PRACTICAL USE OF MOLECULAR MARKERS IN DIAGNOSTIC NEUROPATHOLOGY

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NOTHING TO DISCLOSE
THE PREMISE

• A PHENOTYPE CAN BE ASSOCIATED WITH MULTIPLE GENOTYPES AND VICE VERSA

• THE APPROACH TO THE USE OF MOLECULAR MARKERS SHOULD BE BASED ON A MORPHOLOGICALLY AND CLINICALLY SOUND ALGORITHM
ALGORITHM

- Is it normal or abnormal?
- Is it neoplastic or non-neoplastic?
- Is it benign or malignant?
- Is it glial or non-glial?
- What kind of glial tumor?

↓ C L I N I C A L  D A T A  ↓
↓ R A D I O L O G I C A L  D A T A  ↓
DX
OUTLINE

• SMALL BIOPSY: GLIOSIS OR GLIOMA
• IF IT IS A GLIOMA, DO I NEED ANYTHING OTHER THAN H&E?
• POSTERIOR FOSSA TUMORS IN CHILDREN
THIS LOOKS LIKE A GLIOMA BUT COULD IT BE GLIOSIS
GLIAL MARKERS

- GFAP
- Olig-2
- VIM
- S-100
- EMA
- D2-40
- NSE
TUMOR MARKERS

- MIB-1
- P53
- IDH-1 (R132H)
- ATRX
- WT-1
- 1p19q, EGFR, PTEN, (FISH)
- MGMT, TERT PROMOTER (PCR)
Metabolic Reprogramming: A Cancer Hallmark Even Warburg Did Not Anticipate

PS. Ward, CB. Thompson
CANCER Cell vol 21 no (2012)
IDH STORY

• Useful for diagnosis  YES

• Useful for prognosis  YES

• Predictive for treatment decisions  NO
Clinical Neuropathology practice news 2-2014: ATRX, a new candidate biomarker in gliomas

Christine Haberler and Adelheid Wöhrer

Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma

Jeremy Schwartzentruber1, Andrey Korshunov2, Xiao-Yang Liu3, David T. W. Jones3, Elke Pfaff4, Karine Jacob3, Dominik Sturm5, Adam M. Fontebasso5, Dong-Anh Khuong Quang6, Martje Tonjes7, Volker Hovestadt8, Steffen Albrecht9, Marcel Koot4, Andre Nantel7, Carolin Konermann8, Andreas Lindroth8, Natalie Jäger9, Tobias Rausch10, Marina Ryzhova11, Jan O. Korbel10, Thomas Hielscher12, Peter Hauser13, Miklos Garam13, Almos Klekner14, Laszlo Bogma14, Martin Ehners15, Martin U. Schuhmann16, Wolfram Scheurlen17, Arnulf Pekrum18, Michael C. Frühwald19, Wolfgang Roggenbod20, Christoph Kramm21, Matthias Dürken22, Jeffrey Arkinson23, Pierre Lepage1, Alexandre Montpetit1, Magdalena Zakrzewska24, Krzysztof Zakrzewski25, Paweł Liberski26, Zhifeng Dong26, Peter Siegel26, Andreas E. Kulozik27, Marc Zapatka2, Abhijit Guha28, David Malkin29, Jörg Felsberg30, Guido Reifenberger30, Andreas von Deimling30,31, Koichi Ichimura32, V. Peter Collins32, Hendrik Witt4,5, Till Milde22,33, Olaf Witt7,33, Cindy Zhang28, Pedro Castelo Branco28, Peter Lichter7, Damien Faury1,3, Uri Tabor28,29, Christoph Plass1, Jacek Majewski3, Stefan M. Pfister4,27 & Nada Jabado1,34
TERT MUTATIONS

ALT by FISH

ATRX by IHC

COURTESY OF DR. MELIKE PEKMEZCI, UCSF
ATRX STORY

- Useful for diagnosis: YES
- Useful for prognosis: NO
- Predictive for treatment decisions: NO
FIGURE 5. Proposed mechanism of concurrent 1p and 19q chromosome loss in oligodendro-glioma. One copy each of chromosomes 1 and 19 undergo reciprocal whole-arm exchange at the centromere forming 2 derivative chromosomes:
FISH 1p
FISH - 19q
1P19Q STORY

- Useful for diagnosis: YES
- Useful for prognosis: YES
- Predictive for treatment decisions: YES?
$\textit{MGMT}$ promoter methylation in malignant gliomas: ready for personalized medicine?

Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick & Monika E. Hegi

\textit{Nature Reviews Neurology} 6, 39-51 (January 2010)
MGMT STORY

• Useful for diagnosis  NO

• Useful for prognosis  NO

• Predictive for treatment decisions  YES?
What we now know about adult glioblastoma

The Somatic Genomic Landscape of Glioblastoma


1Human Oncology and Pathogenesis Program, Brain Tumor Center, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
5 distinct genetic/epigenetic/transcriptional subtypes of adult GBM

Brennan et al, Cell October 2013
COURTESY OF DRS. ANNETTE MOLIINARO & MARGARET WRENSCH, UCSF
POSTERIOR FOSSA TUMORS IN CHILDREN
A CHILD WITH A POSTERIOR FOSSA TUMOR

- abnormal
- neoplastic
- low grade or benign
- glial
- type?
FISH analysis for KIAA1549-BRAF shows duplication. IHC suggests downstream pERK activation.
PILOCYTIC AND PILOMYXOID ASTROCYTOMA

Dduplication Or mutation

Mutation

P16 TP53 etc.

SENESCEANCE
A CHILD WITH A POSTERIOR FOSSA TUMOR

- abnormal
- neoplastic
- malignant
- non-gliarial...well NOT SURE
GFAP
MYCC FISH

GREEN: CEP8  RED: MYC-C
MEDULLOBLASTOMA GENETICS

• GROUP A= Wnt Pathway APC, Wnt, β-catenin mutations, classical histology
  TURCOT Syndrome , APC mutations

• GROUP B= SHH Pathway PTCH, SHH, SMOH mutations (nodular/desmoplastic variant)
  GORLIN Syndrome, germline PTCH mutations

• Isochromosome17q in 40% of classic type

• MYC-C & MYC-N amplifications: poor prognosis
  (preferentially in the anaplastic/large cell variant)
Medulloblastomomics: The End of the Beginning

Paul A Northcott¹, David TW Jones¹, Marcel Kool¹, Giles W Robinson², Richard J Gilbertson², Yoon-Jae Cho³, Scott L Pomeroy⁴,⁵, Andrey Korshunov⁶, Peter Lichter⁷, Michael D Taylor⁸,⁹,¹⁰, and Stefan M Pfister¹,¹¹
REMEMBER

- ONE GENOTYPE – ONE PHENOTYPE IS A MYTH, AND A GROSS UNDERESTIMATION OF BIOLOGY
- STARTING POINT IS MORPHOLOGY (TODAY)
- YOU CAN NO LONGER IGNORE MOLECULAR PATHOLOGY AND KEEP YOUR HEAD IN H&E

THANK YOU!!!!