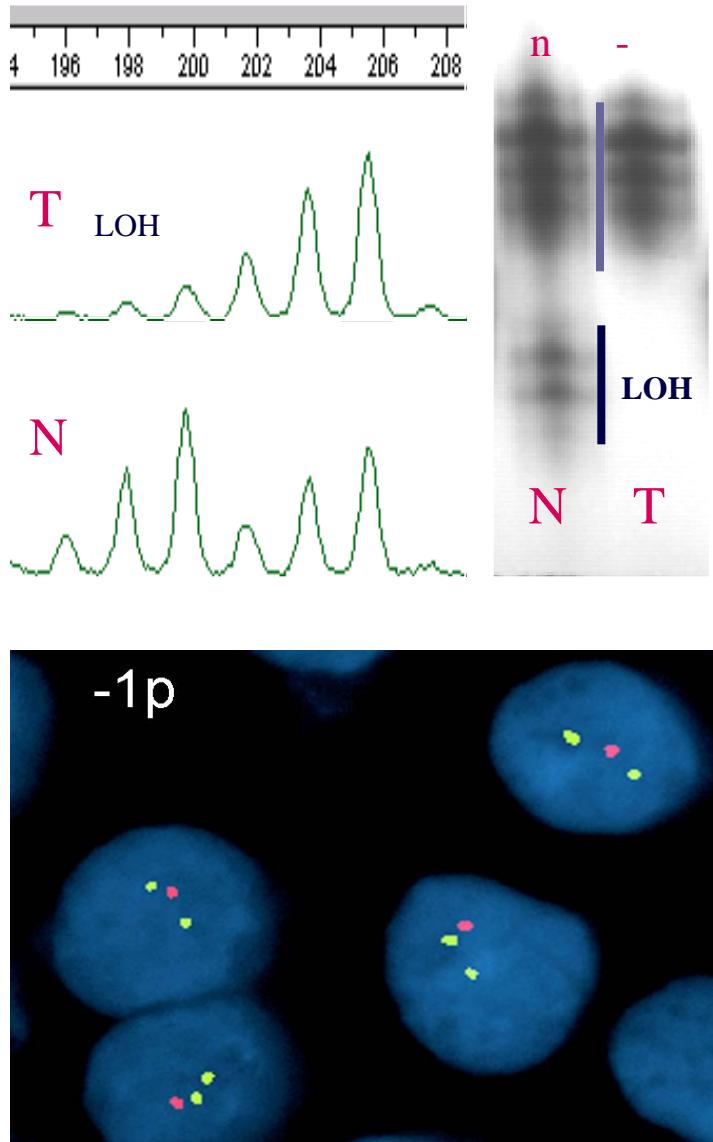
oligodendrogliomen

- Primair een moleculair gedefinieerde diagnose: 1p/19q codeletie met een IDH1/2 mutatie.
- Dit profiel overruled de morfologie: morfologische oligodendrogliomen zonder 1p/19q codeletie en IDH1/2 mutatie zijn biologisch geen oligodendrogliomen!

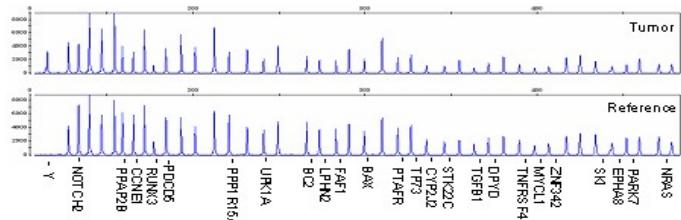
Oligo look alikes

- DNET
- Pilocytair astrocytoom
- Neurocytoom
- ependymoom

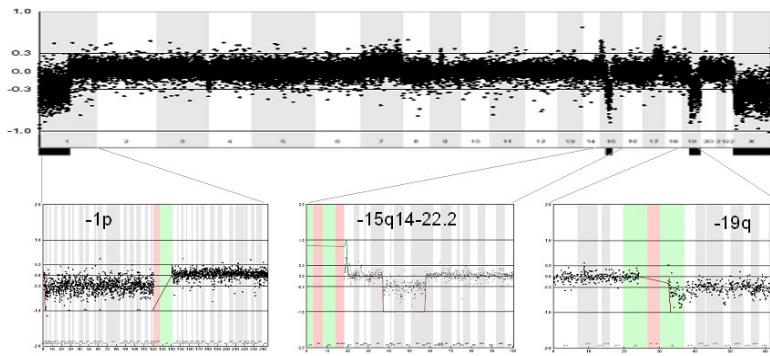
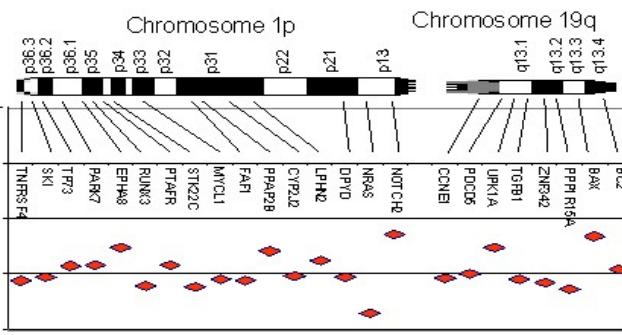
Molecular techniques for 1p/19q analysis



A. Capillary gel electrophoreses



B. Data processing and Interpretation



Courtesy of P. Wesseling

Testen bij variant gliomen

- BRAF-KIAA fusiegen detectie (pilocytair astrocytoom)
- BRAF V600E

MGMT promotor methylation

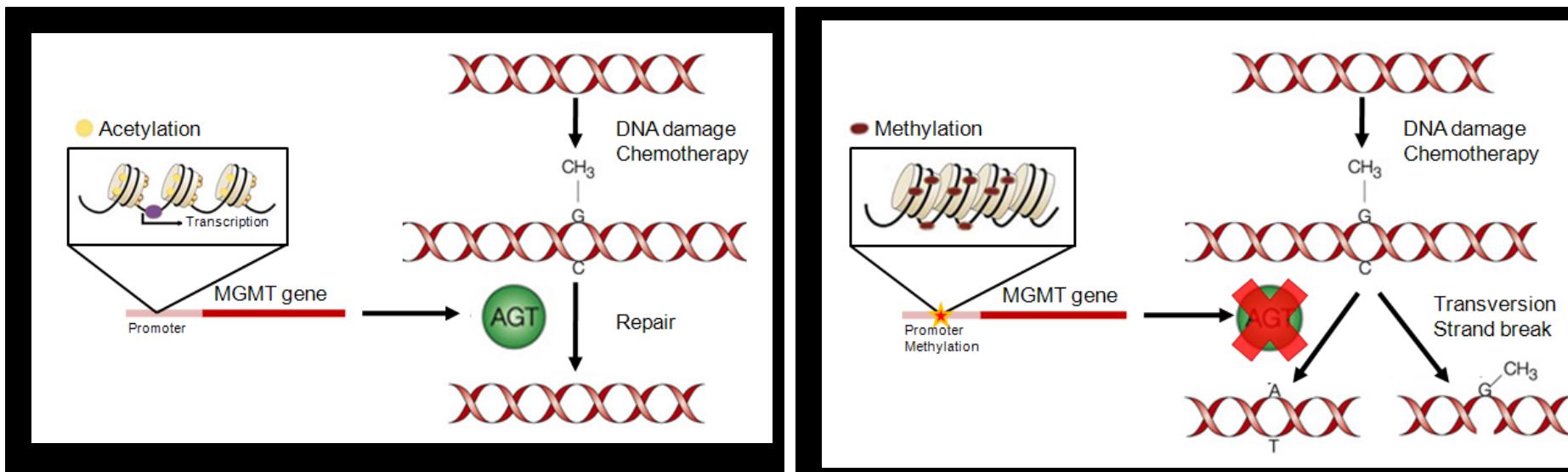
MGMT (gene) O⁶-methylguanine-DNA-methyltransferase
AGT (protein) O⁶-alkylguanine-DNA-alkyltransferase

Unmethylated MGMT promotor

- Expression of AGT
- Repair of methylated DNA
- Tumors are chemoresistant for TMZ

Methylated MGMT promotor

- No expression AGT
- No repair of methylated DNA
- Tumors are chemosensitive for TMZ

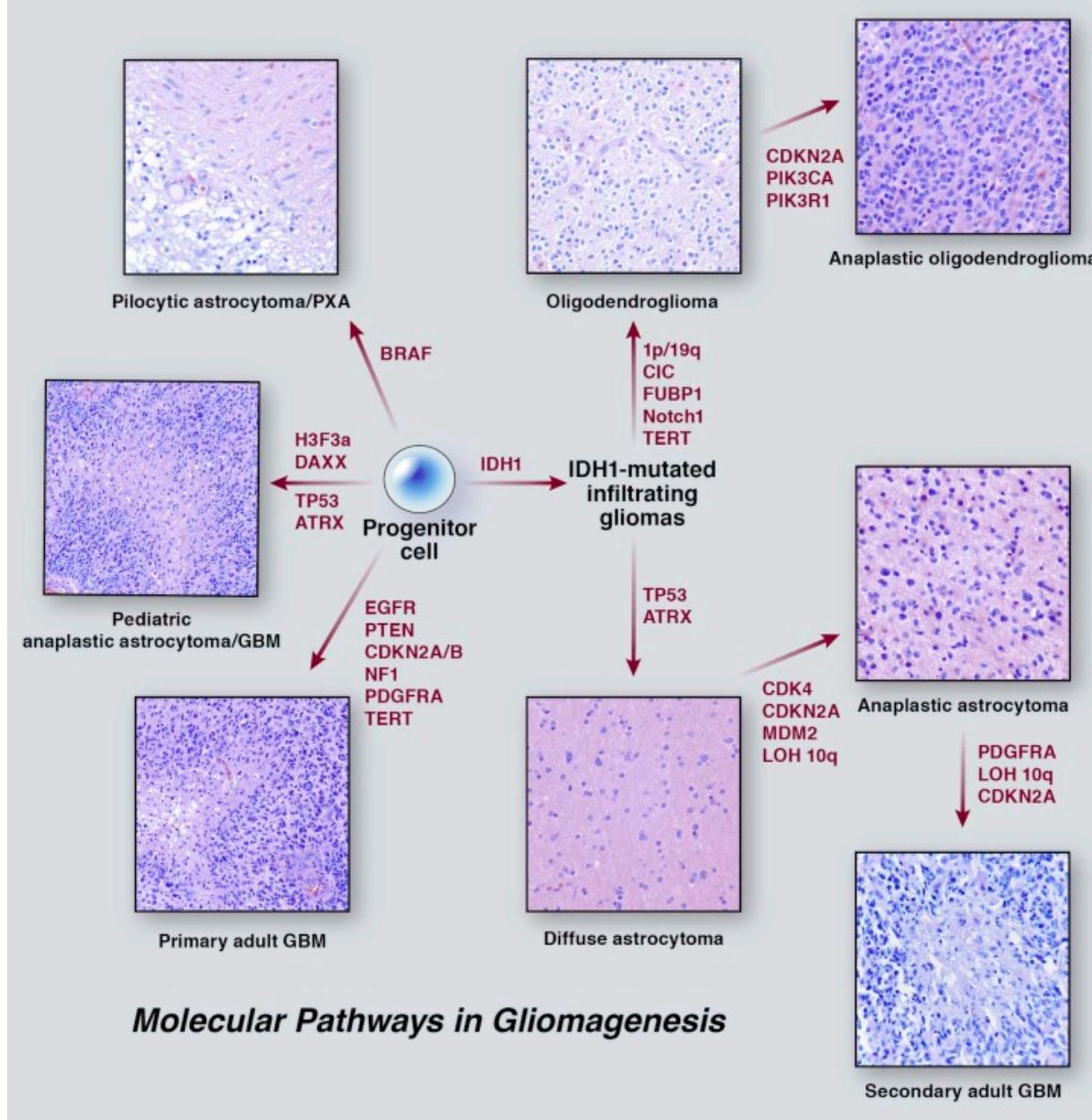


Moleculaire veranderingen in andere primaire hersentumoren

- Ependymomen: RELA gen
- Moleculaire subtypes bij medulloblastomen

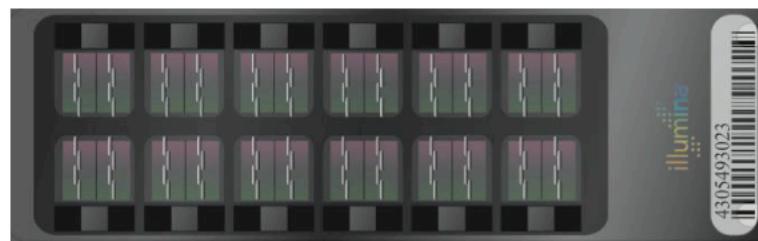
Samenvatting (huidig stand)

- IDH1/2 mutatieanalyse
- Indien IDH1/2 mutatieanalyse + dan 1p/19q status bepaling
- Indien IDH1/2 mutatieanalyse –
 - GBM morfologie>>> MGMT analyse (setting met kliniek bespreken)
 - Non GBM morfologie>>> radiologisch/klinische correlatie>>> toch GBM?
 - Non GBM morfologie>>> aanvullende moleculaire tests (chromosomale afw etc); uitsluiten van een variant glioom)



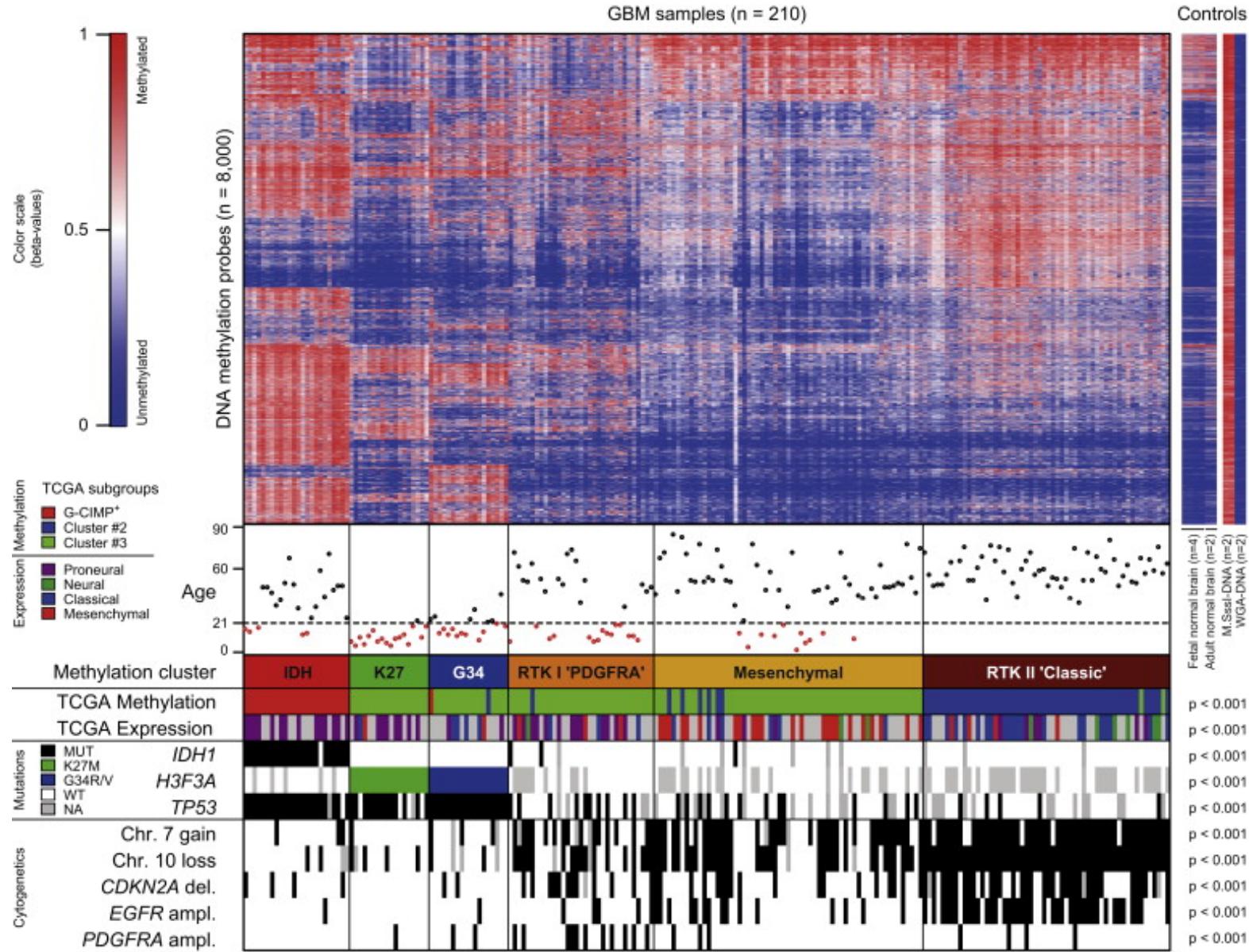
Illumina Infinium HumanMethylation450 (450k) Beadarray

- CpG methylation of over 450.000 individual CpG
- more than 99% of RefSeq-annotated genes covered
- **Material: 500ng DNA from formalin fixed paraffin embedded (FFPE) tissue**



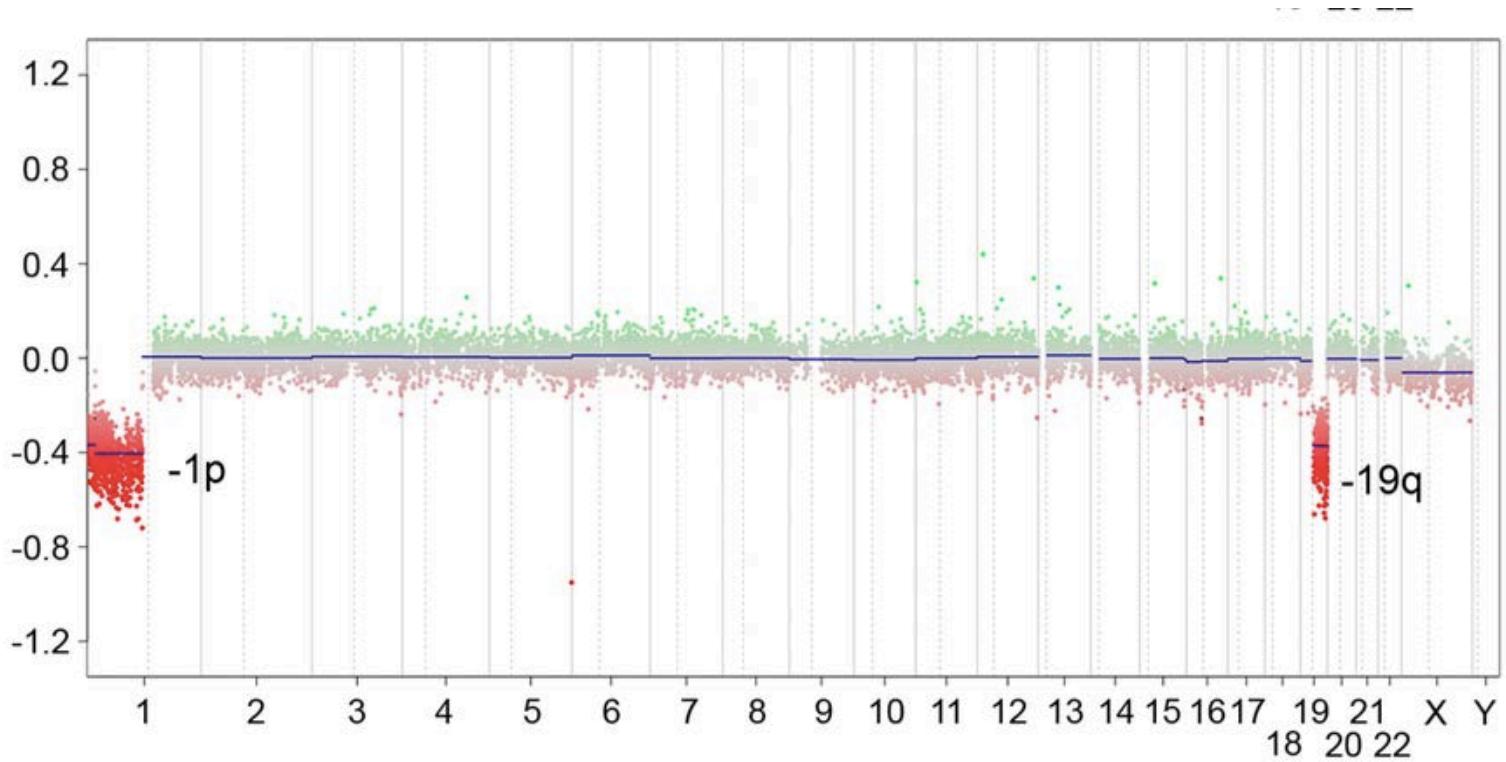
Courtesy of Dr. David Capper, DKFZ/Heidelberg, Germany

Methylation profiling of glioblastomas (n = 210): 6 epigenetic subgroups



INTERMEZZO: Detection of chromosomal copy number aberrations (CNAs)

by methylation profiling



Courtesy of Dr. David Capper, DKFZ/Heidelberg, Germany

Centralisatie?

- Veelal zeer bewerkelijke tests
- Kwaliteitscontrole noodzakelijk
- Nieuwe tests snel ontwikkelen en etableeren
- Uitslagen relateren aan morfologie, IHC, radiologie en kliniek
- >>> kan dit elk lab waarborgen?

Vragen?