Update on Molecular Pathology of Optic Nerve Tumors

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I-Background: Tumors of the Optic Nerve

A variety of tumors may involve the optic nerve primarily or secondarily (Table I). The most frequent primary, intrinsic tumor of the optic nerve is glioma, which almost always is a pilocytic astrocytoma, particularly in children. Another important tumor of the optic nerve sheath is meningioma, usually affecting young to middle age adults. This discussion focuses on astrocytomas and meningiomas of the optic nerve, the major categories with molecular data available.

II-Optic Pathway Gliomas

Clinicopathologic aspects

Pilocytic Astrocytomas (PA) are WHO grade I primary central nervous system (CNS) tumors. They have a 10-year survival rate near 96% after surgery alone(26) and occur predominantly in children and young adults(1). However, tumor progression occurs in approximately 20% of patients (8), which may require additional therapy and result in increased morbidity. Histologically, PA at all sites are characterized by a proliferation of bipolar astrocytes, alternating compact and loose (microcystic areas). Rosenthal fibers and eosinophilic granular bodies are frequent findings.

Pilomyxoid astrocytoma is a unique pilocytic astrocytoma variant characterized histologically by a myxoid vascular, perivascular arrangements of cells and lack of Rosenthal fibers and eosinophilic granular bodies(38). It has a propensity to involve the optic chiasm/hypothalamic region, and is associated with a tendency for aggressive behavior and leptomeningeal dissemination. Therefore, it is assigned a WHO grade II in the most recent (2007) WHO classification(25).

Although the majority of pilocytic astrocytomas occur in the cerebellum, they may involve any CNS compartment including the optic nerve proper and its pathways. In fact, pilocytic astrocytoma is the main histologic subtype of optic pathway glioma (OPG), with a minority representing diffuse gliomas(6).

Optic nerve gliomas have variable clinical presentations:

- Visual loss (most frequent)
- Proptosis
- Optic disc swelling
- Diplopia
- Ptosis
Clinical approaches of optic nerve gliomas involve predominantly observation, but radiation and/or chemotherapy may be indicated in progressive tumors. A subset of tumors may even regress without treatment(27).

**Molecular Genetics**

It is well established at the present time that mitogen-activated protein kinase (MAPK) pathway activation is a basic molecular property of most if not all, low grade pediatric gliomas, including PA. This general RAS/RAF/MEK/ERK signaling cascade mediates intracellular responses to external growth stimuli, and is frequently activated in many human cancers. In PA, the MAPK signaling cascade is mediated in most instances by activation of RAF family members through somatic genetic rearrangements and/or point mutations(18). A tandem duplication of \textit{BRAF} at 7q34 leads to various \textit{KIAA1549:BRAF} gene fusions in the majority of sporadic PA(3, 15, 19, 28, 34, 40), a finding uncovered by recent independent high resolution genomic studies. Frequency of \textit{KIAA1549:BRAF} fusion in low grade glioma/pilocytic astrocytoma varies in the literature, ranging from 60 to 73%(5, 11, 13, 19, 40). However, the prevalence may exceed 90% in cerebellar PA(11), and our data suggests that it is also high in sporadic gliomas of the optic pathway (60%). In addition, using tissue microarrays from gliomas of the optic nerve proper, we identified \textit{BRAF} duplication by fluorescence in situ hybridization in 80% of samples (unpublished data).

In low grade gliomas arising in the setting of the genetic syndrome neurofibromatosis type 1 (NF-1), inactivation of the \textit{NF1} gene leads to MAPK pathway activation(7), a genetic alterations that is mutually exclusive with \textit{BRAF} rearrangements in the majority of cases. Less frequent alterations in sporadic PA, include activating point mutations in \textit{BRAF} and rearrangements of alternative \textit{BRAF} family members (e.g. \textit{RAF1}) (20). Cin et al. reported a novel gene fusion involving \textit{BRAF} and \textit{FAM131B}, resulting from an interstitial deletion(5). Recent insights into these rearrangements support a role for sequence microhomology and the mechanism of “microhomology-mediated break-induced replication”(21). Molecular genetic alterations in PA are summarized in table II.

The frequency of these alterations in low grade gliomas and glioneuronal tumors may vary according to histologic subtype. For example, gangliogliomas and pleomorphic xanthoastrocytomas demonstrate an increased frequency of \textit{BRAF}V600E point mutations (9, 32). The strongest clinicopathological associations of the \textit{KIAA1549:BRAF} fusion are with PA histology and posterior fossa or optic pathway anatomical locations. Lower frequencies of \textit{KIAA1549:BRAF} fusions in supratentorial non-optic PA and adult patients have been previously noted (12, 40). \textit{KIAA1549:BRAF} fusion appears to be specific for PA in some studies(22); however in our experience a subset of difficult to classify “low grade gliomas”, as well as low grade glioneuronal tumors, may have this alteration, albeit at a much lower frequency(24). In some instances this may be secondary to limited diagnostic tissue; however many tumors we have examined were adequate for review, suggesting that a subset of pediatric low grade CNS tumors other than PA may have \textit{BRAF} fusions.

Reasons for frequency differences of \textit{KIAA1549:BRAF} fusions by site (optic pathway/cerebellum) are unclear. Biologic and expression differences have been described in pediatric CNS tumors by
anatomy. PA and ependymomas exhibit similar gene expression profiles to possible regional precursors, even in the absence of histologic differences by site(33, 36).

The prognostic significance of these molecular alterations also remains unclear. Most studies have not found a significant association of BRAF alterations with outcome(5, 14, 19). Our data suggested a non-significant trend of increased progression-free survival in association with KIAA1549:BRAF fusion(24). However, Hawkins et al. in a recent study reported a better outcome in association with KIAA1549:BRAF fusions when restricting their analyses to a “clinically relevant” subgroup of pediatric low grade astrocytoma patients (i.e. those in non-NF1 patients with non-cerebellar tumor location and subtotal resection)(13), a finding that awaits confirmation.

**Oncogene-Induced Senescence**

Recent studies focusing initially on melanoma and melanocytic nevi have uncovered a mechanism of “oncogene-induced senescence” in tumors with BRAF activation. In this model, initial BRAF activation leads to a growth stimulus, which is subsequently antagonized by cellular senescence, resulting in growth arrest. Recent work suggests that a similar mechanism may also operate in PA(16, 30). This phenomenon is associated with increased beta-galactosidase and p16 expression. p16, an important tumor suppressor, may represent an important component of this process, given that PA tumors lacking p16 expression are associated with a worse survival(30). Given the indolent behavior of most optic nerve gliomas, and even regression without treatment(27), senescence may be an important biological phenomenon that merits further study.

**Mouse models of optic glioma**

Optic glioma has been modeled predominantly in mice with Nf1 loss. These models, as other models of NF1, have highlighted the importance of the tumor microenvironment, since complete (homozygous) Nf1 loss in glial precursors is not sufficient for tumor formation, but requires partial (heterozygous) Nf1 loss in non-neoplastic cellular components. Non-neoplastic microglia in particular seem to secrete factors (e.g. MGEA5 and CXCL12) that may enhance the growth of neoplastic precursors (35, 37).

These models have also proven useful to evaluate a role for an additional signaling pathway associated with cell growth in optic glioma: AKT/mTOR(2). In these models, neurofibromin loss leads to mTOR pathway activation, and increased progenitor/stem cell proliferation (23). Our data from tissue microarrays also suggests activation of mTOR pathway components in the majority of optic nerve gliomas (unpublished data).

An additional pathway that may play a role in the pathogenesis of optic nerve tumors includes Notch. In recent experiments, introduction of activated Notch3 led to choroid tumors and gliomas of the optic nerve in mice. However, these gliomas appeared to be more aggressive than conventional PA, with increased proliferation rates and invasion of surrounding tissues (29).

**IV-Meningioma**

Molecular Pathology of Meningiomas(25)
Meningiomas are among the best characterized neoplasms at the cytogenetic level. The most frequent cytogenetic alteration overall is chromosome 22 loss(4). In addition, chromosome arm1p and chromosome 6, 10, 14, 18 and 19 losses are frequently encountered. Additional alterations in atypical and anaplastic subsets occur, consistent with molecular progression. At the molecular genetic level, mutations in the NF2 gene (located in chromosomal arm 22q) are frequent. Meningiomas, commonly multiple, also affect the majority of patients with the neurofibromatosis type 2 syndrome, who in addition develop schwannomas and ependymomas.

**Intraorbital meningioma: clinicopathologic aspects**

Intraorbital meningiomas encompass approximately 4% of all intraorbital neoplasms. Most are low grade (WHO grade I), and histologically of the meningotheelial subtype(17). Broadly speaking, they may be separated in two different categories by anatomy:

1. Primary tumors originating from the optic nerve sheath.
2. Secondary tumors involving the orbit by extension from intracranial primaries.

**Intraorbital meningioma: copy number alterations**

We are currently performing a study of copy number alterations using single nucleotide polymorphism (SNP) arrays on an Illumina platform with formalin fixed paraffin embedded tissue, to identify molecular genetic changes associated with intraorbital meningiomas. Preliminarily, we have investigated 6 WHO grade I intraorbital meningiomas (5 intraorbital and one primary optic nerve example). Genetic copy number alterations were observed in 5 cases:

- The most frequent alteration was chromosome 22/22q loss, followed by 6q loss.
- The single optic nerve meningioma demonstrated a unique genotype, with deletion of 1pter-p35.3, deletion of 2pter-p16.3, deletion 2q22.1-qter and gain of 15q21.3-qter.

Expanded observations of this ongoing study will be presented by Dr. Cheng-Ying Ho in poster form at the 2012 USCAP meeting.

**V-Rare tumors of the optic nerve**

Additional tumors that may involve the optic nerve include melanocytic tumors (melanocytoma and melanoma), hemangiomas, solitary fibrous tumor/hemangiopericytoma, and medulloepithelioma(10). Rosette forming glioneuronal tumor(31) and atypical-teratoid rhabdoid tumor(39) have been rarely reported. In addition, a variety of tumors may involve the optic nerve secondarily, including lymphoma, metastatic carcinoma, and melanoma. Little is known about the molecular alterations involved in the pathogenesis of these tumors.
### Table I: Tumors of Optic Nerve and Optic Nerve Head

#### Primary Tumors
- Astrocytoma
  - Pilocytic Astrocytoma
  - Diffusely Infiltrating Astrocytoma
- Meningioma
- Melanocytic
  - Melanocytoma
  - Melanoma
- Medulloepithelioma
- Hemangioma
- Solitary Fibrous Tumor/Hemangiopericytoma
- Rosette forming glioneuronal tumor
- Atypical teratoid rhabdoid tumor

#### Secondary tumors
- Intraocular
  - Retinoblastoma
  - Melanoma
- Metastatic/systemic
  - Hematopoietic (lymphoma, leukemia)
  - Metastatic (carcinoma, melanoma)

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1. Modified from Font RL, Croxatto JO, Rao NA (10)

2. Probable case reported by Verma and Morriss, described but not illustrated (39)
Table II: Molecular Genetic Alterations in Pilocytic Astrocytoma (PA)

<table>
<thead>
<tr>
<th>Alterations</th>
<th>Alteration type</th>
<th>Frequency in PA</th>
</tr>
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<tbody>
<tr>
<td><em>KIAA1549-BRAF</em></td>
<td>Duplication/gene fusion</td>
<td>60-90% (depending on anatomical site)</td>
</tr>
<tr>
<td><em>NF1</em> inactivation</td>
<td>Inactivating mutation in NF1-associated PA</td>
<td>5-7%</td>
</tr>
<tr>
<td><em>BRAF</em> V600E</td>
<td>Activating mutation</td>
<td>~5%</td>
</tr>
<tr>
<td><em>RAF1-SRGAP3</em></td>
<td>Duplication/gene fusion</td>
<td>Rare (~2%)</td>
</tr>
<tr>
<td><em>FAM131B-BRAF</em></td>
<td>Deletion/gene fusion</td>
<td>Very rare</td>
</tr>
<tr>
<td><em>BRAF</em> insertions</td>
<td>Activating mutation</td>
<td>Rare (~2%)</td>
</tr>
<tr>
<td><em>KRAS</em> activating mutations</td>
<td>Activating mutation</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

References

tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-
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2008;38:1117-1121.
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Update on Molecular Pathology of Optic Nerve Tumors

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Molecular Pathology of Optic Nerve Tumors

- Optic Pathway Gliomas
  - Clinicopathologic aspects
  - Molecular genetics: \textit{BRAF} and \textit{NF1}
  - Signaling pathways: MAPK, mTOR, Notch
  - Mouse models

- Intraorbital Meningiomas
  - Clinicopathologic aspects and grading
  - Current molecular studies
Gliomas
WHO Classification

• I- Astrocytic Tumors
  – Pilocytic Astrocytoma (PA) (WHO grade I)
  – Pleomorphic Xanthoastrocytoma (WHO grade II)
  – Diffuse Astrocytoma (WHO grade II)
  – Anaplastic Astrocytoma (WHO grade III)
  – Glioblastoma (WHO grade IV)
  – Gliomatosis Cerebri

• II- Oligodendroglial tumors
  – Oligodendroglioma and oligoastrocytoma (WHO grade II)
  – Anaplastic Oligodendroglioma and OA (WHO grade III)

• III- Ependymal Tumors
Optic Nerve Glioma

- Variable clinical presentation
  - Visual loss, proptosis, disc swelling
  - Fusiform expansion
  - Confined by dural sheath
- Predominantly pilocytic astrocytoma histology
- Observation currently favored in many cases, particularly in NF1 setting
- May stabilize or even regress
Pilocytic Astrocytoma
Clinical & Pathology

- WHO Grade I tumors that typically affect children and young adults
- Represent the most common primary brain tumor in children
- Most arise in the cerebellum
- Generally favorable outcomes with 5-year overall survival rates of 96% after GTR
Pilomyxoid Astrocytoma

- Pilocytic variant
- Infants, hypothalamic region/chiasm
- Higher propensity for aggressive behavior, CSF dissemination
- WHO grade II
- No Rosenthal fibers, EGBs rare to absent
Pilomyxoid Astrocytoma

Chiasm/Hypothalamus
Pilocytic Astrocytoma

Cytogenetics

• Usually a normal diploid karyotype
• Chromosomal gains (typically involving Chr 7 and 8) occurring in approximately one third of the cases
• Need to use higher-resolution platforms to identify genomic aberrations in these tumors
Pilocytic Astrocytoma
Molecular Genetics

- Genes on Chr7: \textit{BRAF} and \textit{HIPK2}
- Gene on Chr8: \textit{Matrilin 2}
- \textit{BRAF} and \textit{HIPK2}: promote cell growth
- \textit{Matrilin 2}: overexpressed in PA with aggressive clinical behavior
Pilocytic Astrocytoma

*BRAF* Duplication

- Tandem duplication of the *BRAF* kinase domain
- Multiple independent publications in 2008:
  - Bar, E.E., et al., JNEN 2008
Tandem duplication at 7q34 produces a fusion gene between KIAA1549 and BRAF

Jones et al. 2008
Pilocytic Astrocytoma

*BRAF* and *KIAA1549*

- **BRAF**
  - Raf/mil family of serine/threonine protein kinases
  - Oncogenic activation in many tumors
  - NH2-terminal truncation leads to constitutive kinase activity
  - Hotspot at residue 600 (*BRAF*V600E)

- **KIAA1549**
  - Function still unclear
**KIAA1549**: **BRAF** fusion most frequent alteration in pediatric low grade glioma

- KIAA1549:BRAF (48%)
- No alteration (40%)
- BRAF^{V600E} (5%)
- NF1-associated (5%)

KIAA1549:BRAF distribution varies by location and histologic subtype

Modified from:
Pilocytic Astrocytoma
Optic Nerve Glioma in NF1

- 100 patients with NF1 and glioma
- Half of tumors histologically PA
- 24 cases in optic pathway
  - PA (n=14)
  - Low gr indeter (n=4)
  - Diffuse astro (n=4)
  - Pilomyxoid (n=1)
  - Ganglioglioma (n=1)

Modified from
Pilocytic Astrocytoma
Sporadic vs. NF1-associated

• Most PA arise sporadically
• Similar histology in both settings
• Clinical differences
  – Predilection for optic pathway in NF1
    • 15% of NF1-patients develop OPG
  – Better outcome?
Pilocytic Astrocytoma
Sporadic vs. NF1-associated

- **Molecular** differences
  - *NF1* gene inactivation only in NF1 syndrome
  - *BRAF* alterations in sporadic
  - Mutually exclusive alterations (with very rare exceptions)
  - Different gene expression (mRNA) profiles
Pilocytic Astrocytoma
Sporadic vs. NF1-associated

NF1-PA (n=11)                      Sporadic-PA (n=36)

7,516 differentially expressed (student t-test)
191 transcripts with FDR<0.05
Genes differentially expressed by region or nf1-/- vs. wild type murine astrocytes excluded

Affymetrix HG-U133 plus2.0 GeneChip
Pilocytic Astrocytoma
Different Gene Expression Profiles by Site

Pilocytic Astrocytoma
Other Genetic Alterations

- *RAF1*-*SRGAP3* fusion
  - Secondary to 3p25 tandem duplication
- *FAM131B-BRAF* fusion
  - Secondary to 7q34 deletion
- *BRAF* insertions
- *BRAF*^{V600E}
**BRAF Point Mutations**

**BRAF^V600E**

- Frequent in papillary thyroid carcinoma and melanoma
- Absent to extremely rare in GBM, oligodendroglial tumors, ependymomas
- Present in a subset of low grade/pediatric gliomas (Schindler G et al. 2011)
  - 66% of pleomorphic xanthoastrocytomomas
  - 18% of gangliogliomas
  - 9% of pilocytic astrocytomomas
**BRAF** Point Mutation

\[ \text{BRAF}^{V600E} \]

Wild Type

\[ \text{BRAF}^{V600E} \]
BRAF Activation and Senescence


Human Cancer Biology

BRAF Activation Induces Transformation and Then Senescence in Human Neural Stem Cells: A Pilocytic Astrocytoma Model

Eric H. Raabe1, Kah Suan Lim2, Julia M. Kim3, Alan Meeker2, Xing-gang Mao2, Guido Nikkha4, Jarek Maciacyzk5, Ulf Kahler6, Deepali Jain2, Eli Bar2, Kenneth J. Cohen1, and Charles G. Eberhart2


Human Cancer Biology

Genetic Aberrations Leading to MAPK Pathway Activation Mediate Oncogene-Induced Senescence in Sporadic Pilocytic Astrocytomas

Karine Jacob1, Dongh-Anh Quang-Khuong1, David T.W. Jones5,8, Hendrik Witt5, Sally Lambert8, Steffen Albrecht2, Olaf Witt6, Catherine Vezina3, Margret Shirinian3, Damien Faury1,3, Miklos Garami9, Peter Hauser9, Almos Klekner10, Laszlo Bogna10, Jean-Pierre Farmer4, Jose-Luis Montes4, Jeffrey Atkinson9, Cynthia Hawkins11, Andrey Korshunov7, V. Peter Collins8, Stefan M. Pfister5,6, Uri Tabori12, and Nada Jabado1,3
BRAF and Senescence

• BRAF activation also in melanocytic nevi and melanoma
• May lead to “oncogene-induced senescence”
  – Initial oncogenic growth stimulus
  – Subsequent cellular senescence antagonizes further growth
  – Associated with beta-galactosidase and p16 expression
BRAF and Senescence

• Introduction of $BRAF^{V600E}$ in neurospheres from fetal brain
  – Initial MAPK pathway activation
  – Eventual cellular senescence

• Lack of p16 immunostaining in PA (14%) associated with decreased survival

Raabe E. et al. *Clin Cancer Res* 2011
Optic Nerve Glioma Models

- Optic glioma modeled in mice with \( Nf1 \) loss
- Highlight importance of tumor microenvironment
  - Complete \( Nf1 \) loss in astroglial progenitors
  - Heterozygous \( Nf1 \) loss in non-neoplastic stroma
  - Microglia in particular appear early in glioma formation and contribute to glioma growth
  - \( Nf1+/- \) microglia secrete factors (e.g. MGEA5 and CXCL12) that promote astrocyte growth
Optic Nerve Glioma Models

mTOR signaling

- PI3K/AKT/mTOR pathway
  - Important mediator of cellular proliferation and protein synthesis
- mTOR activation in neurofibromin deficient astrocytes
  - Proliferation, blocked with rapamycin
Optic Nerve Glioma Models

mTOR signaling

• Neurofibromin loss in mice leads to progenitor/stem cell proliferation
  – Region dependent (brainstem vs. cortex)
  – Probably mediated by AKT/mTOR activation

• Increased PI3K/AKT/mTOR activation in specific PA subsets (e.g. anaplastic)
Optic Nerve Glioma Models

Notch Signaling

• Invasive gliomas of optic nerve induced by activated Notch3 (in addition to tumors of the choroid)
• Tumors arise in retina/optic nerve, but not in brain
• Invasion of orbital tissues frequent
• Co-expression of GFAP, Nestin, and Notch3

Pierfelice et al. *Can Res* 2011
Optic Nerve Glioma Models
Formation of glial tumors along the optic nerve by Notch

Pierfelice et al.
Can Res 2011
Optic Nerve Glioma Study

• Patients and tumor samples
  – Tumors obtained from 59 patients from the files of the Armed Forces Institute of Pathology
  – Clinical evidence of NF1 in 7 patients
  – Median age at surgery was 9 years (range 3 months-66 years; 33 F, 26 M)
  – Chiasm involvement in 11 patients
  – Tissue microarray constructed from FFPE material, with 2-5 cores (1 mm) per tumor
Optic Nerve Glioma Study

• Immunohistochemical studies
  – mTOR pathway components
  – Microglia (CD68)
  – Senescence (p16)
  – Mutant IDH1

• Fluorescence in Situ Hybridization (FISH)
  – BRAF, CDKN2A (p16), PTEN
Optic Nerve Glioma Study

Immunopreservation of TMA

GFAP immunoreactivity preserved in 53/56 cases (95%)
Frequent mTOR Pathway Activation in OPG
Moderate to strong (2-3+) IHC staining

51%                                           71%

70%                                           40%
Optic Nerve Glioma Study

Increased numbers of senescence markers, microglia and \( BRAF \) duplication

Positive (81%) 2-3+ (46%)

Only 1 case+ Dup 79%
Optic Nerve Glioma Study

Additional Results

• Heterozygous \textit{PTEN} deletions in 2/25 (8%)
• \textit{CDKN2A} (\textit{p16}) deletions absent in all cases tested (\textit{n}=29)
• Polysomies for chromosome 7, 9, and 10 in 2 (14%), 2 (7%), and 1 (4%) cases respectively
Cell Signaling Pathways in PA

- Deletions/mutations
- Levels/Activation

RTK

RAS:GTP ↔ RAS:GDP

NF1

BRAF RAF1

MEK/ERK

PI3K

PIP2 → PIP3

AKT

mTORC1

mTORC2

PTEN

S6K1

S6

Cell growth, survival
Proliferation Apoptosis

Sporadic PA
- BRAF dup
- BRAF V600E
- RAF1 dup
Intraorbital Meningiomas
Meningiomas
General Molecular Pathology

• Cytogenetic abnormalities
  – Chr 22 loss (most common)
  – Also 1p, Chr 6, 10, 14, 18 and 19 loses
  – Additional alterations in atypical and anaplastic subsets

• Molecular genetic abnormalities
  – NF2 mutations frequent
Meningiomas
General Molecular Pathology

• Syndrome associations
  – Meningiomas, commonly multiple, occur in majority of NF2 patients
  – Germline SMARCB1/INI1 mutations present in 30% of patients with familial schwannomatosis
  – Germline SMARCB1/INI1 mutation, and somatic NF2 mutations, in one family with multiple meningiomas
  – SMARCB1/INI1 mutations very rare in familial multiple meningiomas
Intraorbital Meningiomas

Clinical

• Approximately 4% of intraorbital neoplasms
• Vast majority are meningothelial, WHO grade I
• Two different categories by anatomy
  – Primary tumors originating from the optic nerve sheath
  – Secondary tumors involving orbit by extension from intracranial primaries
Intraorbital Meningiomas Study

Ho C. et al. (2012 USCAP abstract)

- Global copy number alterations
  - 6 intraorbital meningiomas (5 orbital, 1 optic nerve)
  - All WHO grade I
  - SNP array analysis from FFPE tissues using Illumina array
Intraorbital Meningiomas Study

Ho C et al. (USCAP abstract 2012)

• Genetic alterations in 5 cases
  – Most frequent Chr 22/22q loss, followed by 6q loss
  – Single optic nerve meningioma unique genotype (deletion of 1pter-p35.3, deletion of 2pter-p16.3, deletion 2q22.1-qter and gain of 15q21.3-qter)
  – *Ongoing study*
Other Optic Nerve Tumors

- Melanocytoma/melanoma
- Hemangiomas
- Hemangiopericytoma/solitary fibrous tumor
- Medulloepithelioma

*Little known about molecular pathology aspects*
Summary

- Pilocytic astrocytoma most frequent neoplasm of optic nerve
- Recent molecular advances in our understanding of pilocytic astrocytoma
  - Alterations in *BRAF* and *NF1*
  - MAPK, mTOR signaling pathways
  - Phenomenon of oncogene-induced senescence
  - Role of the non-neoplastic microenvironment (e.g. microglia)
Summary

• Molecular alterations in intracranial meningioma well studied
  – Further work needed in intraorbital meningiomas
Acknowledgments

**Johns Hopkins**
*Neuropathology/Ophthalmic Pathology*
Charles Eberhart
Eli Bar
Cheng-Ying Ho

*Molecular Pathology*
Denise Batista
Christopher Gocke
Stacy Mosier

**Armed Forces Institute of Pathology**
J. Douglas Cameron
Elisabeth J. Rushing

**New York University**
Matthias Karajannis
David Zagzag

**Brigham and Women’s**
Azra Ligon
Keith Ligon