Cutaneous Mesenchymal Neoplasms with EWSR1 Rearrangement

By Konstantinos Linos MD, FCAP, FASDP
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Assistant Professor of Pathology
Dartmouth-Hitchcock
Geisel School of Medicine at Dartmouth
Hanover, NH, USA
Financial disclosures

- Book Royalties
Ewing Sarcoma/Primitive Neuroectodermal Tumor (ES/PNET)
Superficial Ewing’s sarcoma family of tumors: a clinicopathological study with differential diagnoses

Isidro Machado\textsuperscript{1,2}, Beatriz Liombart\textsuperscript{3}, Silvia Calabuig-Fariñas\textsuperscript{1} and Antonio Liombart-Bosch\textsuperscript{1}

Primary cutaneous Ewing sarcoma/primitive neuroectodermal tumour: a clinicopathological analysis of seven cases highlighting diagnostic pitfalls and the role of FISH testing in diagnosis

M V Shingde\textsuperscript{,} M Buckland\textsuperscript{,} K J Busam\textsuperscript{,} S W McCarthy\textsuperscript{,} J Wilmott\textsuperscript{,} J F Thompson\textsuperscript{,} R A Scolyer\textsuperscript{1,2,3,4,6}
• Can occur at **any body site**
  • Extremities most common
  • Followed by trunk and Head&Neck regions
• **Usually small** (<2.5cm) and localized to the dermis and subcutis
• **Metastasize less frequently** comparing to bone and soft tissue counterparts
• **Clinico-radiological correlation critical to exclude metastasis**
Morphologic and Immunophenotypic Diversity in Ewing Family Tumors
A Study of 66 Genetically Confirmed Cases

Andrew L. Folpe, MD,* John R. Goldblum, MD,† Brian P. Rubin, MD, PhD,‡ Bahig M. Shehata, MD,* Wendy Liu, MD,† Angelo P. Dei Tos, MD,§ and Sharon W. Weiss, MD*


Adamantinoma-like ES
CD99
Pancytokeratin

Desmin

Fluorescent In Situ Hybridization (FISH) for EWSR1
FUS/ERG Gene Fusions in Ewing’s Tumors

ERG IHC

- ERG is a useful marker for confirming endothelial differentiation in both benign and malignant neoplasms.
- Potentially useful marker to distinguish Leukemia Cutis vs reactive myeloid infiltrates.
- Expression can also be seen in a subset of epithelioid sarcomas and a small percentage of Ewing sarcomas, as well as approximately 45% to 50% of prostatic carcinomas.
- ERG can be seen in selected bone and soft tissue tumor with cartilaginous differentiation.
Utility of a Monoclonal ERG/FLI1 Antibody for Immunohistochemical Discrimination of Ewing's Family Tumors

Scott A. Tomlins, M.D., Ph.D.¹, Nallasivam Palanisamy, Ph.D.¹, J. Chad Brenner, Ph.D.¹, Jennifer N. Stall, M.D.¹, Javed Siddiqui, M.S.¹, Dafydd G. Thomas, M.D., Ph.D.¹, David R. Lucas, M.D.¹, Arul M. Chinnaiyan, M.D., Ph.D.¹,²,³,⁴, and Lakshmi P. Kunju, M.D.¹.
¹Michigan Center for Translational Pathology, Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA


Expression of ERG, an Ets family transcription factor, identifies ERG-rearranged Ewing sarcoma

Wei-Lien Wang¹, Nimesh R Patel², Mara Caragea³, Pancreas CW Hogendoorn⁴, Dolores López-Terrada⁵, Jason L Hornick⁶ and Alexander J Lazar⁷,⁸
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Ewing Sarcoma with EWSR1-ERG
Ewing sarcoma with EWSR1-FLI1
EWSR1, FLI1, ERG and their fusion proteins in Ewing Sarcoma
Evaluation of NKX2-2 expression in round cell sarcomas and other tumors with \textit{EWSR1} rearrangement: imperfect specificity for Ewing sarcoma

Yin P Hung, Christopher DM Fletcher and Jason L Hornick

Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
<table>
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<th>Tumor type</th>
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<td>NUT midline carcinoma</td>
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<td>Wilms tumor</td>
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<td>Merkel cell carcinoma</td>
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<td><strong>Other EWSR1-associated tumors</strong></td>
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<td>Angiomatoid fibrous histiocytoma</td>
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<td>Extraskeletal myxoid chondrosarcoma</td>
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<td>Desmoplastic small round cell tumor</td>
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<td>Soft tissue and cutaneous myoepitheliomas</td>
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<td>Myoepithelial carcinoma</td>
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Differential Diagnosis

- Round blue cell tumors
  - Lymphoblastic lymphoma
  - Merkel cell carcinoma
  - Small cell melanoma
  - Poorly differentiated synovial sarcoma
  - Rhabdomyosarcoma
  - CIC and BCOR re-arranged round cell sarcomas
Lymphoblastic lymphoma

- Diffusely positive for CD99 and Fli-1
- Often CD45 negative
- ERG often negative but may be expressed in myeloid leukemia
- Always include TdT, CD10 and CD43
• Metastatic small cell carcinoma
  • Usually lacks CD99
  • More extensive immunoreactivity for cytokeratins, synaptophysin, chromogranin, and CD56

• Merkel cell carcinoma
  • Diffusely express neuroendocrine markers
  • More specific cytokeratins such as CK20
  • IHC for Merkel cell polyoma virus large T antigen

• Small cell melanoma
  • Strongly positive for Melan-A, HMB45, SOX-10
CD99 expression in Merkel cell carcinoma: a case series with an unusual paranuclear dot-like staining pattern

Ashwyn Rajagopalan¹, Debra Browning² and Samih Salama²

J Cutan Pathol 2013: 40: 19–24
• Poorly differentiated of Synovial Sarcoma
  • Typically more classic areas of monophasic and biphasic synovial sarcoma
  • Positive for high-molecular weight keratins
  • Positive of TLE-1
  • Negative for FLI-1/ERG

• Alveolar rhabdomyosarcoma
  • Greater nuclear variability
  • Positive for myogenin and Myo-D1
Sarcomas With CIC-rearrangements Are a Distinct Pathologic Entity With Aggressive Outcome
A Clinicopathologic and Molecular Study of 115 Cases

ristina R. Antonescu, MD,* Adepitan A. Owosho, DDS,† Lei Zhang, MD,* Sonja Chen, MD,*
Zenal Deniz, MD,‡ Joseph M. Huryn, MD,† Yu-Chien Kao, MD,*§ Shih-Chiang Huang, MD,*||
Samuel Singer, MD,† William Tap, MD,¶ Inga-Marie Schaefer, MD,#
and Christopher D. Fletcher, MD#

(Am J Surg Pathol 2017;41:941–949)

BCOR-CCNB3 Fusion Positive Sarcomas
A Clinicopathologic and Molecular Analysis of 36 Cases With Comparison to Morphologic Spectrum and Clinical Behavior of Other Round Cell Sarcomas

Yu-Chien Kao, MD,*† Adepitan A. Owosho, DDS,‡§ Yun-Shao Sung, MSc,* Lei Zhang, MD,*
Yumi Fujisawa, MS,* Jen-Chieh Lee, MD, PhD,|| Leonard Wexler, MD,¶ Pedram Argani, MD,#
David Swanson, BSc,** Brendan C. Dickson, MD,** Christopher D. M. Fletcher, MD, FRCPa,††
and Cristina R. Antonescu, MD*

Angiomatoid Fibrous Histiocytoma (AFH)
Angiomatoid Malignant Fibrous Histiocytoma
A Follow-up Study of 108 Cases with Evaluation of Possible Histologic Predictors of Outcome

Michael J. Costa, M.D., and Sharon W. Weiss, M.D.

Angiomatoid “Malignant” Fibrous Histiocytoma: A Clinicopathologic Study of 158 Cases and Further Exploration of the Myoid Phenotype

J.C. Fanburg-Smith, MD, and M. Miettinen, MD
Angiomatoid fibrous histiocytoma: unusual sites and unusual morphology

Gang Chen¹, Andrew L Folpe², Thomas V Colby³, Kesavan Sittampalam⁴, Martine Patey⁵, Ming-Guang Chen⁶ and John KC Chan⁷

¹Department of Pathology, Fujian Provincial Tumor Hospital, Fuzhou, Fujian, China; ²Department of Pathology, Mayo Clinic, Rochester, MN, USA; ³Department of Pathology, Mayo Clinic, Scottsdale, AZ, USA; ⁴Department of Pathology, Singapore General Hospital, Singapore; ⁵Department of Pathology, Hopital Robert Debre—CHU, Cedex, France; ⁶Department of Pathology, The First Affiliated Hospital in Nanping of Fujian Medical University, Nanping, Fujian, China and ⁷Department of Pathology, Queen Elizabeth Hospital, Kowloon, Hong Kong
Pleomorphic angiomatoid fibrous histiocytoma: a case confirmed by fluorescence in situ hybridization analysis for EWSR1 rearrangement

Ilan Weinreb¹,², Brian P. Rubin³ and John R. Goldblum³

¹Department of Pathology, University Health Network, Toronto, Ontario, Canada,
²Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada and
³Department of Pathology, Cleveland Clinic Foundation, Cleveland, OH, USA
Utility of FISH in the diagnosis of angiomatoid fibrous histiocytoma: a series of 18 cases

Munir R Tanas¹, Brian P Rubin¹, Elizabeth A Montgomery³, Sondra L Turner², James R Cook², Raymond R Tubbs², Steven D Billings¹ and John R Goldblum*¹

¹Department of Anatomic Pathology, Pathology and Laboratory Medicine Institute, The Cleveland Clinic and The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA; ²Department of Molecular Pathology, Pathology and Laboratory Medicine Institute, The Cleveland Clinic and The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA and ³Department of Pathology, Johns Hopkins Hospital, Johns Hopkins University, Baltimore, MD, USA

\[ t(2;22)(q33;q12) = \text{EWSR1/CREB1} \]
\[ t(12;22)(q13;q12) = \text{EWSR1/ATF1} \]
\[ t(12;16)(q13;p11) = \text{FUS/ATF1} \]
Differential Diagnosis

- Metastasis involving a lymph node
- Undifferentiated pleomorphic sarcoma
- Vascular tumor
- Benign fibrous histiocytoma with prominent intratumoral hemorrhage
- Ewing Sarcoma in cases with “small cell” morphology
- Follicular dendritic cell tumors
Myoepithelial Tumors
Cutaneous myoepithelial tumors

• Chondroid syringoma (mixed tumor)
  • Tubuloductal differentiation
  • Rearrangement of the PLAG1 gene (8q12)
• Cutaneous myoepithelioma
  • Pure myoepithelial cell population
• Myoepithelial carcinoma
Myoepithelial Tumors of Soft Tissue
A Clinicopathologic and Immunohistochemical Study of 101 Cases With Evaluation of Prognostic Parameters
Jason L. Hornick, MD, PhD, and Christopher D. M. Fletcher, MD, FRCPath

Cutaneous Myoepithelioma:
A Clinicopathologic and Immunohistochemical Study of 14 Cases
JASON L. HORNICK, MD, PHD, AND CHRISTOPHER D. M. FLETCHER, MD, FRCPATH

Myoepithelial Carcinoma of Soft Tissue in Children:
An Aggressive Neoplasm Analyzed in a Series of 29 Cases
Briana C. Gleason, MD and Christopher D. M. Fletcher, MD, FRCPath
Absence of INI1 in myoepithelial carcinomas
10% (adults)
40% (children)
Cutaneous Syncytiial Myoepithelioma
Clinicopathologic Characterization in a Series of 38 Cases

Vickie Y. Jo, MD,* Cristina R. Antonescu, MD,† Lei Zhang, MD,† Paola Dal Cin, PhD,* Jason L. Hornick, MD, PhD,* and Christopher D.M. Fletcher, MD, FRCPath*

Am J Surg Pathol • Volume 37, Number 5, May 2013
**EWSR1-POU5F1 Fusion in Soft Tissue Myoepithelial Tumors. A Molecular Analysis of Sixty-Six Cases, Including Soft Tissue, Bone, and Visceral Lesions, Showing Common Involvement of the EWSR1 gene**


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**Diagram:**

- **EWSR1-POU5F1**
- **EWSR1-ZNF444**
- **EWSR1-PBX1**
- **EWSR1-ATF1**
Frequent *PLAG1* Gene Rearrangements in Skin and Soft Tissue Myoepithelioma with Ductal Differentiation

Cristina R. Antonescu, Lei Zhang, Sung Yun Shao, Juan-Miguel Mosquera, Ilan Weinreb, Nora Katabi, and Christopher D. M. Fletcher

*GENES, CHROMOSOMES & CANCER 52:675–682 (2013)*

A Subset of Cutaneous and Soft Tissue Mixed Tumors are Genetically Linked to Their Salivary Gland Counterpart

Armita Bahrami, James D. Dalton, Jeffrey F. Krane, and Christopher D. M. Fletcher

*GENES, CHROMOSOMES & CANCER 51:140–148 (2012)*
EMA positivity in epithelioid fibrous histiocytoma: a potential diagnostic pitfall

Leona A. Doyle and Christopher D. M. Fletcher

Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Juvenile Xanthogranuloma in Childhood and Adolescence

A Clinicopathologic Study of 129 Patients From the Kiel Pediatric Tumor Registry

Dirk Janssen, MD and Dieter Harms, MD
Differential Diagnosis

- Epithelioid fibrous histiocytoma
- Early stage juvenile xanthogranuloma
- Epithelioid sarcoma
- Spitz nevus
Prognosis and treatment

• Cutaneous myoepithelioma has a benign clinical course
  • Local recurrence in 20% of cases
• Syncytial subtype very low local recurrence rate
• Myoepithelia carcinomas (also contain EWSR1 rearrangements) pursue a more aggressive clinical course
Clear Cell Sarcoma

CLEAR-CELL SARCOMA OF TENDONS AND APONEUROSES

An Analysis of 21 Cases

FRANZ M. ENZINGER, M.D.
Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

Markus Hantschke, MD,* Thomas Mentzel, MD,* Arno Rütten, MD,* Gabriele Palmedo, PhD,* Eduardo Calonje, MD,† Alexander J. Lazar, MD,‡ and Heinz Kutzner, MD*

(Am J Surg Pathol 2010;34:216–222)
• Usually lesions relatively small (<5cm)
  • Primary cutaneous <1cm
    • Otherwise similar clinical and pathologic features

• Natural history clinically protracted
  • Multiple local recurrences
  • Late metastases in lymph nodes, lung, bone

• Wide local excision with adjuvant radiation
S100-Protein

Melan-A
Compound clear cell sarcoma misdiagnosed as a Spitz nevus

Malja Kiuru¹,², Meera Hameed³ and Klaus J. Busam³

Dartmouth-Hitchcock | GEISEL SCHOOL OF MEDICINE AT DARTMOUTH
Dual-color, break-apart fluorescence in situ hybridization for EWS gene rearrangement distinguishes clear cell sarcoma of soft tissue from malignant melanoma

Rajiv M Patel¹, Erinn Downs-Kelly², Sharon W Weiss¹, Andrew L Folpe¹, Raymond R Tubbs², Ralph J Tuthill², John R Goldblum² and Marek Skacel²

Modern Pathology (2005) 18, 1585–1590

t(12;22)(q13;q12)
EWSR1-ATF1

t(2;22)(q34;q12)
EWSR1-CREB1
# Receptor Tyrosine Kinase Pathway Analysis Sheds Light on Similarities Between Clear-Cell Sarcoma and Metastatic Melanoma

Tiziana Negri,† Silvia Brich,† Elena Conca, Fabio Bozzi, Marta Orsenigo, Silvia Stacchiotti, Marco Alberghini, Valentina Mauro, Alessandro Gronchi, Giuseppina F. Dusio, Giuseppe Pelosi, Piero Picci, Paolo G. Casali, Marco A. Pierotti, and Silvana Pilotti

*GENES, CHROMOSOMES & CANCER* **51:**111-126 (2012)

## Table: Genes and Mutations

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Atypical Ewing sarcoma breakpoint region 1 fluorescence in-situ hybridization signal patterns in bone and soft tissue tumours: diagnostic experience with 135 cases

A Cristina Vargas,¹,* Christina I Selinger,¹,* Laveniya Satgunaseelan,¹,² Wendy A Cooper,¹,³,⁴ Ruta Gupta,¹,³ Paul Stalley,⁵,⁶,⁸,⁹,¹⁰ Wendy Brown,⁷ Judy Soper,⁷ Julie Schatz,⁷ Richard Boyle,⁵,⁶,⁸,⁹,¹⁰ David M Thomas,¹¹ Martin H N Tattersall,³,⁵ Vivek A Bhadri,³,⁵ Fiona Maclean,² S Fiona Bonar,²,⁸,¹² Richard A Scolyer,¹,³ Rooshdiya Z Karim,¹,³ Stanley W McCarthy,¹,³ Annabelle Mahar¹ & Sandra A O'Toole¹,³,¹¹

Histopathology 2016, 69, 1000–1011. DOI: 10.1111/his.13031
Differential Diagnosis

- Melanoma
- Perivascular Epithelioid Cell Neoplasm (PEComa)
- Cellular Blue Nevus
- Cutaneous Melanocytoma with CRTC1-TRIM11 Fusion
Cellular Blue Nevus
Melanoma ex blue nevus

A

B

C

D
Primary cutaneous perivascular epithelioid cell tumor (PEComa): Five new cases and review of the literature

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Cutaneous Melanocytoma With CRTC1-TRIM11 Fusion
Report of 5 Cases Resembling Clear Cell Sarcoma

Lucie Cellier, MD,* Emilie Perron, MD, MSc,*†‡ Daniel Pissaloux, PhD,* Marie Karanian, MD,* Veronique Haddad, PharmD,* Laurent Alberti, PhD,*
and Arnaud de la Fouchardiére, MD, PhD*

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Benign/Low Grade Fibroblastic Tumors

- Calcifying aponeurotic fibroma
  - Recurrent FN1-EGF fusion
- Fibrous hamartoma of infancy
  - EGFR internal tandem tandem duplications
- Myofibroma/myopericytoma
  - PDGFR mutations
- Lipofibromatosis-like neural tumors
  - Recurrent NYRK1-related gene fusions
Novel *EWSR1-SMAD3* Gene Fusions in a Group of Acral Fibroblastic Spindle Cell Neoplasms

Yu-Chien Kao, MD,* Uta Flucke, MD, PhD,† Astrid Eijkelenboom, PhD,† Lei Zhang, MD,‡ Yun-Shao Sung, MSc,‡ Albert J.H. Suurmeijer, MD, PhD,§ and Cristina R. Antonescu, MD‡

(Am J Surg Pathol 2018;00:000–000)

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age (y)/Sex</th>
<th>Location</th>
<th>Depth</th>
<th>Size (cm)</th>
<th>ERG</th>
<th>CD34</th>
<th>SMA</th>
<th>S100</th>
<th>Follow-up</th>
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<tr>
<td>1</td>
<td>1/M</td>
<td>Heel</td>
<td>Dermis and subcutis</td>
<td>1.0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LR (14 mo)</td>
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<tr>
<td>2</td>
<td>61/F</td>
<td>Foot</td>
<td>Subcutis</td>
<td>2.0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NA</td>
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<tr>
<td>3</td>
<td>58/F</td>
<td>Toe</td>
<td>Dermis and subcutis</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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EWSR1 Genetic Rearrangements in Salivary Gland Tumors
A Specific and Very Common Feature of Hyalinizing Clear Cell Carcinoma

Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract

Fluorescence in situ hybridization analysis of extraskeletal myxoid chondrosarcomas using EWSR1 and NR4A3 probes

Desmoplastic Small Round Cell Tumor-Clinicopathological Spectrum, Including Unusual Features and Immunohistochemical Analysis of 45 Tumors Diagnosed at a Tertiary Cancer Referral Centre, with Molecular Results t(11; 22) (p13; q12) (EWS-WT1) in Select Cases
Relevance of Translocation Type in Myxoid Liposarcoma and Identification of a Novel EWSR1-DDIT3 Fusion

Primary Pulmonary Myxoid Sarcoma With EWSR1-CREB1 Fusion: A New Tumor Entity

EWSR1-CREB3L1 Gene Fusion
A Novel Alternative Molecular Aberration of Low-grade Fibromyxoid Sarcoma

A novel EWS-CREB3L3 gene fusion in a mesenteric sclerosing epithelioid fibrosarcoma
A subset of ectomesenchymal chondromyxoid tumours of the tongue show EWSR1 rearrangements and are genetically linked to soft tissue myoepithelial neoplasms: a study of 11 cases

Clear Cell Odontogenic Carcinomas Show EWSR1 Rearrangements
A Novel Finding and a Biological Link to Salivary Clear Cell Carcinomas

A Benign Vascular Tumor With a New Fusion Gene EWSR1-NFATC1 in Hemangioma of the Bone
Recurrent Rearrangement of the Ewing’s Sarcoma Gene, \textit{EWSR1}, or Its Homologue, \textit{TAF15}, with the Transcription Factor \textit{CIZ/NMP4} in \textbf{Acute Leukemia}^1

\textit{EWSR1} Fusions With CREB Family Transcription Factors Define a \textbf{Novel Myxoid Mesenchymal Tumor With Predilection for Intracranial Location}

A Subset of \textbf{Malignant Mesotheliomas} in Young Adults Are Associated With Recurrent \textit{EWSR1/FUS-ATF1} Fusions
• Specific gene breakpoints
• Cell type in which the fusion occurs
• Tissue site/microenvironment
• Epigenetic changes
• Other genetic alterations
Morphology, Morphology, Morphology, Morphology

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