Recent Advances in Medulloblastoma
And Pilocytic Astrocytoma

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Pilocytic Astrocytoma, WHO Grade I

Well differentiated astrocytic neoplasm, generally low grade and slow growing

Occurs mostly in pediatric population in specific sites: cerebellum, optic tracks, temporal lobe, brain stem

Favorable long term prognosis

Often confused with other astrocytic neoplasms, especially “diffuse” astrocytomas
Pilocytic Astrocytoma, WHO grade I
Neurofibromatosis 1 (NF1): “Optic Glioma”
Pilocytic Astrocytoma
Pilocytic Astrocytoma
Pilocytic Astrocytoma
Pilomyxoid Astrocytoma, WHO grade II

More common in infants and young children
Midline tumor involving the hypothalamus or 3rd Ventricle
Rosenthal fibers and EGBs are not present
Molecular Pathways in LGG

RTK

Ras GDP ↔ Ras GTP

Neurofibromin

BRAF → MEK → ERK → Cyclin D1

PI3K → Akt → mTOR → Translation Growth Cell cycle

Diagnosis
Prognosis
Predictive Value

Modified from Qaddoumi *Biol Ther* (2009) and Dan Bowers
The BRAF gene duplication/amplification forms a fusion gene with unregulated kinase activity.

The diagram illustrates the BRAF gene with its kinase domain and RAS binding domain. Exon 18 is located at the N-term end, and the predicted telomeric end of 7q34 gain is indicated by two vertical lines.

Charles Eberhart
Distribution of KIAA1549:BRADF fusion subtypes

Lin et al J Neuropathol Exp Neurol Volume 71, Number 1, January 2012
# BRAF Alterations in Pilocytic Astrocytoma

<table>
<thead>
<tr>
<th></th>
<th>KIAA: BRAF</th>
<th>BRAF V600E</th>
<th>BRAF ins598T</th>
<th>SRGAP: RAF1</th>
<th>RAS mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pfister et al.</strong></td>
<td>28/53 (53%)</td>
<td>3/53 (6%)</td>
<td>0/53 (0%)</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td><strong>Jones et al.</strong></td>
<td>29/44 (66%)</td>
<td>2/44 (5%)</td>
<td>1/44 (2%)</td>
<td>1/44 (2%)</td>
<td>0/44 (0%)</td>
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<tr>
<td><strong>Bar et al.</strong></td>
<td>17/25 (68%)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td><strong>Sievert et al.</strong></td>
<td>17/22 (77%)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Forshew et al.</strong>*</td>
<td>30/32(94%)</td>
<td>0/32 (0%)</td>
<td>0/32 (0%)</td>
<td>1/32 (3%)</td>
<td>1/32 (3%)</td>
</tr>
</tbody>
</table>

**KIAA:BRAF** in 53% to 94% of JPA

**BRAF V600E** in 0% to 6% of JPA
RAF gene fusions are specific to pilocytic astrocytoma in a broad paediatric brain tumour cohort

Andrew R. J. Lawson · Ruth G. Tatevosian · Kim P. Phipps · Simon R. Picker · Antony Michalski · Denise Sheer · Thomas S. Jacques · Tim Forshaw
Analysis of *BRAF* V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma

Genevieve Schindler · David Capper · Jochen Meyer · Wibke Janzarik · Heymut Omran · Christel Herold-Mende · Kirsten Schmieder · Pieter Wesseling · Christian Mawrin · Martin Hasselblatt · David N. Louis · Andrey Korshunov · Stefan Pfister · Christian Hartmann · Werner Paulus · Guido Reifenberger · Andreas von Deimling

42 of 64 PXA (66%)

14 of 77 Ganglioglioma (18%)

9 of 97 Pilocytic Astrocytoma (9%, mostly outside cerebellum)
BRAF and Outcome in Pilocytic Astrocytoma

DOI 10.1007/s00401-009-0634-9

ORIGINAL PAPER

Association of molecular alterations, including BRAF, with biology and outcome in pilocytic astrocytomas

Craig Horbinski · Ronald L. Hamilton · Yuri Nikiforov · Ian F. Pollack

• 147 Pilocytic Astrocytomas Analyzed

• BRAF fusions more common in cerebellar tumors, but not associated with clinical outcome
BRAF Alterations and Outcome in LGG

(Horbinski C, et al)
BRAF Mutations and Outcome in LGG
(Horbinski C, et al)
BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low grade astrocytoma

Cynthia Hawkins¹,⁴*, Erin Walker²,⁴*, Nequesha Mohamed¹,⁴, Cindy Zhang²,⁴, Karine Jacob⁵, Margret Shirinian⁵, Noa Alon², Daniel Kahn², Iris Fried², Katrin Scheinemann⁶, Elena Tsangaris², Peter Dirks³,⁴, Robert Tressler⁷, Eric bouffet², Nada Jabado⁵ and Uri Tabori²,⁴.
Molecular Pathways in LGG

RTK

Ras
GDP

Ras
GTP

Neurofibromin

BRAF

MEK

ERK

Cyclin D1

PI3K

Akt

mTOR

Translation

Growth

Cell cycle

Modified from Qaddoumi *Biol Ther* (2009) and Dan Bowers
43 conventional PA, 24 clinically aggressive/recurrent PA, 25 histologically anaplastic PA

PTEN deletion in 32% and p16 deletion in 20% of anaplastic PA (FISH), but none of the others
Neurofibromatosis 1 (NF1)

Autosomal dominant, prevalence, 1:4000

Mutated Neurofibronin gene (chrom. 17)

> 300 known mutations

Ras-GAP function

Loss leads to Ras activity, Raf, Rac, PI-3-kinase
Medulloblastoma, WHO grade IV

Cerebellar embryonal tumor that is most frequent malignant brain tumor of childhood

Aggressive natural history

5-year survival: 60-80% with therapy

Favorable and unfavorable variants

Progression by local expansion and dissemination
Medulloblastoma

Histologic Variants, WHO 2007:

Classic
Large Cell /Anaplastic
Desmoplastic
Extensive Nodularity
Medulloblastoma Subtypes

A: Classic
B: Large Cell/Anaplastic
C: Nodular/Desmoplastic
Medulloblastoma with Extensive Nodularity

- Rare variant with >90% nodular differentiation
- Mostly in infants < 3 years old
- Often better clinical outcomes
Medulloblastoma
Medulloblastoma
Desmoplastic Medulloblastoma
Medulloblastoma: Survival

Average risk Medulloblastoma

Non-metastatic Medulloblastoma
Large Cell/Anaplasticic Medulloblastoma

- Typically in younger children (< 5 yrs)
- Anaplastic or large cells and apoptotic lakes
- More frequent c-myc amplification
- More aggressive than classic medulloblastoma
- Often disseminated at clinical presentation
Molecular Stratification of Medulloblastoma

• Array-based CGH analysis of 80 medulloblastomas
  1) Loss of 6q
  2) 6q and 17q balanced
  3) 17q gain
  4) 6q gain
  5) c-MYC/MYCN amplification

• Follow-up validation of 260 patients by FISH

Molecular Stratification of Medulloblastoma

Molecular staging proposed:
1) Loss of 6q
2) 6q and 17q balanced
3) 17q gain
4) 6q gain
5) c-MYC/MYCN amplification

Wnt in Medulloblastoma

- Turcot’s syndrome patients with inherited APC loss develop medulloblastoma

- Wnt pathway activation also occurs in sporadic medulloblastoma

[CANCER RESEARCH 58, 896–899, March 1, 1998]

**Advances in Brief**

**Sporadic Medulloblastomas Contain Oncogenic β-Catenin Mutations**

Russell H. Zurawel, Sharon A. Chiappa, Cory Allen, and Corey Raffel

Department of Neurosurgery, Mayo Clinic and Foundation, Rochester, Minnesota 55905
ß-Catenin Status Predicts a Favorable Outcome in Childhood Medulloblastoma: The United Kingdom Children's Cancer Study Group Brain Tumour Committee

David W. Ellison, Olabisi E. Onilude, Janet C. Lindsey, Meryl E. Lusher, Claire L. Weston, Roger E. Taylor, Andrew D. Pearson, Steven C. Clifford
Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups

David W. Ellison · James Dalton · Mehmet Kocak · Sarah Leigh Nicholson · Charles Fraga · Geoff Neale · Anna M. Kenney · Dan J. Brat · Arie Perry · William H. Yong · Roger E. Taylor · Simon Bailey · Steven C. Clifford · Richard J. Gilbertson

WNT Pathway Activation
IHC: Beta-Catenin IHC
Molecular Stratification of Medulloblastoma

- Loss of 6q
- Desmosplastic Histology
- Wnt pathway/β-catenin signaling

Good Prognosis

- IHC: β-catenin

- c-MYC/MYCN amplification
- Large Cell Histology

Poor Prognosis

- FISH: c-MYC
Li Fraumeni Syndrome

- Autosomal dominant, rare
- Inherited TP53 mutation (germline)
- p53 is “gatekeeper” of the genome: regulates cell cycle, response to DNA damage, apoptosis.
- Loss of second allele leads to neoplasms
Li Fraumeni Syndrome

Increased Risk for:
Breast Ca (21%), Sarcomas (19%),
Brain tumors (14%), Lung Ca (4%), Stomach (3%)…..

Histology of Brain Tumors
Astrocytomas (36%)
Medulloblastomas (5%)
Unclassified (44%)
Nevoid Basal Cell Carcinoma Syndrome (Gorlin’s Syndrome)

Autosomal dominant, 1:57,000
Germline mutation of *PTCH*
Ptch is receptor for Hedgehog (Shh)

Mutated ptch does not bind Shh, results in activated signal transduction, gene transcription
Nevoid Basal Cell Carcinoma Syndrome (Gorlin’s Syndrome)

**CNS features:**
Medulloblastoma
  younger (2-3 yrs)
  Desmoplastic subtype
  better prognosis
CNS calcification
macrocephaly

**Other Features:**
Multiple basal cell carcinomas
Odontogenic keratocysts
Turcot Syndrome
Syndrome of Colon cancer and Brain tumors

**Type 1**
Glioblastoma
Hereditary non-polyposis colorectal carcinoma (HNPCC):
Germline mutations of hPMS2, hMSH2, hMLH1

**Type 2**
Medulloblastoma
Familial Adenomatous Polyposis (FAP):
Germline mutations of Adenomatous polyposis coli (APC) gene