SMARCB1-Deficient Vulvar Neoplasms

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Overview

• SMARCB1
• Tumors showing SMARCB1 alterations
• Our recent experience with SMARCB1-deficient vulvar neoplasms
SMARCB1 (INI1, SNF5, BAF47)

- Ubiquitously expressed
- 22q11.2
- SWI/SNF chromatin remodeling complex
- Displaces DNA from histones, allowing transcription
SMARCB1 in Rhabdoid Tumor

Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer

Isabella Versteeght, Nicolas Sévenett, Julian Langet, Marie-Francoise Rousseau-Mercxt, Peter Ambrost, Rupert Handgretinger, Alain Aurias, & Olivier Delatret*

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‡ Universität Kinderklinik, Rämistrasse 23, D-72070 Tübingen, Germany

Alterations of the hSNF5/INI1 Gene in Central Nervous System Atypical Teratoid/Rhabdoid Tumors and Renal and Extrarenal Rhabdoid Tumors

Jaclyn A. Biegel, Lu Tan, Fan Zhang, Luanne Weinwright, Pierre Russo, and Lucy B. Rorke

from all sites contained deletions and/or mutations of the INI1 gene. Specific mutations were non-randomly associated with anatomical site.

Absence of expression of SMARCB1/INI1 in malignant rhabdoid tumors of the central nervous system, kidneys and soft tissue: an immunohistochemical study with implications for diagnosis

Ellen Sigauke, Dinesh Rakheja, Deborah L Maddox, Christa L Hladik, Charles L White III, Charles P Timmons, and Jack Raisman
Rhabdoid Tumor Predisposition Syndrome

**Advances in Brief**

Germ-Line and Acquired Mutations of INI1 in Atypical Teratoid and Rhabdoid Tumors

Jaclyn A. Biegel, Jun-Ying Zhou, Lucy B. Rorke, Cindy Stenstrom, Luanne M. Wainwright, and Benjamin Fogelgren

**Spectrum of SMARCB1/INI1 Mutations in Familial and Sporadic Rhabdoid Tumors**

Katherine W. Eaton, et al.

**TABLE III. Germline Alterations in Rhabdoid Tumors by Anatomic Site**

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>Total</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>65</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Kidney</td>
<td>12</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Multiple primaries</td>
<td>6</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Extra-renal</td>
<td>17</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>
Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice

Charles W. M. Roberts*, Shelly A. Galusha*, Mairin E. McMenamin†, Christopher D. M. Fletcher†, and Stuart H. Orkin*†
Malignant Rhabdoid Tumor

- Beckwith and Palmer (1978): originally regarded as “rhabdomyosarcomatoid variant of Wilms’ tumor,”
- Renal, CNS (atypical teratoid/ rhabdoid tumor, AT/RT), soft tissue (malignant extrarenal rhabdoid tumor, MERT) and disseminated presentations
- Renal MRT and AT/RT: children < 1 year of age; aggressive clinical course
- Disseminated MRT: often lack clear primary tumor; may be part of familial rhabdoid tumor predisposition syndrome
- MERT
  - Deep axial locations, paraspinal region and neck
  - Much broader age range than renal MRT, although still far more common in children
  - Vimentin-positive; less often CK-positive
  - Usually CD34-negative
  - Aggressive clinical behavior, with <50% of patients alive at 5 years
MERT: Entity or Pattern?

Rhabdoid phenotype may be seen in essentially any tumor.

Has been suggested that many MERT in adults represent other tumors, especially proximal-type epithelioid sarcoma.
INI1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas

Arie Perry, Christine E Fuller, Alexander R Judkins, Louis P Dehner and Jaclyn A Biegel

Composite Rhabdoid Tumor (Melanoma)
SMARCB1 in Schwannomatosis

Germline Mutation of INI1/SMARCB1 in Familial Schwannomatosis

SMARCB1/INI1 germline mutations contribute to 10% of sporadic schwannomatosis
Guillaume Rousseau, Tetsuro Noguchi, Violaine Bourdon, Hagay Soba, Sylvaine Olischwarz

Expression of SMARCB1 (INI1) mutations in familial schwannomatosis

Department of Neurology, Massachusetts General Hospital Cancer Center, Center for Human Genetic Research, Division of Neuropathology, Pappas Center for Neuro-oncology, Massachusetts General Hospital, Boston, MA 02114, USA
Received June 21, 2012; Revised August 10, 2012; Accepted August 28, 2012
SMARC1 mutations in schwannomatosis and genotype correlations with rhabdoid tumors
Miriam J. Smith, Andrew J. Wallace, Naomi L. Bowers, Helen Eaton, D. Gareth R. Evans

Table 4  Mutation positional differences between schwannomatosis and AT/RT

<table>
<thead>
<tr>
<th>Exon</th>
<th>Schwannomatosis, no. of carriers/no. of patients</th>
<th>AT/RT no. of carriers/no. of patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 1</td>
<td>16/48</td>
<td>3/77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exons 2–7</td>
<td>14/48</td>
<td>43/77</td>
<td>0.005</td>
</tr>
<tr>
<td>Exon 8</td>
<td>4/48</td>
<td>0/77</td>
<td>0.02</td>
</tr>
<tr>
<td>Exon 9 and 3'UTR</td>
<td>14/48</td>
<td>0/77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Whole gene</td>
<td>0/48</td>
<td>34/77</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Table 5  Differences in germline mutation type between schwannomatosis and AT/RT

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>Schwannomatosis no. of carriers/no. of patients</th>
<th>AT/RT no. of carriers/no. of patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsense</td>
<td>5/48</td>
<td>25/77</td>
<td>0.005</td>
</tr>
<tr>
<td>Frameshift</td>
<td>5/48</td>
<td>15/77</td>
<td>0.2</td>
</tr>
<tr>
<td>Splice site</td>
<td>10/48</td>
<td>3/77</td>
<td>0.005</td>
</tr>
<tr>
<td>Missense</td>
<td>10/48</td>
<td>0/77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3'UTR</td>
<td>14/48</td>
<td>0/77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In-frame deletion</td>
<td>4/48</td>
<td>0/77</td>
<td>0.02</td>
</tr>
<tr>
<td>Whole gene</td>
<td>0/48</td>
<td>34/77</td>
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<td>34/77</td>
<td>&lt;0.0001</td>
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</table>

deletion/single or multiexon
deletion or duplication
MRT or E-MPNST Arising in Schwannomatosis

Epithelioid Malignant Peripheral Nerve Sheath Tumor Arising in a Schwannoma, in a Patient With “Neuroblastoma-like” Schwannomatosis and a Novel Germline SMARCB1 Mutation

Jodi M. Carter, MD, PhD,1 Carolyn O’Hara, MD, MD2 George Dundas, MD,3 Darina Gilevaja, MD,3 Mark S. Collins, MD,3 Katherine Eaton, BS;1 Alexander R. Judkins, MD,4 Jocelyn A. Beigel, PhD,4|| and Andrew L. Folpe, MD,5

Familial occurrence of schwannomas and malignant rhabdoid tumour associated with a duplication in SMARCB1

J J Swensen,1 J Keyser,2 C M Coffin,2 J A Beigel,4 D H Viskochil,1 M S Williams6
SMARCB1 Loss in Other Tumors

_**SMARCB1/INI1 Tumor Suppressor Gene Is Frequently Inactivated in Epithelioid Sarcomas**_


Units of Molecular Cytogenetics and Molecular Pathology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy; and Department of Genetics, Portuguese Oncology Institute, Porto, Portugal.

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**Loss of INI1 Expression is Characteristic of Both Conventional and Proximal-type Epithelioid Sarcoma**

Jason L. Hornick, MD, PhD. Paola Dal Cin, PhD. and Christopher D. M. Fletcher, MD, FRCPath

Abstract: _INI1_ (hSNF5/SMARCB1), a member of the SWI/SNF chromatin remodeling complex located on chromosome 22q11.2, is deleted or mutated in strictly defined malignant rhabdoid tumors (MRT) of infancy. Recent studies suggest that some epithelioid sarcomas (ES) also show inactivation of _INI1_. However, very few cases of ES have been studied, and _INI1_ distinguish epithelioid MPNST from metastatic melanoma in a subset of cases.

Key Words: INI1, Snf5, epithelioid sarcoma, malignant rhabdoid tumor


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**Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior**

Jason X Cheng, Maria Tretiakova, Can Gong, Saptarshi Mandal, Thomas Krausz and Jerome B Taxy
# SMARCB1-Deficient Tumor Family

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>SMARCB1-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid Sarcoma</td>
<td>~ 90%</td>
</tr>
<tr>
<td>Myoepithelial CA</td>
<td>10-40%</td>
</tr>
<tr>
<td>Rhabdoid tumor</td>
<td>~ 100%</td>
</tr>
<tr>
<td><em>Epithelioid MPNST</em></td>
<td>40-50%</td>
</tr>
<tr>
<td><em>Renal medullary CA</em></td>
<td>100%</td>
</tr>
<tr>
<td><em>Extracellular myxoid CS</em></td>
<td>~ 20%</td>
</tr>
</tbody>
</table>
Epithelioid Sarcoma

- Classical ES typically presents as a small, superficial lesion of the distal extremities in adolescents and young adults.
- Proximal-type ES occurs as a large, deep mass in older adults.
Pathological Features

- Nodular, vaguely circumscribed but infiltrative
- Garland-like appearance with necrosis
- Relatively bland epithelioid cells
- Modulates from epithelioid to spindled
- PTES shows greater pleomorphism, rhabdoid cells, geographic necrosis
- Variants with chronic inflammation, hyalinized collagen, bone, myxoid or pseudovascular change
Inflammatory
Myxoid
Pseudoglandular
Calcifying
Immunohistochemistry

- LMWCK, HMWCK, EMA-positive
- Vimentin co-expression
- CD34 expression (50-60%)
- SMARCB1 loss (90%)
- Generally negative for more specific endothelial markers (CD31, FLI1/ERG)
- Generally negative for p63 and p40
Outcome

- Not graded by either French or NCI systems
- Over 70% recur and nearly 50% metastasize
- Often recur in more proximal soft tissue as multiple nodules
- Adverse prognostic factors include male sex, proximal location, size > 5cm, deep location
- Proximal variant may metastasize earlier
PTES vs MERT

Prognostic significance of dysadherin expression in epithelioid sarcoma and its diagnostic utility in distinguishing epithelioid sarcoma from malignant rhabdoid tumor

Teiyu Izumi1, Yoshinao Oda1, Tadashi Hasegawa2, Yukihito Nakashi2, Hiroshi Iwasaki1, Hiroshi Sonobe3, Hiroaki Goto4, Hidenori Kasakobe1, Tomonari Takahira1, Chikashi Kobayashi1, Ken-ichi Kawaguchi1, Tatsuyoshi Saito1, Hidetaka Yamamoto1, Sadafumi Tamiya1, Yukihide Iwamoto1 and Masazumi Tsuneyoshi1

Differential microRNA expression profiles between malignant rhabdoid tumor and epithelioid sarcoma: miR193a-5p is suggested to downregulate SMARCB1 mRNA expression

Kenichi Kohashi1, Hidetaka Yamamoto1, Reiko Kumagai1, Yuichi Yamada1, Yuka Hotokobuchi1, Tomoaki Taguchi2, Yukihide Iwamoto1 and Yoshinao Oda1
## Epithelioid sarcoma is associated with a high percentage of $SMARCB1$ deletions

Lisa M Sullivan\(^1\), Andrew L Folpe\(^2\), Bruce R Pawel\(^1\), Alexander R Judkins\(^3\) and Jaclyn A Biegel\(^1,4\)

\(^1\)Department of Pathology and Laboratory Medicine, The Children’s Hospital of Philadelphia, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; \(^2\)Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; \(^3\)Department of Pathology and Laboratory Medicine, Children’s Hospital Los Angeles, Keck School of Medicine University of Southern California, Los Angeles, CA, USA and \(^4\)Department of Pediatrics, The Children’s Hospital of Philadelphia, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Subtype</th>
<th>Homozygous Deletion</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid Sarcoma</td>
<td>All</td>
<td>10/12 (83%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td></td>
<td>Proximal</td>
<td>6/7 (86%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>4/5 (80%)</td>
<td></td>
</tr>
<tr>
<td>Malignant Rhabdoid Tumor</td>
<td>All</td>
<td>44/183 (24%)</td>
<td>139/183 (76%)</td>
</tr>
<tr>
<td></td>
<td>Soft Tissue</td>
<td>12/19 (63%)</td>
<td>7/19 (37%)</td>
</tr>
</tbody>
</table>
Myoepithelioma

- Parachordoma described initially by Laskowski (1951), and more fully by Dabska (1977); controversial and rare
- Myoepithelioma/ mixed tumor of soft parts described by Kilpatrick et al (1997); relatively large number of subsequent reported cases
- The WHO currently considers both terms to be essentially synonymous
Clinical Features

- Adults in 2nd-4th decades of life (mean 35-38 years)
- No sex predilection
- Subcutis or deep soft tissues of the thigh, calf, arm, head/neck
- Painless mass
- All have potential for recurrence and/or metastasis
  - Histologically benign tumors may metastasize
  - Histologically malignant tumors have a greater risk of distant metastases
- Wide excision; unclear role for adjuvant therapy
Pathological Features

• Circumscribed but often subtly infiltrative, vaguely lobular
• Cords, chains and nests of spindled to epithelioid cells in a myxoid/ chondroid matrix
• Hepatoid, glomoid, plasmacytoid and vacuolated (“physaliferous”) cells
• Cytologic atypia, mitotic activity, vascular invasion, necrosis in a minority of cases
• Positive for cytokeratins and S100 protein; less often positive for muscle markers, p63 and GFAP; brachyury-negative
Cytokeratin
S100 protein
Genetics

- EWSR1 rearrangements present in 45% of cases

- **EWSR1-POU5F1**, **EWSR1-PBX1**, **EWSR1-ZNF444**, **EWSR1-??**
SMARCB1-Deficient Vulvar Tumors

Review
“Proximal-type” epithelioid sarcoma vs. malignant rhabdoid tumor of the vulva: A case report, review of the literature, and an argument for consolidation

Peter A. Argenta *, Sajeena Thomas, Justin C. Chura

Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Women’s Health, University of Minnesota, MN, USA

Received 6 April 2007
Available online 8 August 2007

Case Report
Myoepithelial Carcinoma of the Vulva Mimicking Bartholin Gland Abscess in a Pregnant Woman: Case Report and Review of Literature

Maria A. Kyrizzi, M.D., Elemi E. Cavarounis, M.D., P.D., Maria Ktistou, M.D., Nikolaos Arkadopoulos, M.D., P.D., Eleftheria Nicolaidou, M.D., P.D., Stylianos Fotiou, M.D., P.D., and Vassilios Smyrnios, M.D., P.D.
SMARCB1-deficient Vulvar Neoplasms

A Clinicopathologic, Immunohistochemical, and Molecular Genetic Study of 14 Cases

Andrew L. Folpe, MD,* J. Kenneth Schoolmeester, MD,* W. Glenn McCluggage, FRCPath,† Lisa M. Sullivan, MD,‡ Katharine Castagna, MS,‡ William A. Ahrens, MD.§ Esther Oliva, MD,∥ Jaclyn A. Biegel,‡∥ and G. Petur Nielsen, MD∥

• 14 adults (mean 46 years of age)
• Variably sized masses (mean 4.7 cm)
• Previously coded as “CES (4), PTES (2), MERT (3), myoepithelial CA (3) and “sarcoma, NOS” (2)
• IHC for keratins, S100 protein, SMA, desmin, CD34, SMARCB1
• EWSR1 FISH
• SMARCB1 Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA)
Classical-type ES (N=1)
Proximal-type ES (N= 6)
Myoepithelial CA (N=4)
SMARCB1(-) Sarcoma NOS (N=3)
Genetic Findings

- Homozygous deletions (4 PTES, 2 myoepithelial CA, 3 sarcomas NOS)
- Heterozygous deletions (2 PTES, 1 myoepithelial CA)
- Exon 5 c.528delC mutation in 1 otherwise typical PTES
- \textit{EWSR1} FISH negative in 3 myoepithelial CA
- No association between tumor classification and genetic findings
Follow-Up

- 13 patients (5-72 months, mean 31 months)
- 4 patients with metastases to pelvic and RP LN’s, lung, and brain
  - 3 PTES, 1 myoepithelial CA
- 3 DOD
- 2 alive with metastatic disease
- 8 alive without disease
- No association between tumor classification and outcome
Differential Diagnosis

- Squamous cell carcinoma
  - Associated dysplasia, keratinization
  - CD34, SMARCB1, p63, p40
- Melanoma
- Epithelioid smooth muscle tumors
- PEComa
- Angiosarcoma
- Lymphoma
- Cellular angiofibroma/ angiomyofibroblastoma