AT/RT and Related Tumors: Pathology and Diagnosis of SMARCB1-deficient Neoplasms

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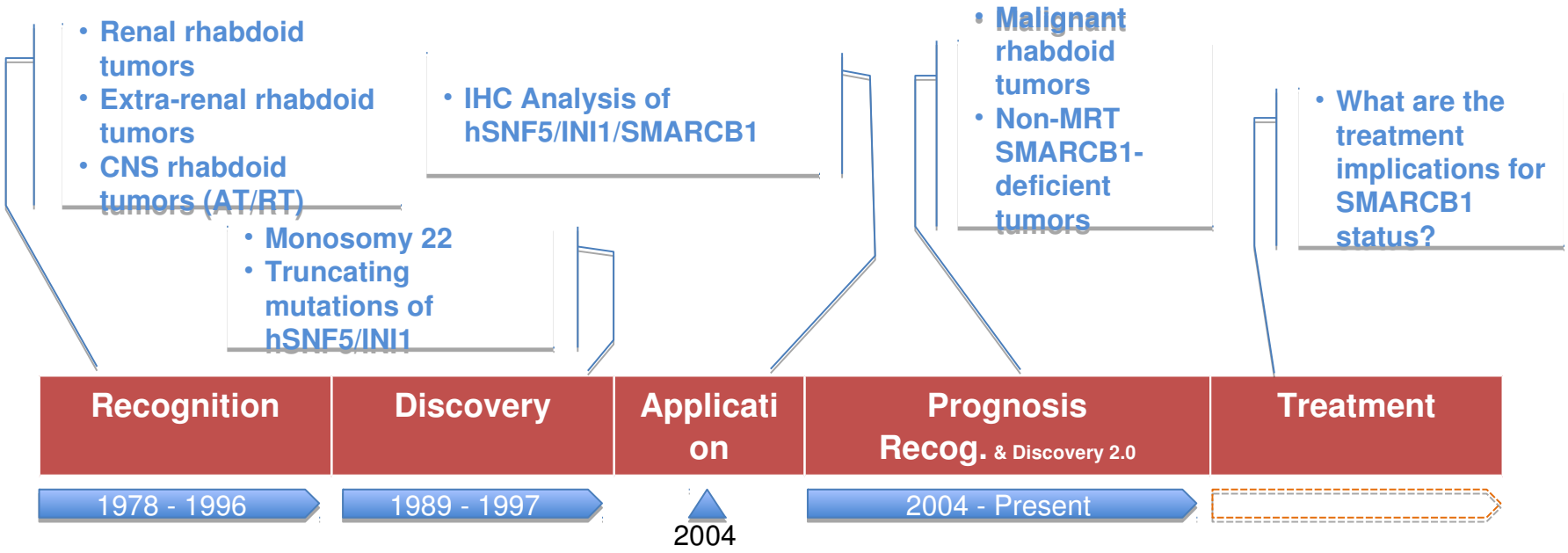
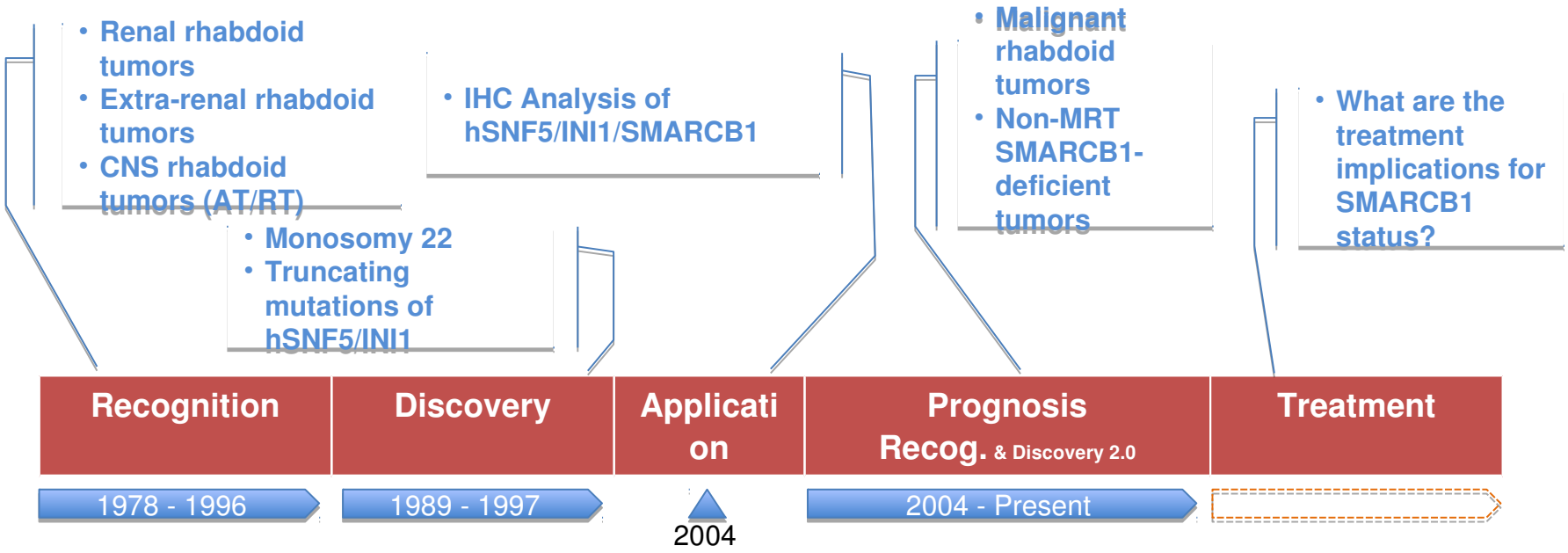
“So the last shall be first, and the first last …”

“What does it mean when you have a newly diagnosed patient with SMARCB1 inactivation?”

The Journey (Pathology POV)



The Journey (Pathology POV)



Original Description

HISTOPATHOLOGY AND PROGNOSIS OF WILMS TUMOR

Results from the First National Wilms' Tumor Study

J. B. BECKWITH, MD, AND N. F. PALMER, MB, BS

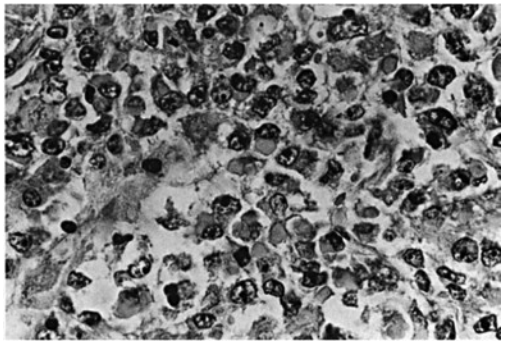
Detailed histological analysis of 427 cases entered on the first National Wilms' Tumor Study revealed that lesions with foci of marked cytological atypism (anaplasia), and those composed predominantly of sarcomatous stroma, were associated with unfavorable outcome. Twenty-five patients had anaplasia, and 24 had sarcomatous lesions of which a total of 28 (57.1%) died of tumor. Three hundred and seventy-eight patients had tumors which showed neither of these features, and only 26 (6.9%) died of tumor. Seven of ten deaths due to tumor in patients diagnosed before two years of age were associated with sarcomatous lesions. Three sarcomatous patterns were recognized, of which one, designated "clear cell" sarcoma, had a predilection for bony metastases. Using criteria defined and illustrated in this paper it is possible to identify in advance those patients likely to do poorly using current therapeutic approaches.

Cancer 41:1937–1948, 1978.

TABLE 4. Significance of Anaplasia in NWTS I.*

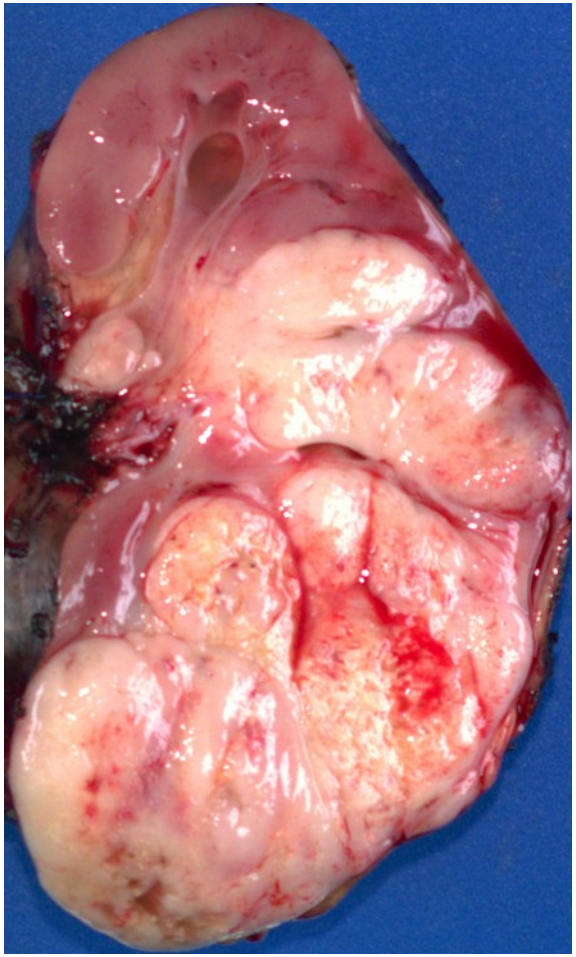
Degree of Anaplasia	No. Cases	Survivors No.	Survivors %	Relapse Free No.	Relapse Free %
Absent	364	338	92.9	305	88.8
Focal	15	9	60.0	8	53.3
Diffuse	10	2	20.0	1	10.0

* This table excludes the 24 sarcomatous cases, and also 14 non sarcomatous cases dying without evidence of tumor.



Recognition

Renal Rhabdoid Tumor



Recognition

Renal Rhabdoid Tumor

Rhabdoid Tumor of Kidney

A Report of 111 Cases from the National Wilms' Tumor Study Pathology Center

Douglas A. Weeks, M.D., J. Bruce Beckwith, M.D.,
Gary W. Mierau, Ph.D., and Dennis W. Luckey, Ph.D.

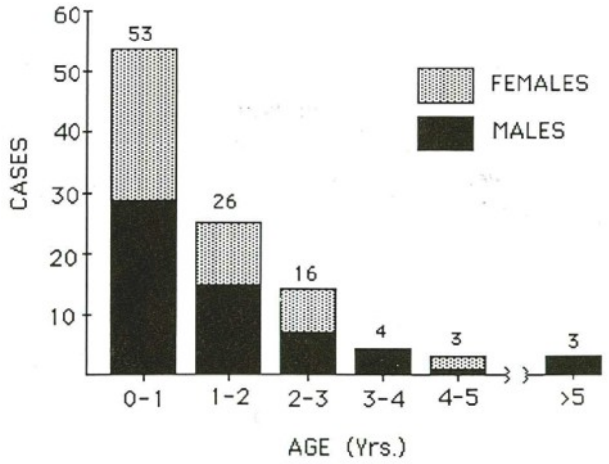


FIG. 2. Age distribution of 105 patients for whom age and sex were recorded.

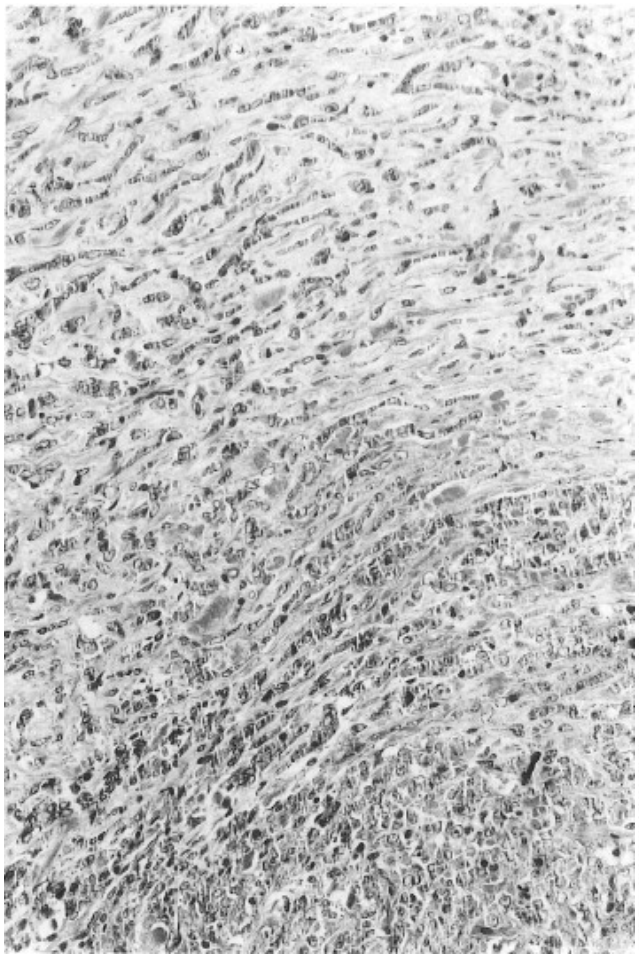
There was an unexpected range of pattern variations, as follows:

Classical
Sclerosing patterns
  Fibrotic
  Osteocarcomatous
  Chondroid
Epithelioid patterns
  Trabecular
  Mucoid
  Alveolar
  Pseudoglandular
Spindled patterns
  Broad fascicles
  Myxoid
  Hemangiopericytomatous
  Storiform
  Palisaded
Lymphomatoid patterns
  Solid
  Histiocytoid
Vascular patterns
  CCSK-like
  Organoid (or paragangliomatous)

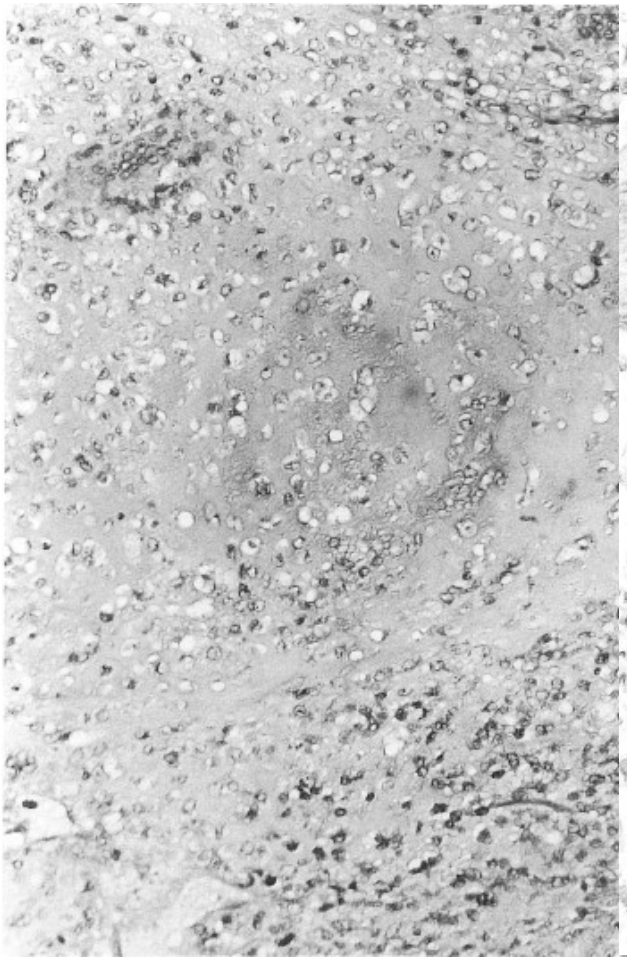
Recognition

The American Journal of Surgical Pathology *13(6): 439–458, 1989*

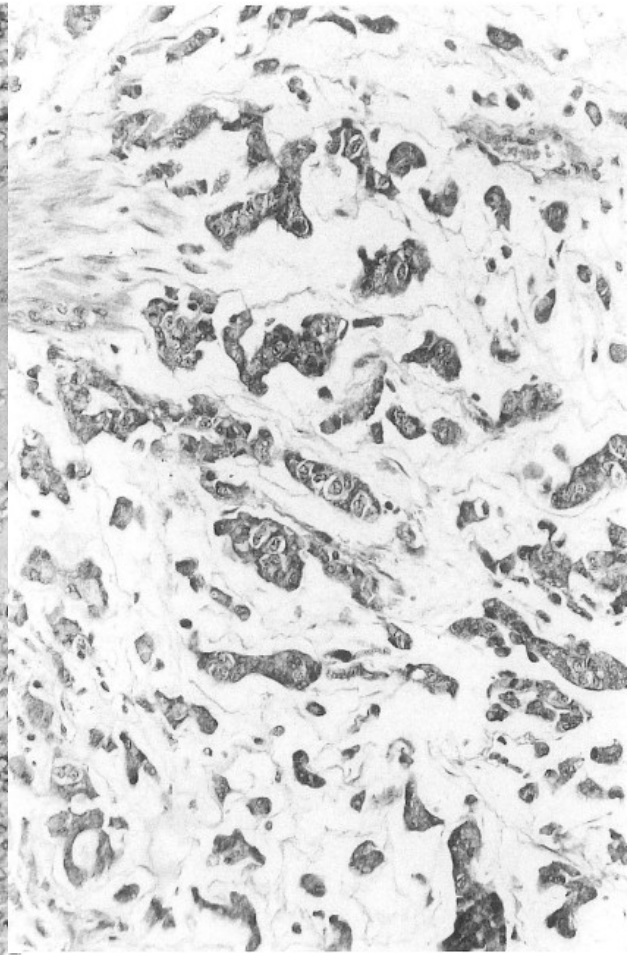
Renal Rhabdoid Tumor Patterns



Hyalinizing

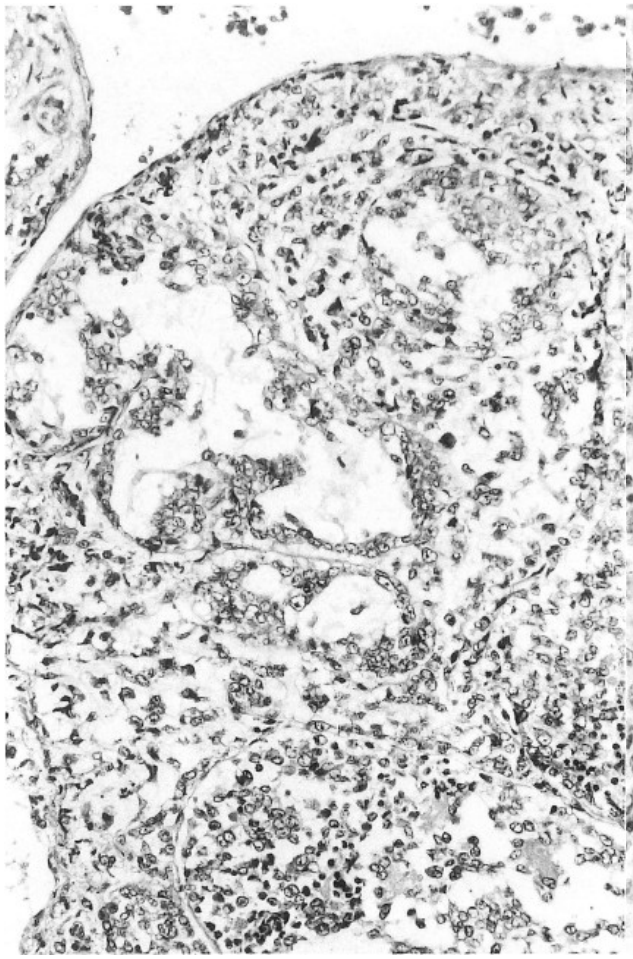


Chondroid

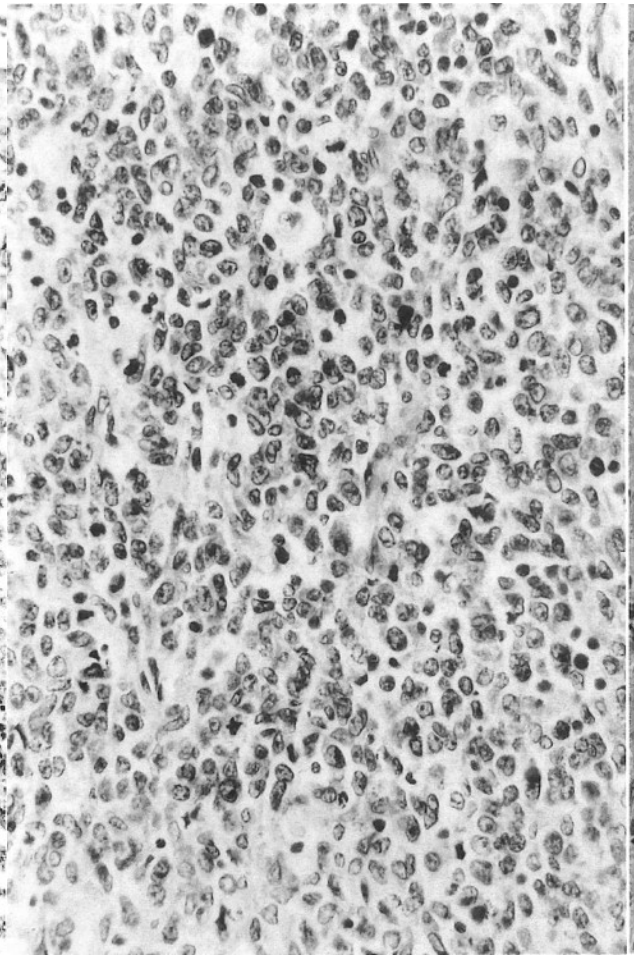


Trabecular

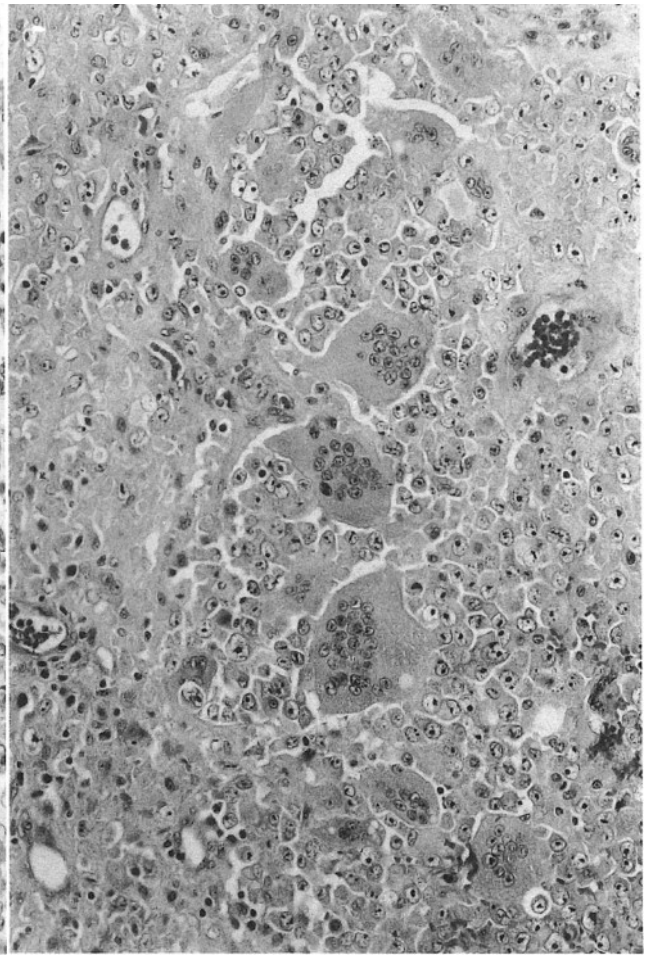
Renal Rhabdoid Tumor Patterns



Pseudoglandular

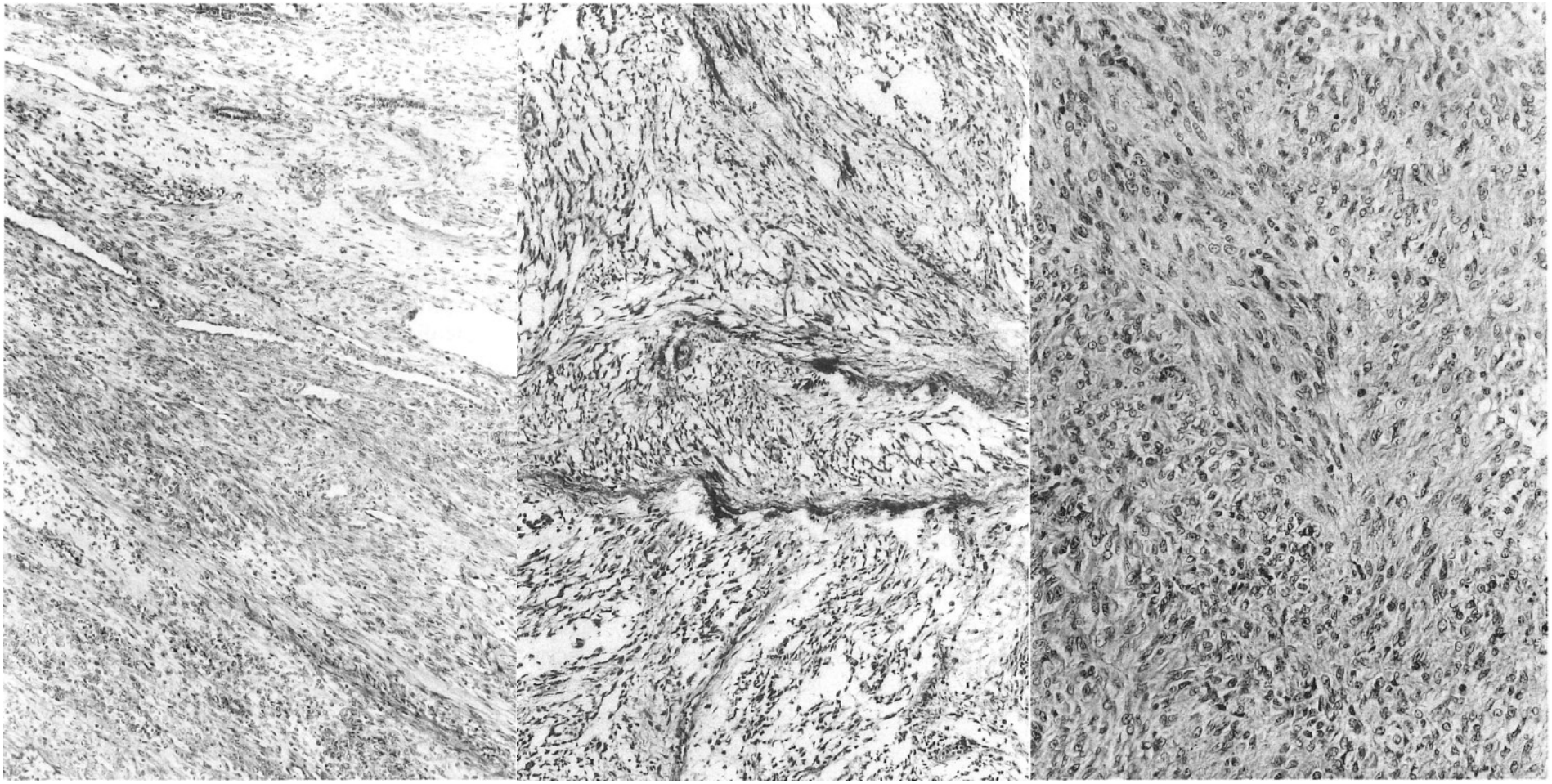


Lymphomatoid



Histiocytoid

Renal Rhabdoid Tumor Patterns

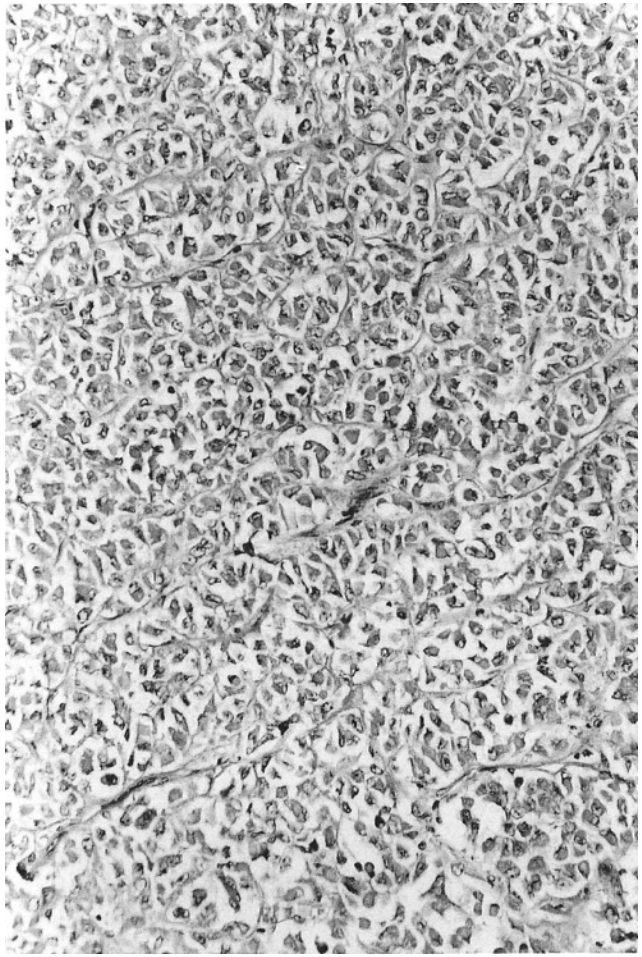


Spindled

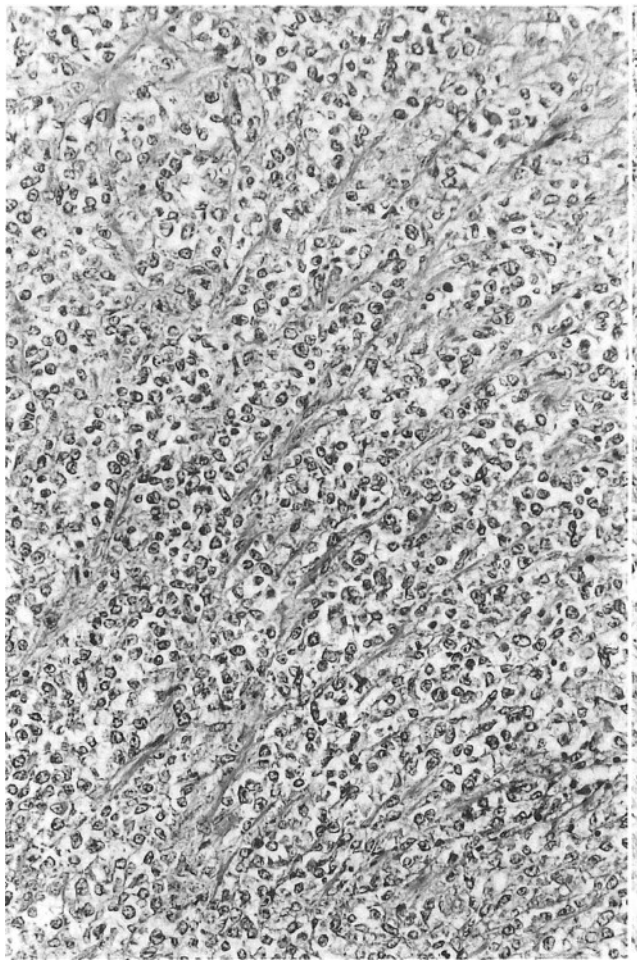
Myxoid

“Mesenchymal”

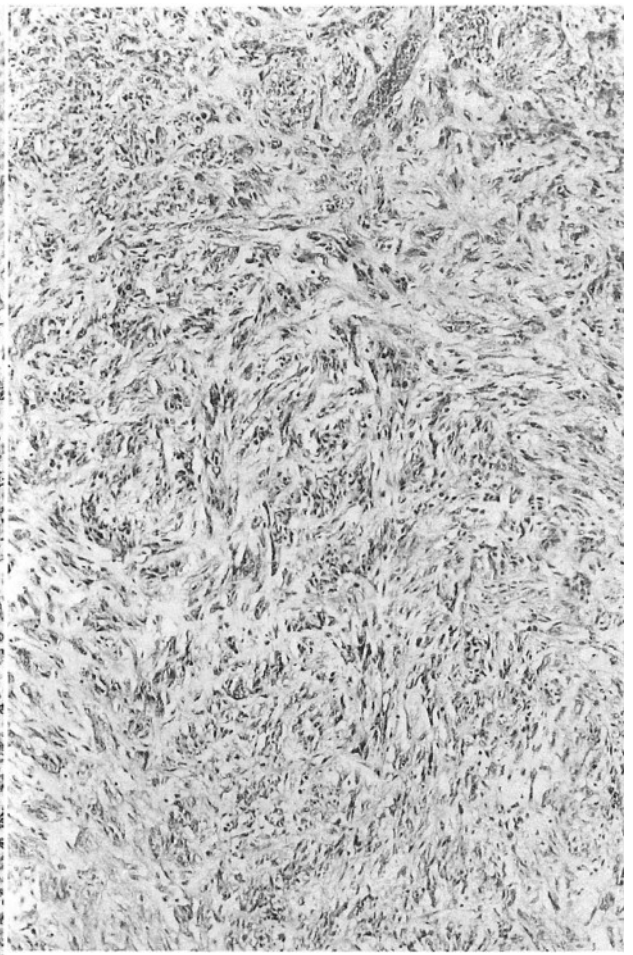
Renal Rhabdoid Tumor Patterns



Organoid/
Paraganglioglioma tous

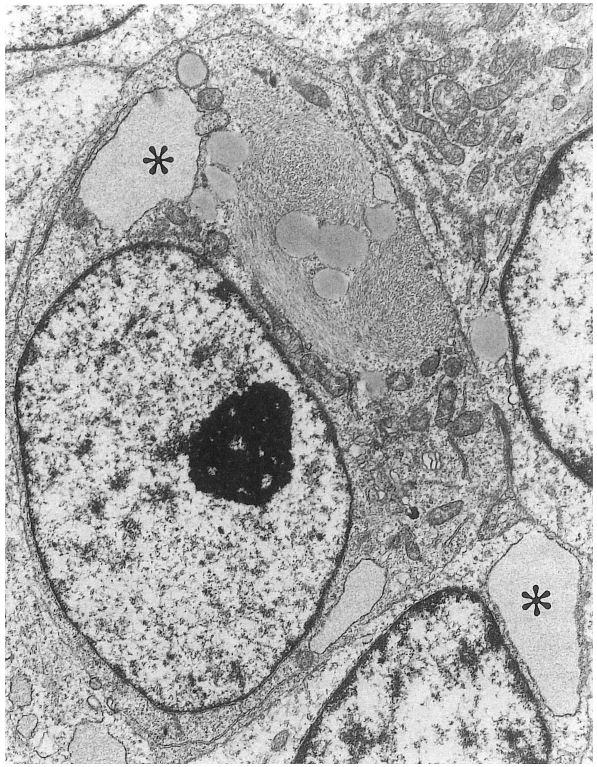


Clear cell sarcoma of kidney(CCSK) like

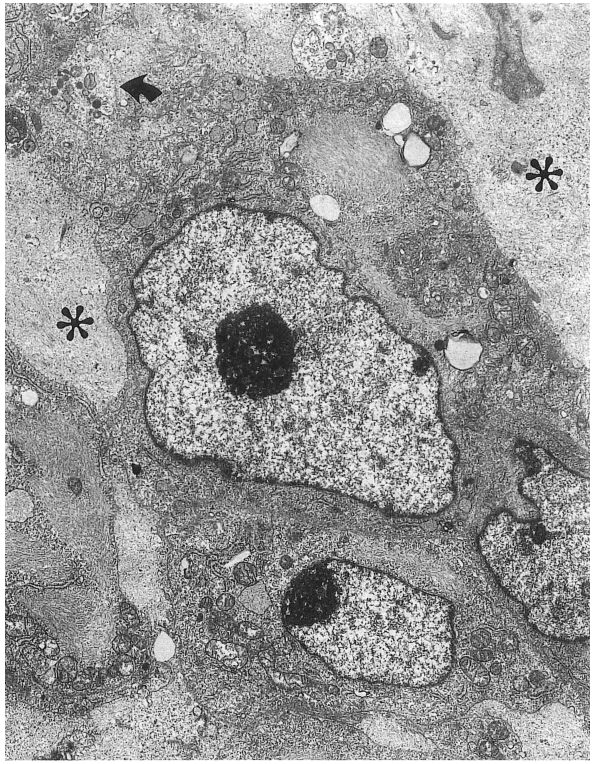


Palisaded Pattern

Renal Rhabdoid Tumor Ultrastructure



Classic



Sclerosing

Soft Tissue Rhabdoid

Malignant Soft Tissue Neoplasms with the Histologic Features of Renal Rhabdoid Tumors:

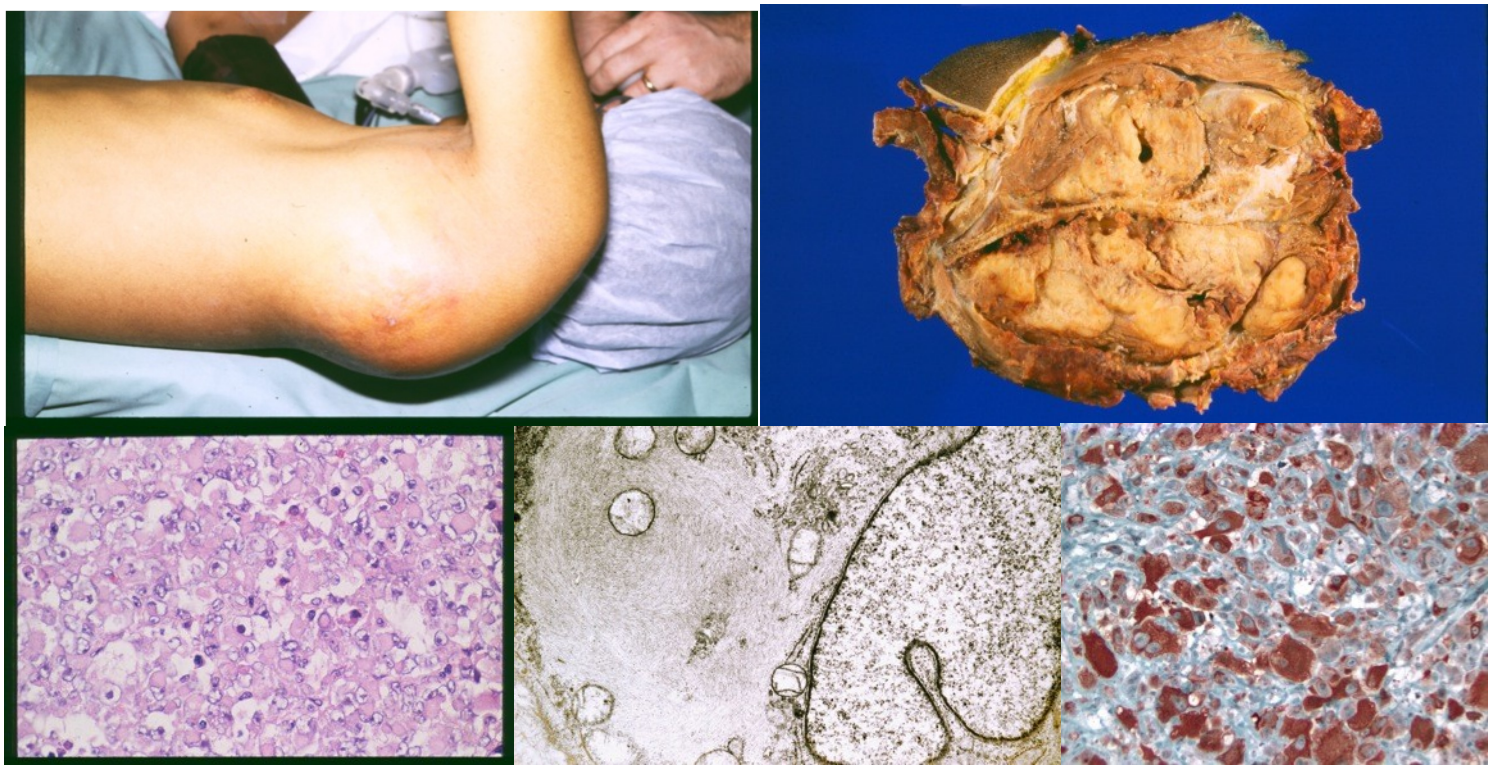
An Ultrastructural and Immunohistochemical Study

MASAZUMI TSUNEYOSHI, MD, YUTAKA DAIMARU, MD,
HIROSHI HASHIMOTO, MD, AND MUNETOMO ENJOJI, MD

Five round cell neoplasms of the soft parts that histologically resembled malignant rhabdoid tumors of the kidney were studied. The tumors were composed mainly of poorly differentiated round or, sometimes, polygonal cells, with a minority of elongated cells; the cytoplasm of many of the cells contained filament-laden acidophilic inclusions. Ultrastructurally, the intracytoplasmic structures were seen to consist of aggregates of 10-nm intermediate filaments, and immunohistochemical staining revealed the presence of cytokeratin and vimentin. All five patients with this tumor had an aggressive clinical course; three of the patients died shortly after the initial diagnosis. As this tumor does not seem to be linked to any known entity, it is referred to as malignant rhabdoid tumor of the soft parts and could be a heterogeneous entity. HUM PATHOL 16:1235–1242, 1985.

Recognition

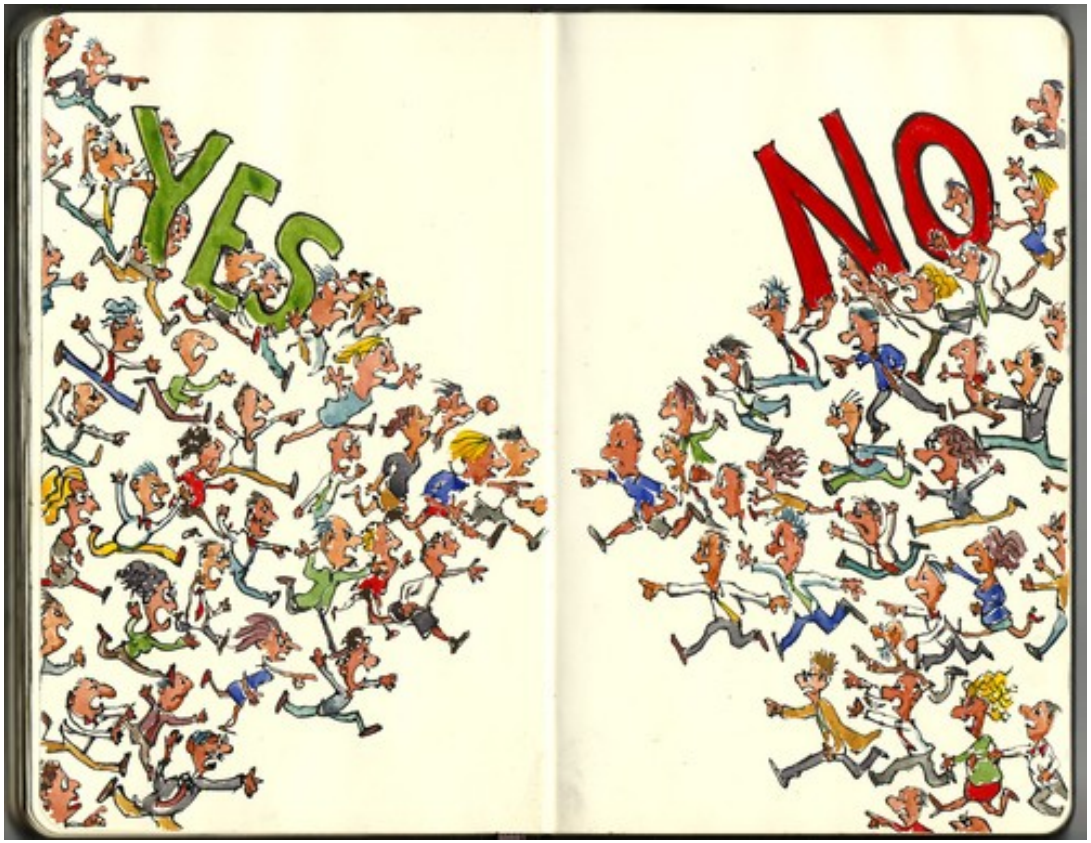
Soft Tissue Rhabdoid



Recognition

Images from Dr. David Parham

Soft Tissue Rhabdoid



Recognition

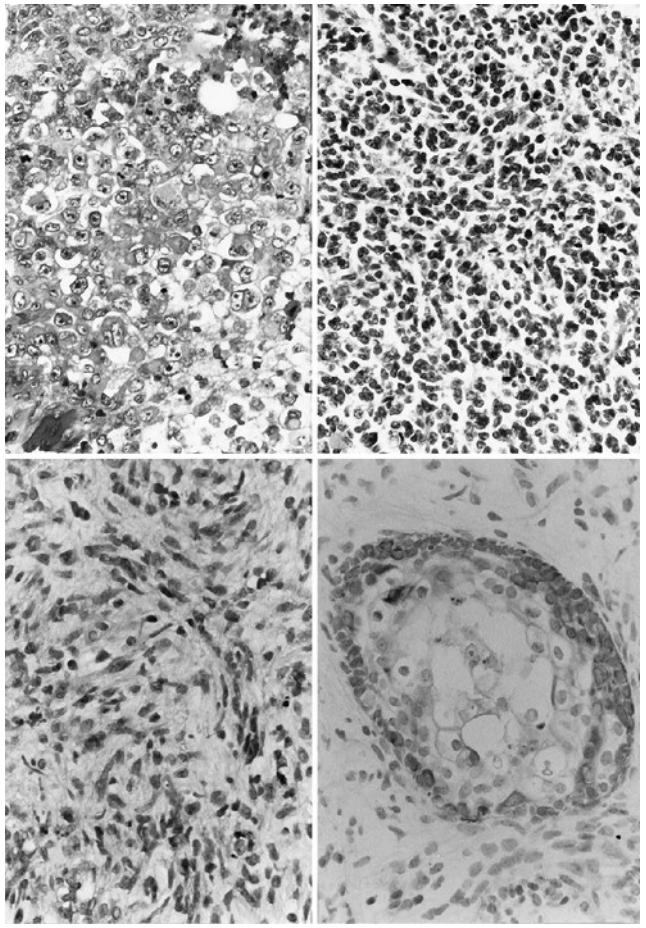
CNS Rhabdoid (AT/RT)

J Neurosurg 85:56–65, 1996

Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity

LUCY BALIAN RORKE, M.D., ROGER J. PACKER, M.D., AND JACLYN A. BIEGEL, PH.D.

Department of Pathological Anatomy and Division of Human Genetics and Molecular Biology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and Department of Neurology, Children's National Medical Center, Washington, D.C.



Recognition

PMID: 8683283

CNS Rhabdoid (AT/RT)

TABLE 4

Routine light microscopic features of 52 primary central nervous system atypical teratoid/rhabdoid tumors in infants and children

Histological Feature	No. of Patients (%)
rhabdoid cells	52 (100)
pure rhabdoid	7 (13)
primitive neuroectodermal tumor	35 (67)
mesenchymal	16 (31)
epithelial	13 (25)
adenomatous	11 (21)
squamous	1 (2)
nests	1 (2)

TABLE 5

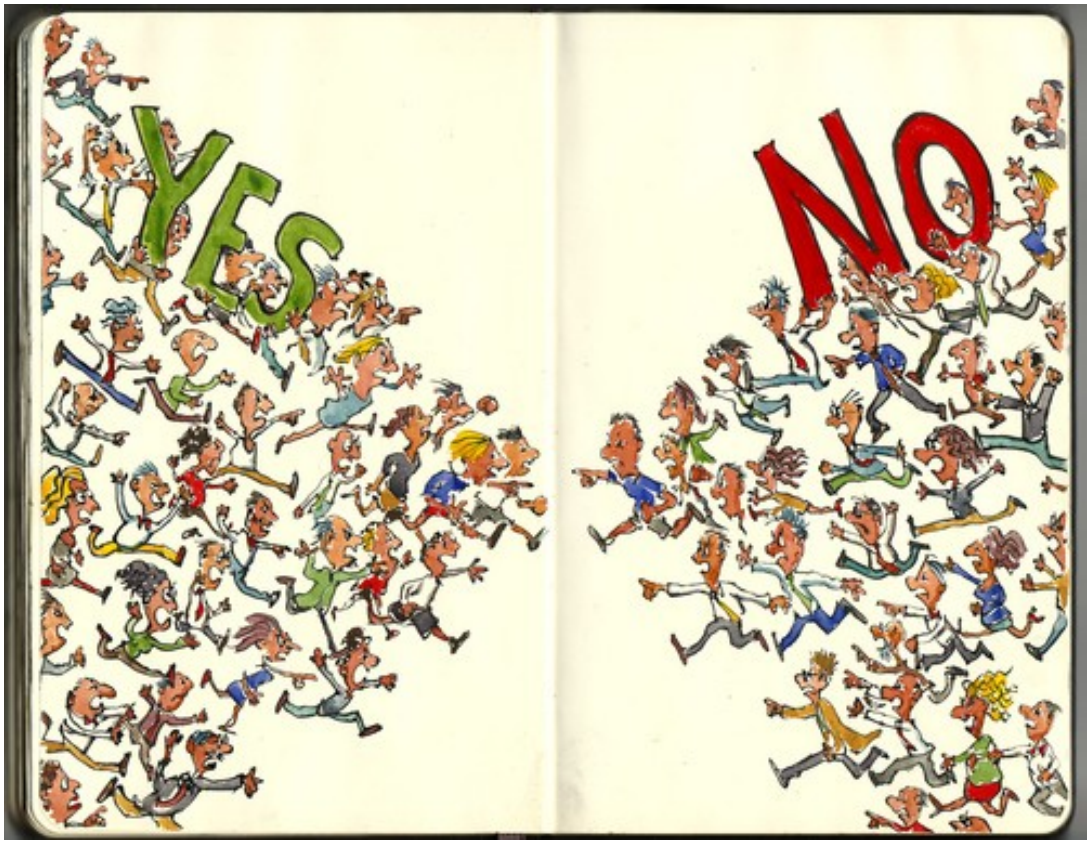
Immunohistochemical features of 52 central nervous system atypical teratoid/rhabdoid tumors in infants and children

Antibody	No. Studied	% Positive
epithelial membrane antigen	50	100
vimentin	46	100
smooth-muscle actin	36	97
glial fibrillary acidic protein	51	73
keratin	32	66
neurofilament protein	37	38
desmin	31	9

Recognition

PMID: 8683283

CNS Rhabdoid (AT/RT)



Recognition

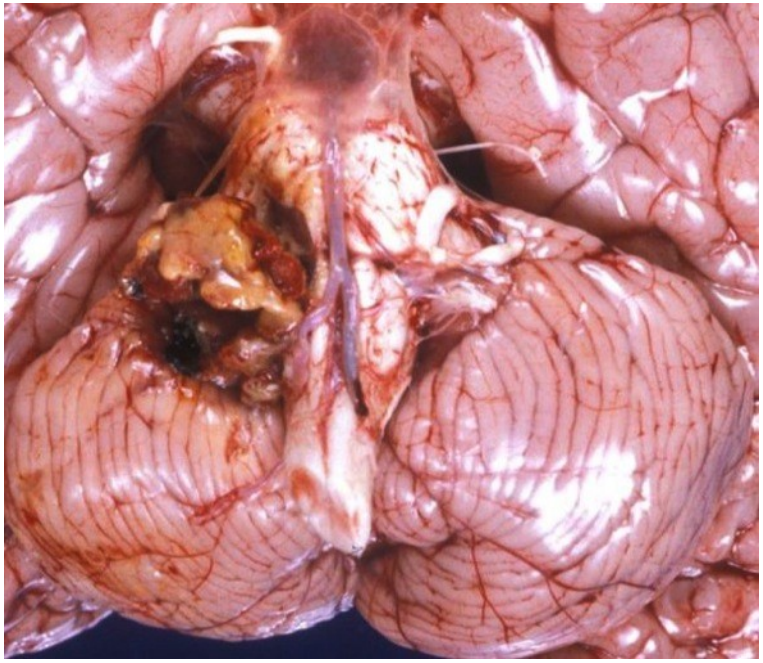
CNS Rhabdoid (AT/RT)

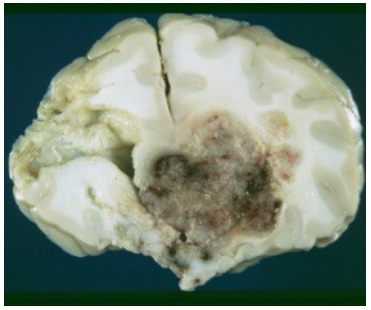
General Features

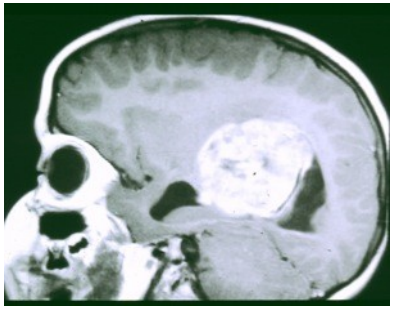
- Location

Site	≤ 12 month in age (n = 15)		13 months–18 years in age (n = 25)	
	n	%	*n*	%
Posterior fossa	11	73.3	13	52
Cerebrum	0		9	36
Pineal	3	20	2	8
Supra/infratentorial	1	6.6	0	
Extramedullary cervical	0		1	4

- Macroscopic
  - Cystic
  - Heterogeneous
  - Hemorrhage or necrosis







Recognition

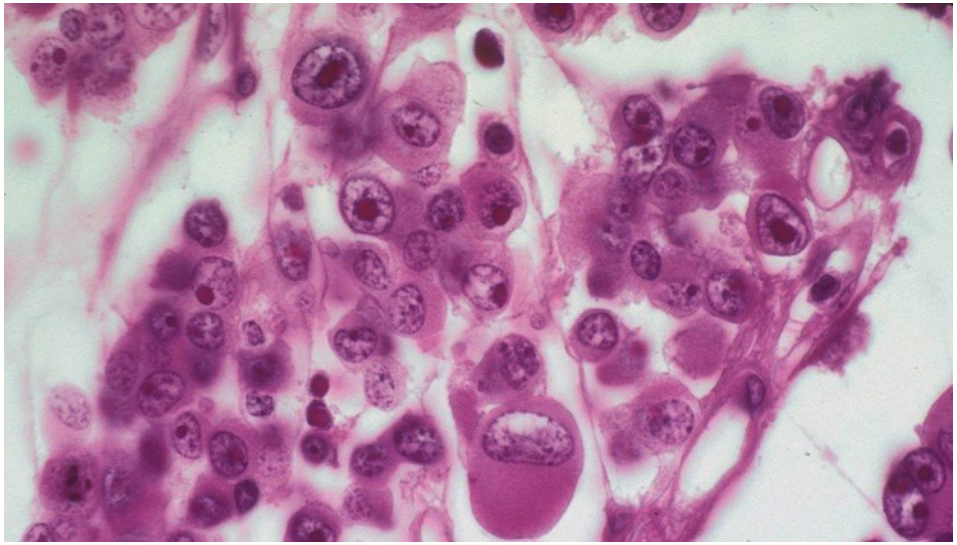
Data courtesy of Dr. Rorke-Adams; images Drs. Rorke-Adams & Parh

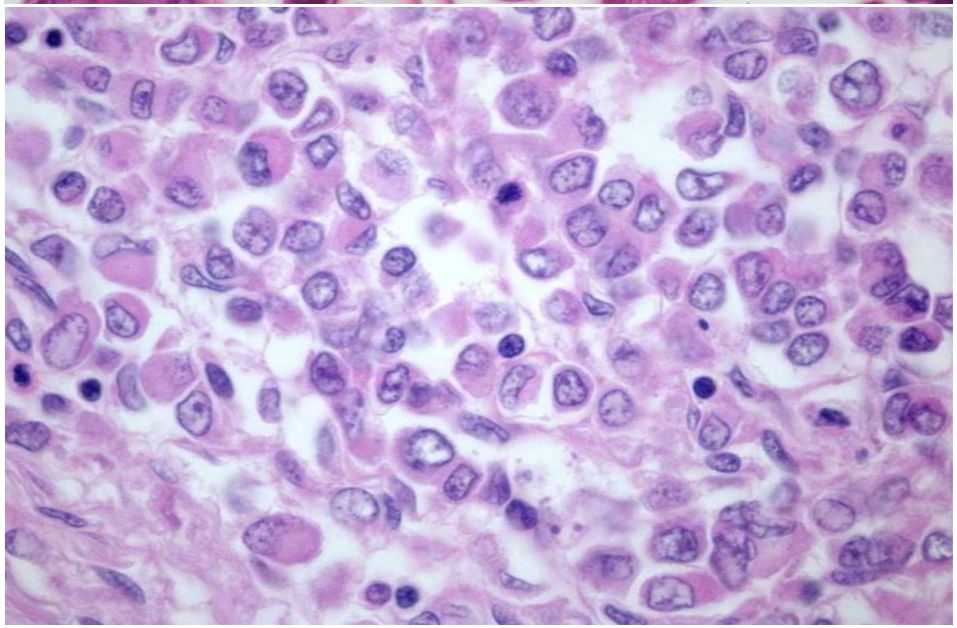
CNS Rhabdoid (AT/RT)

Microscopic Pathology

- Predominant Pattern Type
  - Sheets of tumor with infiltrative growth through adjacent parenchymal and leptomeninges
- Predominant Cell Type
  - Primitive neuroectodermal cells
  - Rhabdoid cells
  - Mesenchymal/epithelial cells
- Cytology of Rhabdoid cells
  - Vesicular chromatin staining
  - Prominent eosinophilic nucleoli

Recognition

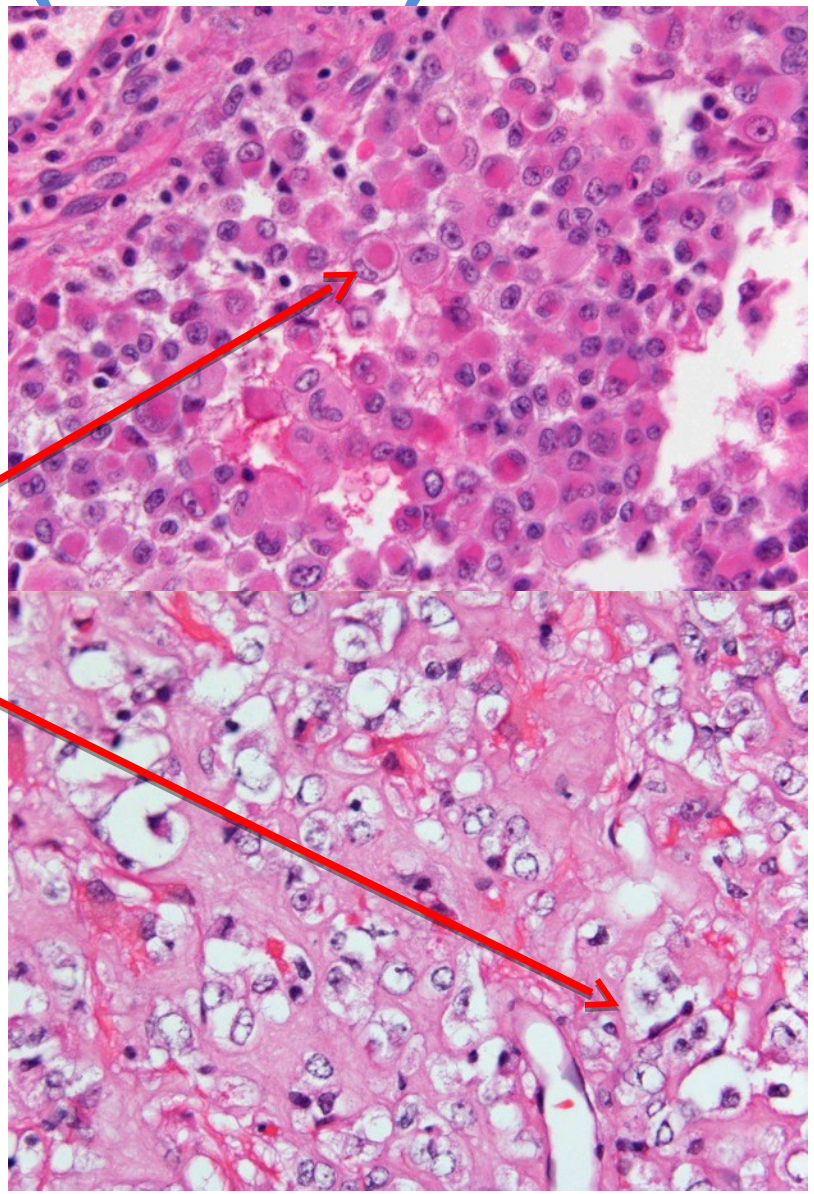




CNS Rhabdoid (AT/RT)

Microscopic Pathology, Cont'd.

- Histologic Features
  - Prominent cell borders
  - Abundant eosinophilic cytoplasm
  - Vacuolar cytoplasmic degeneration
  - Variable mitotic activity
  - Karyorrhectic debris
  - Necrosis



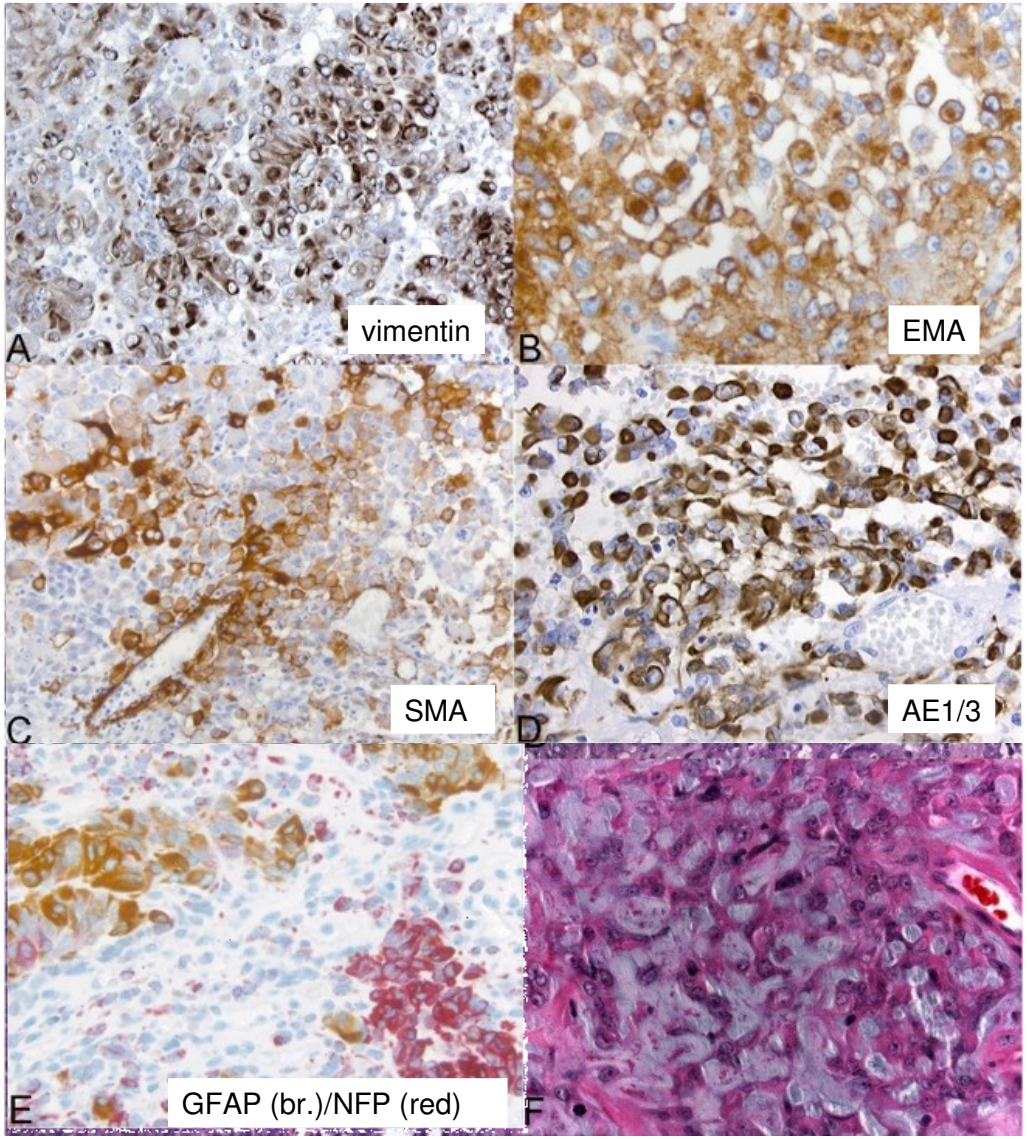
Recognition

CNS Rhabdoid (AT/RT)

Microscopic Pathology, Cont'd.

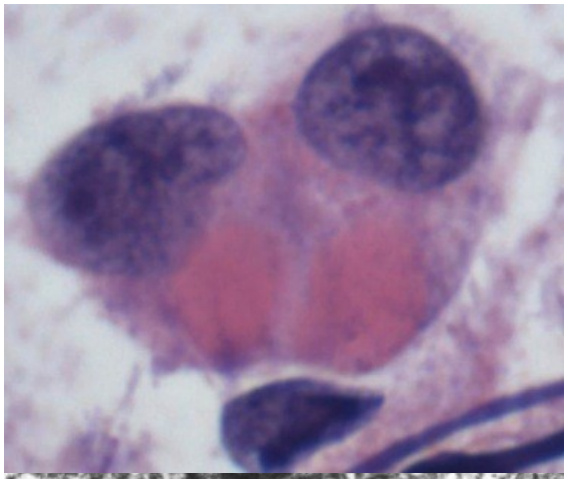
- Histologic Features
  - Rhabdoid cells may be focal or rare
  - Epithelioid cells may be more common than rhabdoid cells
  - PNET/MB component often predominates and occasionally is all there is
  - Poorly differentiated epithelial structures are occasionally identified
  - Spindle cell mesenchymal differentiation
  - Chordoid pattern with abundant extracellular myxohyaline material

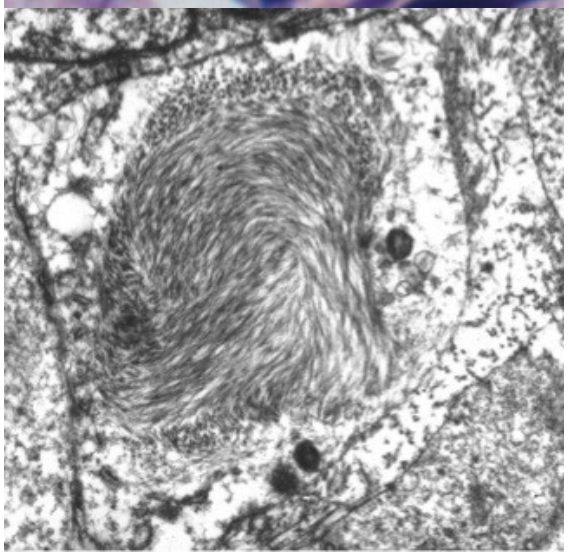
Recognition



Rhabdoid Tumors: Common Features

- Histology
  - Rhabdoid cells*
  - Polymorphic features
    - Primitive, epithelial and mesenchymal elements are most frequently identified
    - Spectrum of histologic patterns can be observed in ***all*** rhabdoid tumors
  - Biologically aggressive
    - Infiltrative margins
    - Frequent lymphatic invasion
    - Necrosis
    - High proliferative rate/mitotic rate (typically)





Recognition

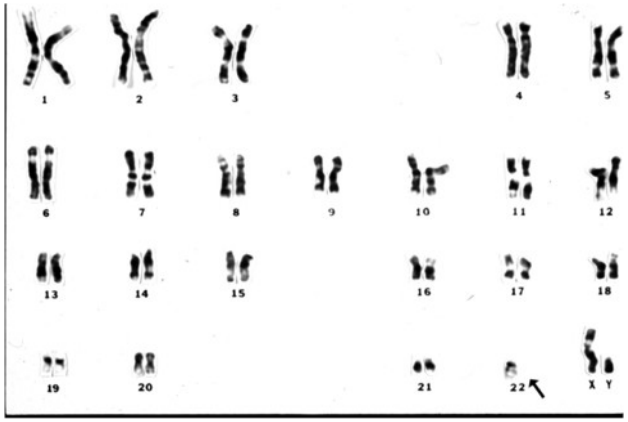
Rhabdoid Tumors: Common Features

- Immunohistochemistry
  - Polyphenotypic tumors
  - Markers of divergent differentiation:
    - Neuroepithelial
    - Epithelial
    - Mesenchymal
  - Intermediate filaments
  - Markers of myogenic differentiation are not typically expressed

	Expression
Vimentin	All
EMA	Most - All
Actin*	Most - All
GFAP	Most
Neural (NSE, synapto, NFP)	Most
Cytokeratin	Many
CD99	Many
Desmin	Some
Myogenin/Myoglobin	Negative (?)

Recognition

Monsomy 22



Discovery

MONOSOMY 22 IN RHABDOID OR ATYPICAL TERATOID TUMORS OF THE BRAIN

To the Editor: We have analyzed chromosomes in three cases of atypical teratoid or primary rhabdoid tumors of the brain, which represent a subset of malignant brain tumors that occur in very young children. Such tumors have a rapid, progressive clinical course that is usually resistant to current therapeutic protocols. Histologically, these tumors are composed of either pure rhabdoid cells or a mixture of rhabdoid elements with neuroepithelial, peripheral epithelial, and mesenchymal tissues.[1] They are often misclassified as medulloblastomas or primitive neuroectodermal tumors (PNETs) of the central nervous system.

Three infants 6 to 11 months of age presented with tumors of the posterior fossa. After surgical resection, one tumor was diagnosed as an atypical teratoid tumor and two were diagnosed as pure rhabdoid tumors. Cytogenetically, all three tumors were characterized by a simple monosomy 22. The patients' constitutional karyotypes were normal.

The deletion of chromosome 22 has been observed in several benign tumors of the nervous system, such as meningioma[2] and acoustic neuroma.[3] Chromosome 22 abnormalities are rarely seen in PNETs, however, in contrast to i(17q), which is a common structural abnormality in these tumors.[4] The finding of a simple monosomy 22 in the tumor karyotype therefore offers an additional means of distinguishing atypical teratoid or rhabdoid tumors from other malignant brain tumors found in children. Likewise, it should no longer be assumed that brain tumors with monosomy 22 are meningiomas. Cytogenetic studies of a large series of atypical teratoid and rhabdoid tumors of the brain are needed to confirm these findings before they can be used in a clinical setting.

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BEVERLY S. EMANUEL, PH.D.
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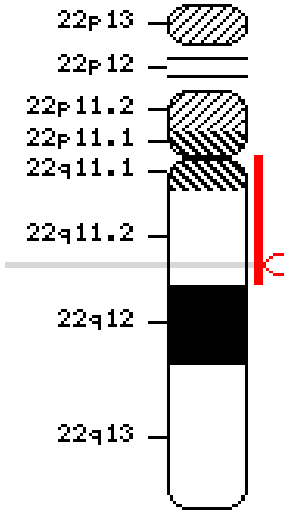
N Engl J Med. 1989 Sep 28;321(13):906.

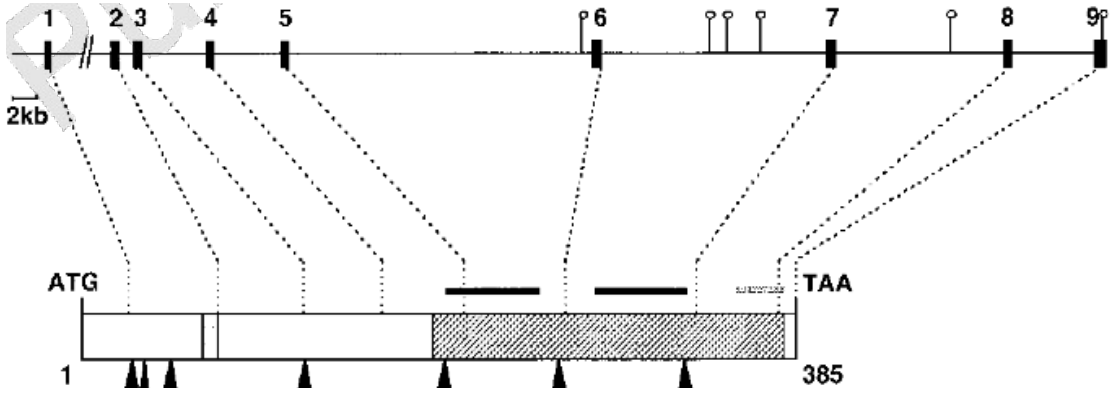
Truncating mutations of hSNF5/INI1/SMARCB1

Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer

Isabella Versteege*, Nicolas Sévenet*, Julian Lange*, Marie-Françoise Rousseau-Merck*, Peter Ambros†, Rupert Handgretinger‡, Alain Aurias* & Olivier Delattre*

* *Laboratoire de Pathologie Moléculaire des Cancers, Section de Recherche, Institut Curie, 26 rue d'Ulm, 75248 Paris Cedex 05, France*
† *CCRI, St Anna Kinderspital, Kinderspitalgasse 6, A-1090 Vienna, Austria*
‡ *Universität Kinderklinik, Rümelinstrasse 23, D-72070 Tübingen, Germany*





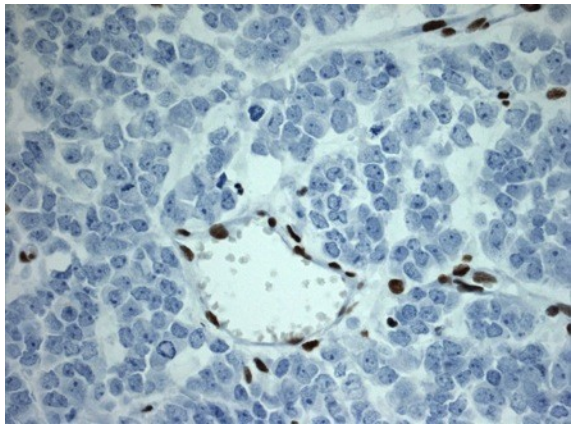
Discovery

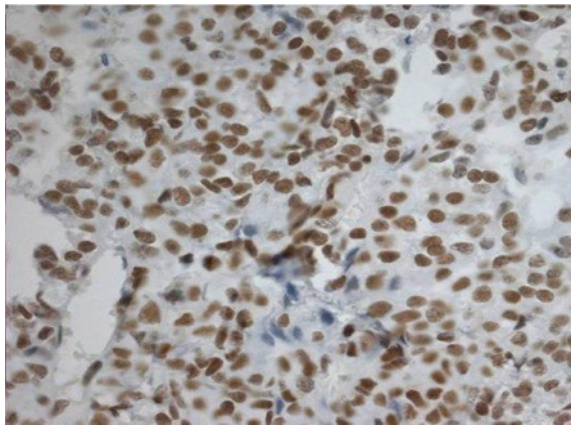
PMID: 9671307

IHC Analysis of hSNF5/INI1/SMARCB1

Immunohistochemical Analysis of hSNF5/INI1 in Pediatric CNS Neoplasms

Alexander R. Judkins, MD, Joanne Mauger, AS HT, IHC (ASCP),* Lucy B. Rorke, MD,* and Jaclyn A. Biegel, PhD†*





Application

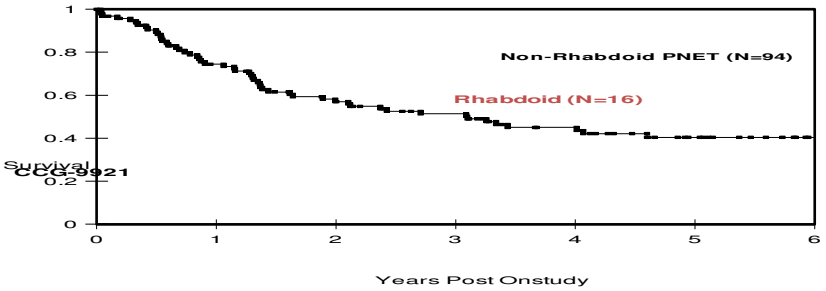
Am J Surg Pathol. 2004 May;28(5):644-50.

Prognostic Implications

Recognizing AT/RT

- Differential Diagnosis:
  - Embryonal CNS tumors (PNET/MB)
  - Choroid plexus carcinoma
  - Ependymoma
  - Germ cell tumor
- Initially many cases were classified as PNET/MB

Clinical Outcome Data

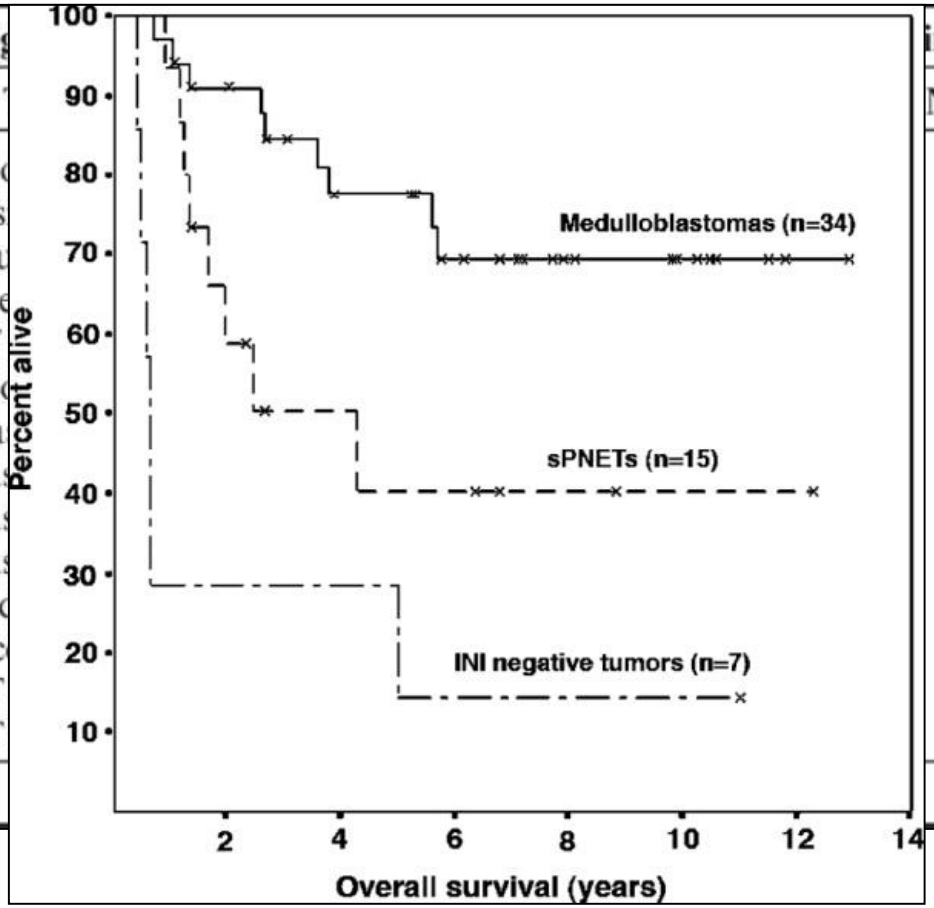


Prognostic Implications

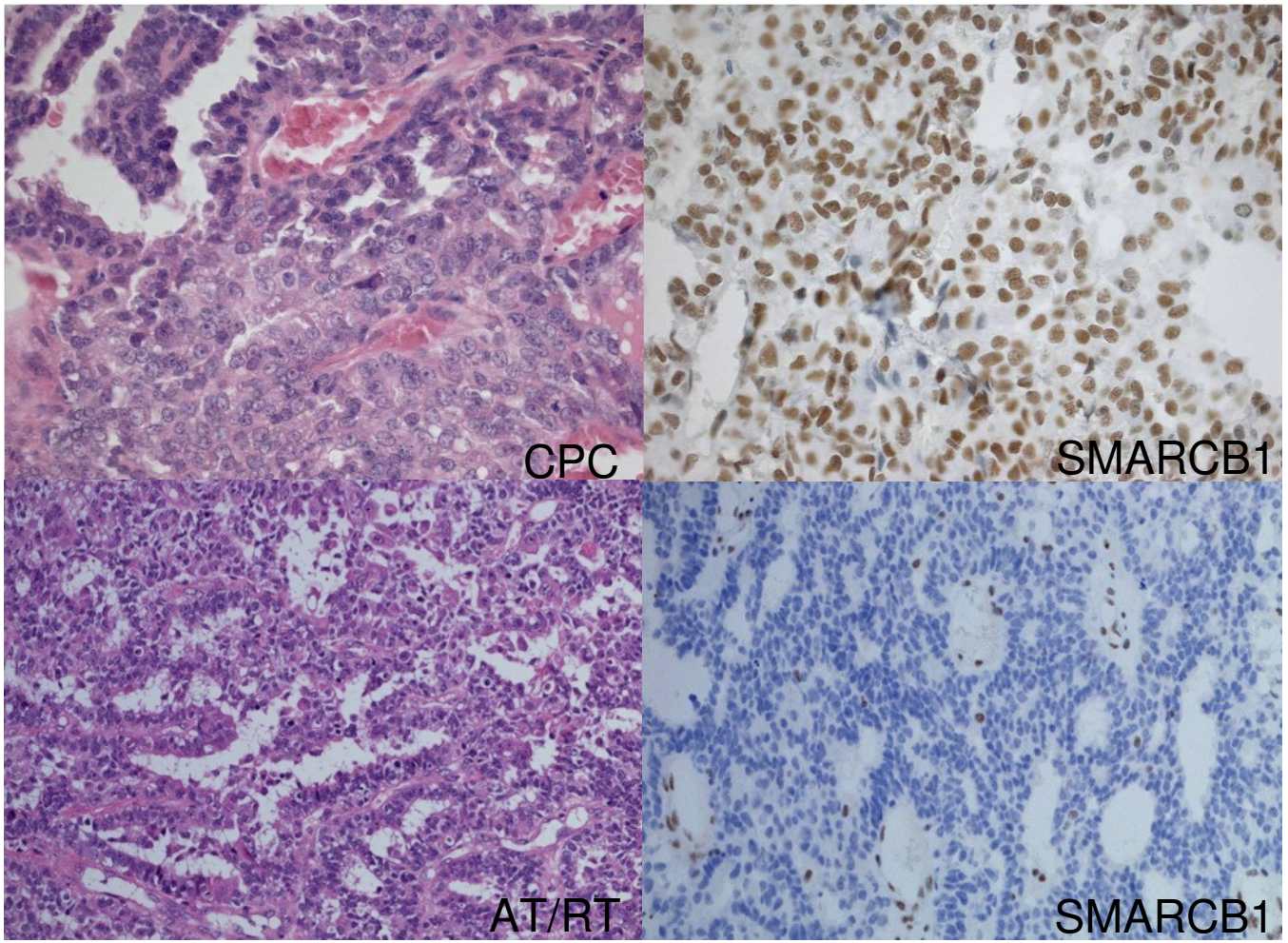
Immunohistochemical Analysis of INI1 Protein in Malignant Pediatric CNS Tumors: Lack of INI1 in Atypical Teratoid/Rhabdoid Tumors and in a Fraction of Primitive Neuroectodermal Tumors without Rhabdoid Phenotype.
Haberler, Christine; Laggner, Ute; Slavc, Irene; Czech, Thomas; Ambros, Inge; Ambros, Peter; Budka, Herbert; Hainfellner, Johannes

American Journal of Surgical Pathology. 30(11):1462-1468, November 2006.
DOI: 10.1097/01.pas.0000213329.71745.ef

Histolog		ining
Tumor		Negative
Medull		6
Class		6
Nodu		0
Large		0
sPNET		2
Medull		0
Gliobla		0
Anaplas		0
Anaplas		0
Anaplas		0
Choroi		0
Germ c		0
AT/RT		1
AT/RT		17
Total		26

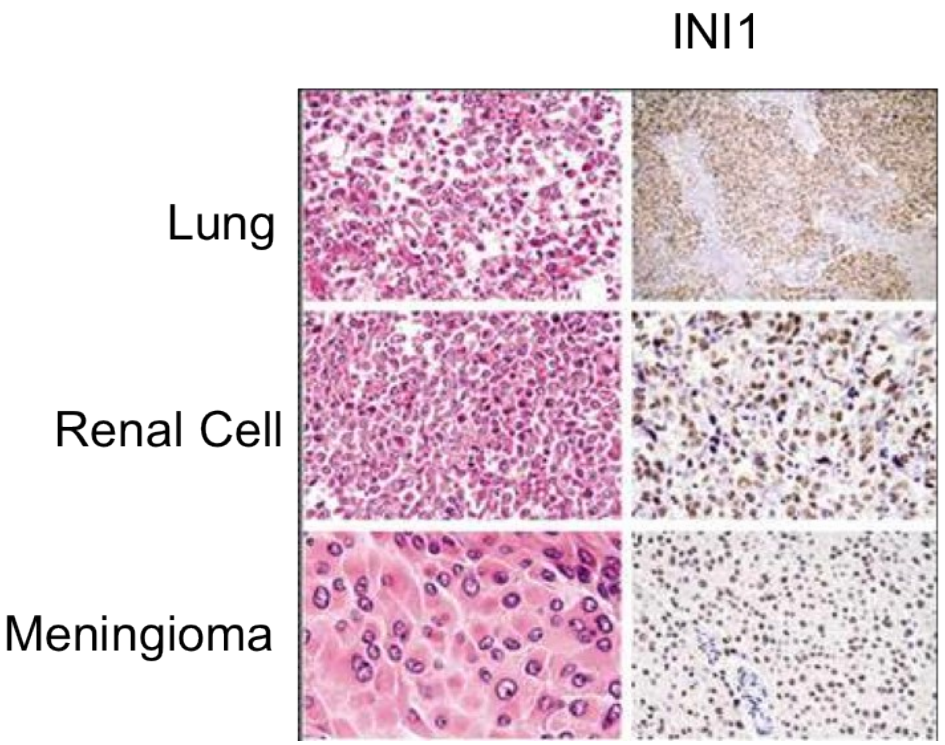


Prognostic Implications



Re-recognition

- Not all tumors with rhabdoid features are rhabdoid tumors
- Loss of SMARCB1 expression does not occur in other tumors with rhabdoid features
- Loss of SMARCB1 expression is observed in adult AT/RT (rare)



Prognosis
Recog. & Discovery 2.0

PMID: 15761491; 1577923

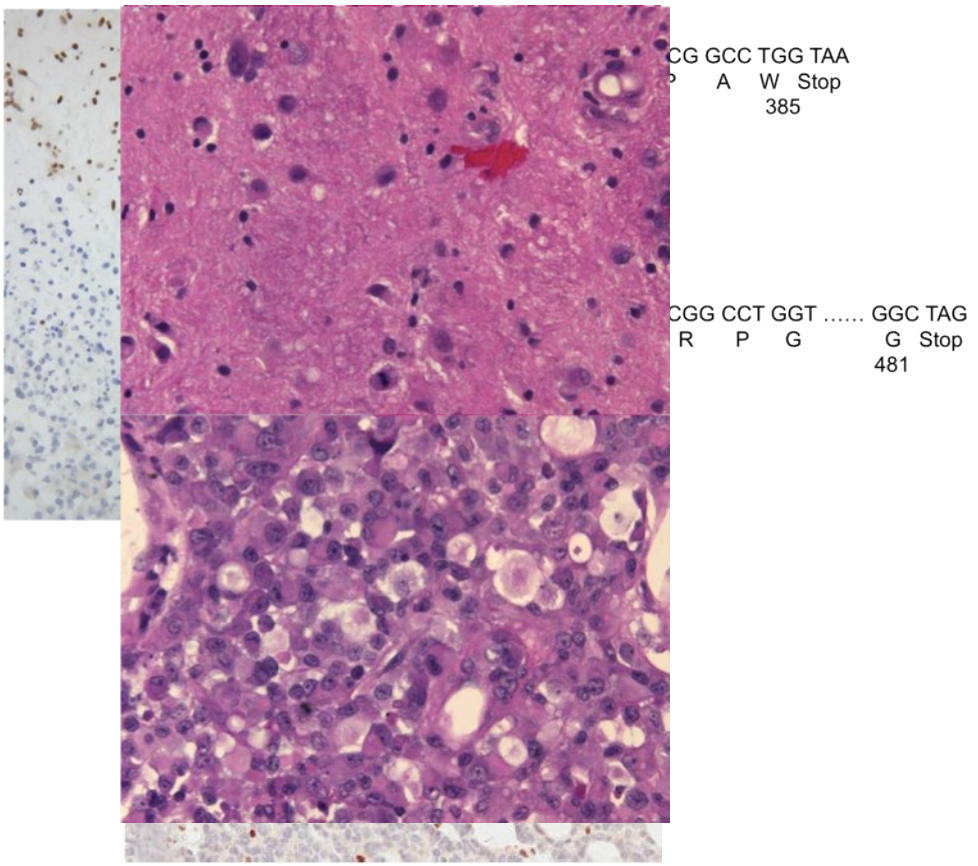
Recognition

Other tumors may show inactivation of SMARCB1

Central Nervous System

- Malignant transformation of low grade CNS tumors (rare)
- Cribriform neuroepithelial tumor (CRINET)

Malignant transformation

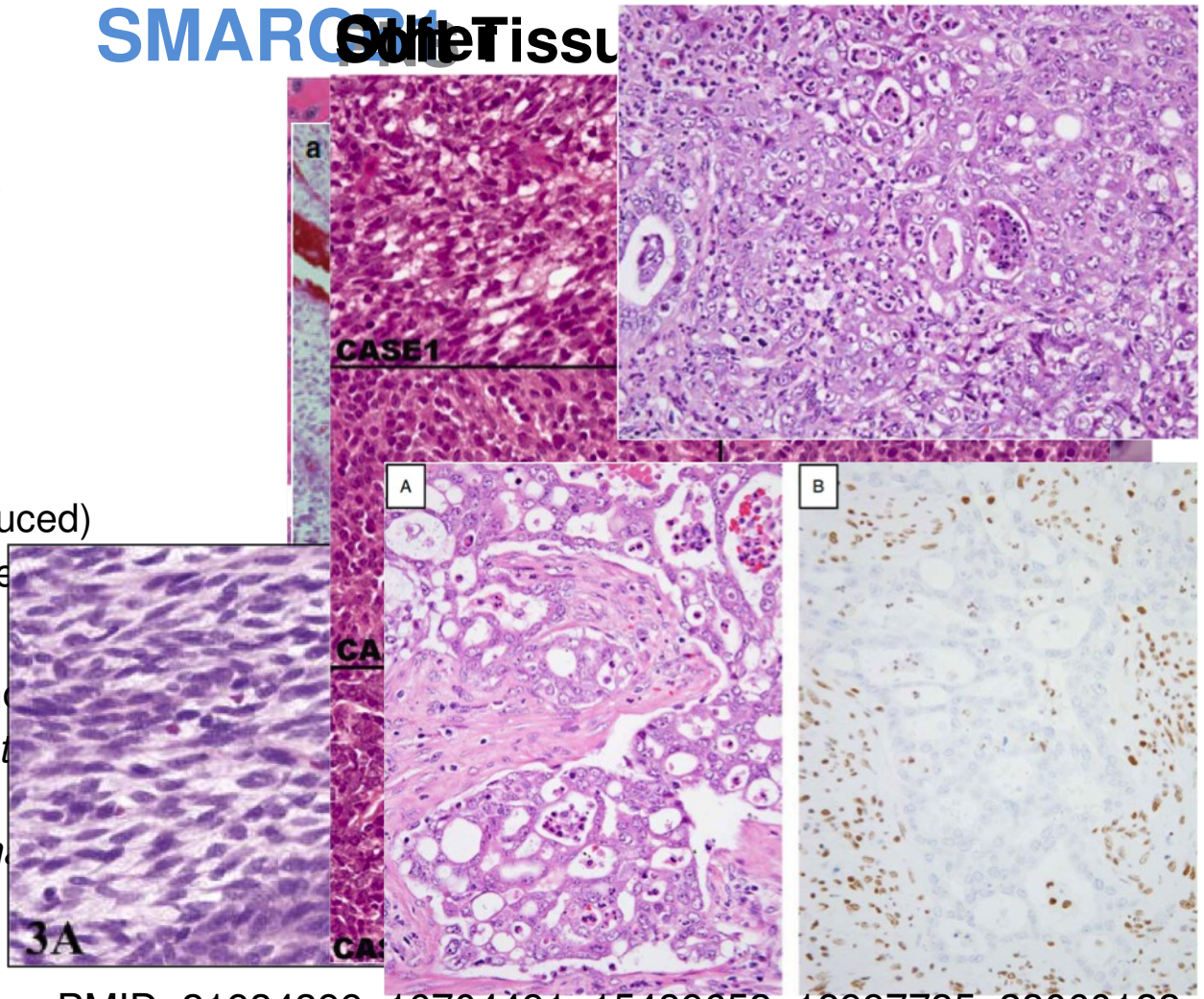


Recognition

Other tumors may show inactivation of SMARCB1

Extra-CNS

- PNS
  - Schwannoma (mosaic)
  - Epitheliod MPNST
- Soft Tissue
  - Epithelioid Sarcoma
  - Extraskeletal myxoid chondrosarcoma
  - Synovial sarcoma (reduced)
  - Pediatric undifferentiate
- Other
  - Renal medullary carcin
  - *Small cell undifferentiat hepatoblastoma*
  - *Myoepithelial carcinom*



Prognosis
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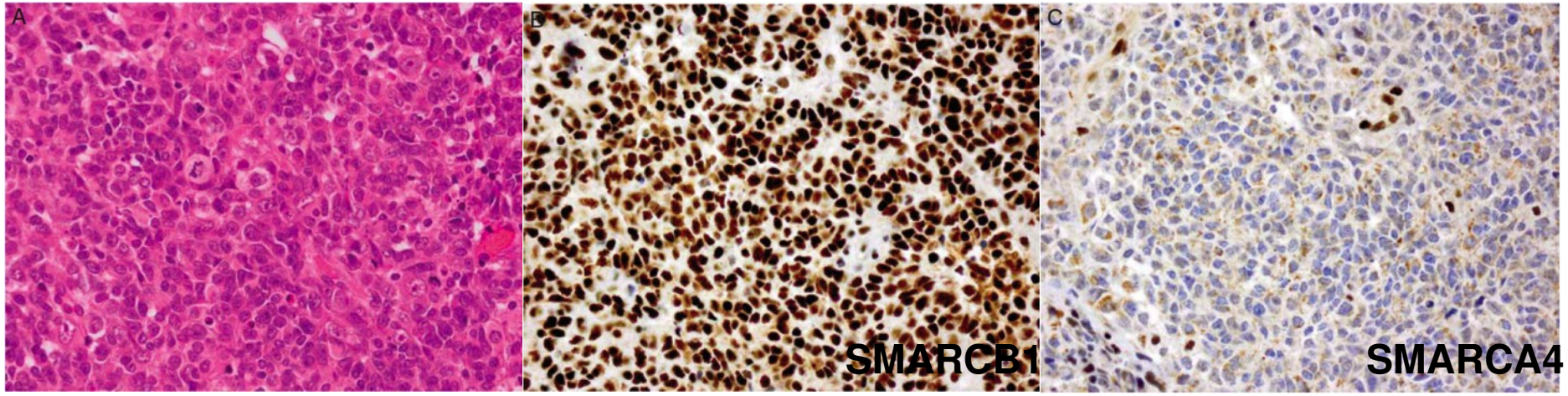
Images PMID: 21934399; 16704491; 15489652; 18997735; 23060122

Rhabdoid Tumors May Have Retained SMARCB1 Expression*

* Very rarely!!!

Nonsense Mutation and Inactivation of SMARCA4 (BRG1) in an Atypical Teratoid/Rhabdoid Tumor Showing Retained SMARCB1 (INI1) Expression

Martin Hasselblatt, MD, Stefan Gesk, MD,†‡ Florian Oyen,§ Sabrina Rossi, MD,‖ Elisabetta Viscardi, MD,¶ Felice Giangaspero, MD,#** Caterina Giannini, MD, PhD,†† Alexander R. Judkins, MD,‡‡§§ Michael C. Frühwald, MD, PhD,‖‖ Tobias Obser,§ Reinhard Schneppenheim, MD, PhD,§ Reiner Siebert, MD,†‡ and Werner Paulus, MD**



Prognosis

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(*Am J Surg Pathol* 2011;35:933–935)

Germline SMARCB1 Abnormalities Are Common in Rhabdoid Tumors

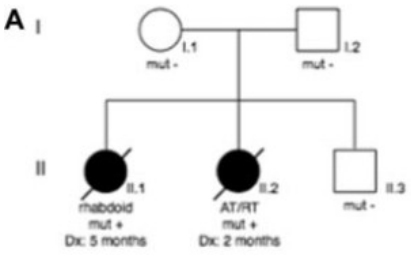
Pediatr Blood Cancer 2011;56:7–15

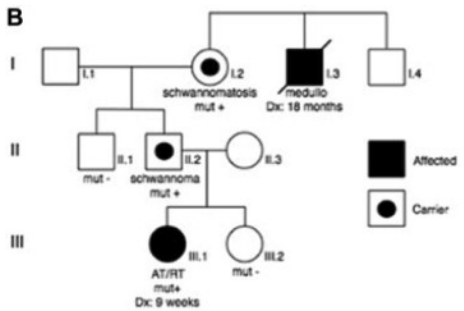
Spectrum of *SMARCB1/INI1* Mutations in Familial and Sporadic Rhabdoid Tumors

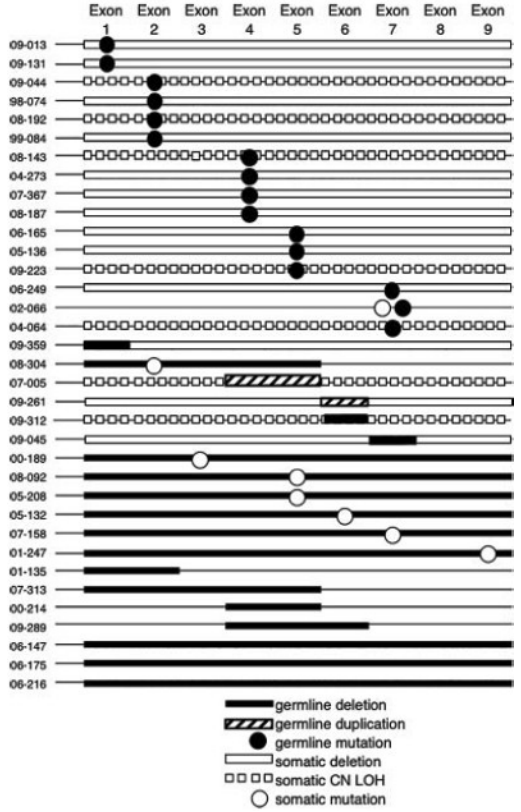
Katherine W. Eaton, BS,[1] Laura S. Tooke, BS,[2] Luanne M. Wainwright, BS,[2]
Alexander R. Judkins, MD,[2,3] and Jaclyn A. Biegel, PhD[1,2,4]*

TABLE III. Germline Alterations in Rhabdoid Tumors by Anatomic Site

Anatomic site	Total	Number (%)
CNS	65	23 (35)
Kidney	12	3 (25)
Multiple primaries	6	6 (100)
Extra-renal	17	3 (18)







Prognosis
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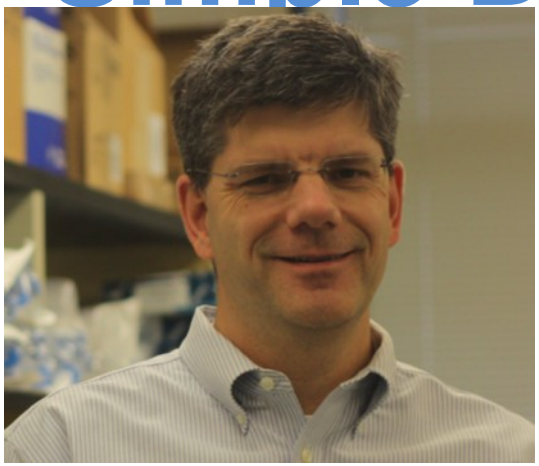
“A Remarkably Genetically Simple Disease”

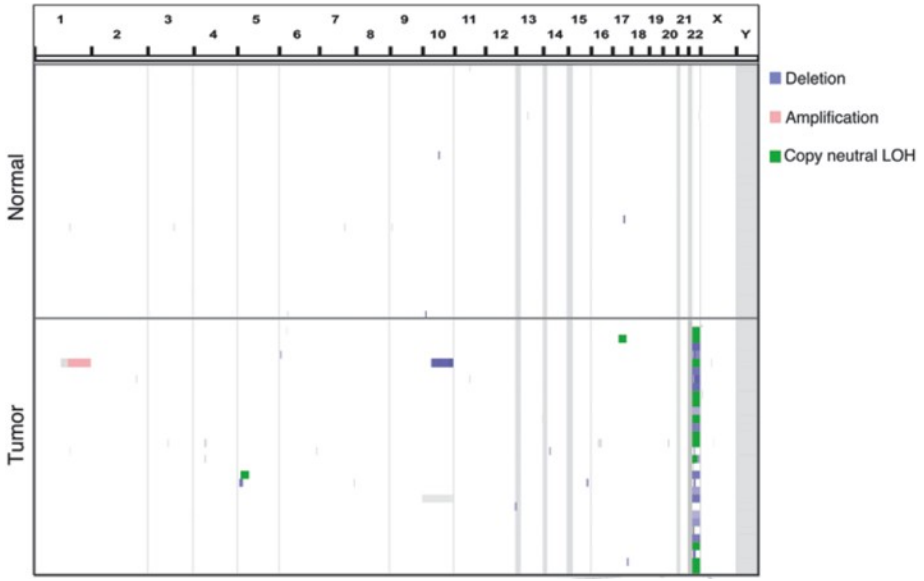


A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers

Ryan S. Lee,[1,2] Chip Stewart,[3] Scott L. Carter,[3] Lauren Ambrogio,[3] Kristian Cibulskis,[3] Carrie Sougnez,[3] Michael S. Lawrence,[3] Daniel Auclair,[3] Jaume Mora,[4] Todd R. Golub,[1,2,3,5] Jaclyn A. Biegel,[6,7] Gad Getz,[3] and Charles W.M. Roberts[1,2,8]

[1]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA. [2]Harvard Medical School, Boston, Massachusetts, USA. [3]Broad Institute, Cambridge, Massachusetts, USA. [4]Department of Pediatric Oncology, Hospital Sant Joan de Déu, Barcelona, Spain. [5]Howard Hughes Medical Institute, Chevy Chase, Maryland, USA. [6]Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA. [7]Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. [8]Division of Hematology/Oncology, Children's Hospital Boston, Boston, Massachusetts, USA.

Cancer is principally considered a genetic disease, and numerous mutations are thought essential to drive its growth. However, the existence of genomically stable cancers and the emergence of mutations in genes that encode chromatin remodelers raise the possibility that perturbation of chromatin structure and epigenetic regulation are capable of driving cancer formation. Here we sequenced the exomes of 35 rhabdoid tumors, highly aggressive cancers of early childhood characterized by biallelic loss of *SMARCB1*, a subunit of the SWI/SNF chromatin remodeling complex. We identified an extremely low rate of mutation, with loss of *SMARCB1* being essentially the sole recurrent event. Indeed, in 2 of the cancers there were no other identified mutations. Our results demonstrate that high mutation rates are dispensable for the genesis of cancers driven by mutation of a chromatin remodeling complex. Consequently, cancer can be a remarkably genetically simple disease.



Prognosis

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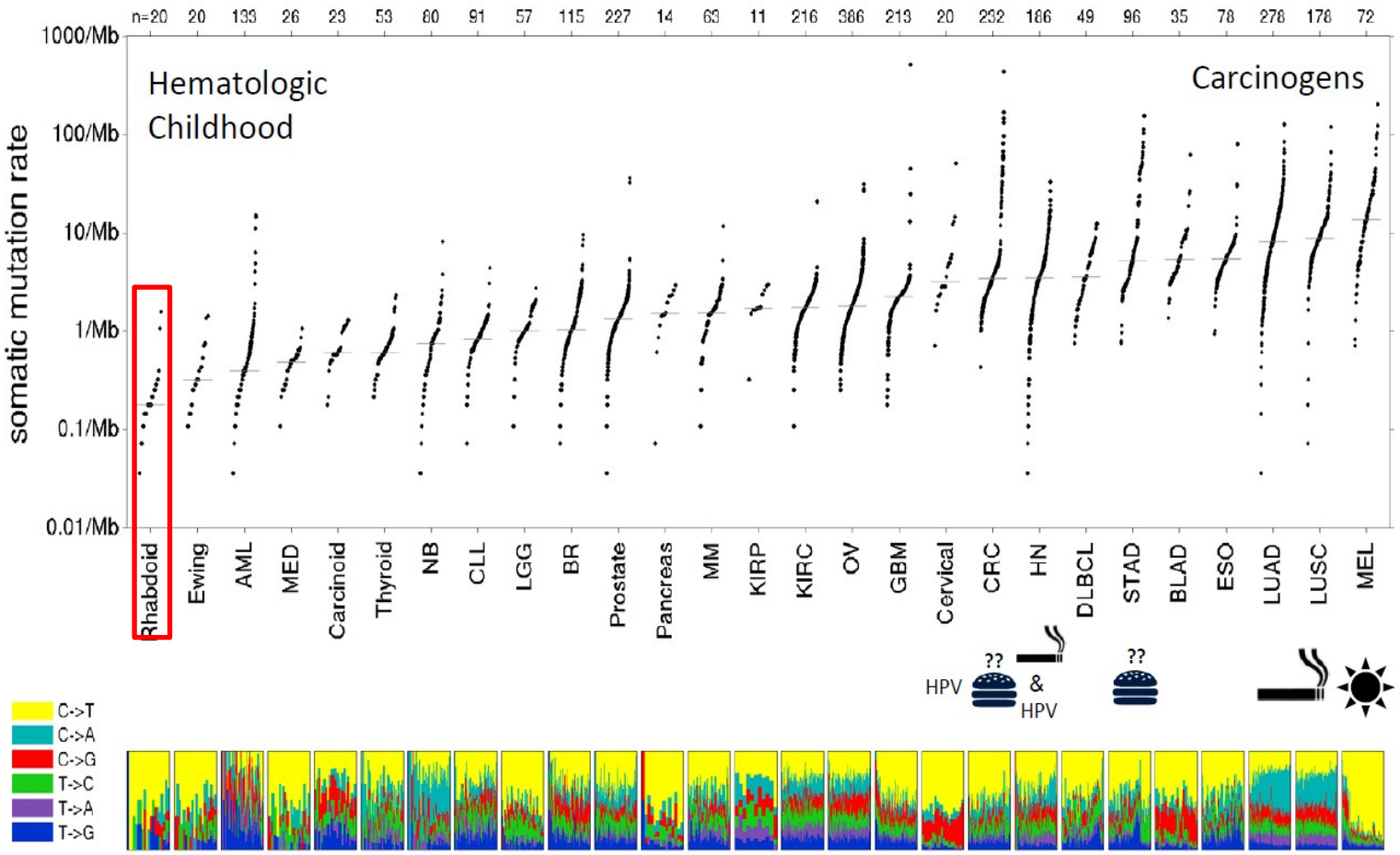
PMID: 22797305

"A Remarkably Genetically Simple Disease"



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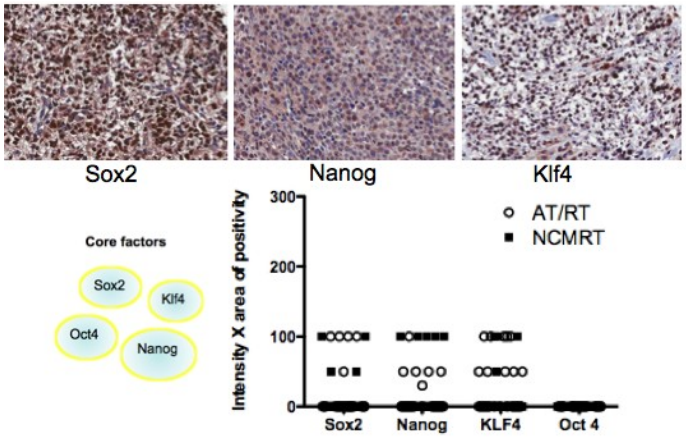
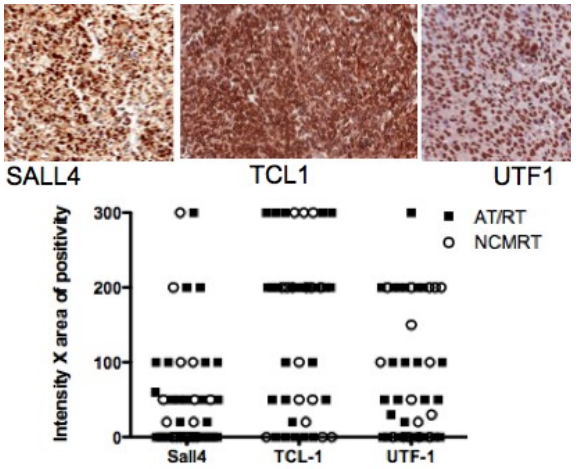
Lawrence *et al., Nature* 2013

Malignant Rhabdoid Tumors Express Stem Cell Factors, EZH2 & Id Proteins

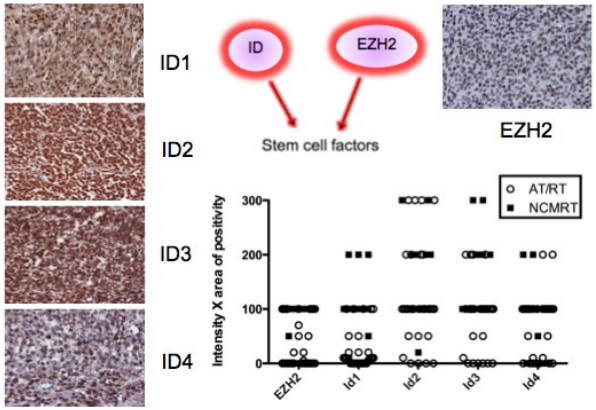
Summary- stem cell factors in MRT



MRT - stem cell factors



MRT - ID proteins, EZH2



Regression analysis

Value	ID1	ID2	ID3	ID4	EZH2
Slope	0.1724	0.1694	0.1571	0.2799	0.3169
F value	6.94	15.63	8.76	17.64	15.63
p value	**0.0087**	**0.0002**	**0.0033**	**<0.0001**	**<0.0001**

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Am J Surg Pathol • Volume 35, Number 10, October 2011

Growth and Developmental Pathways

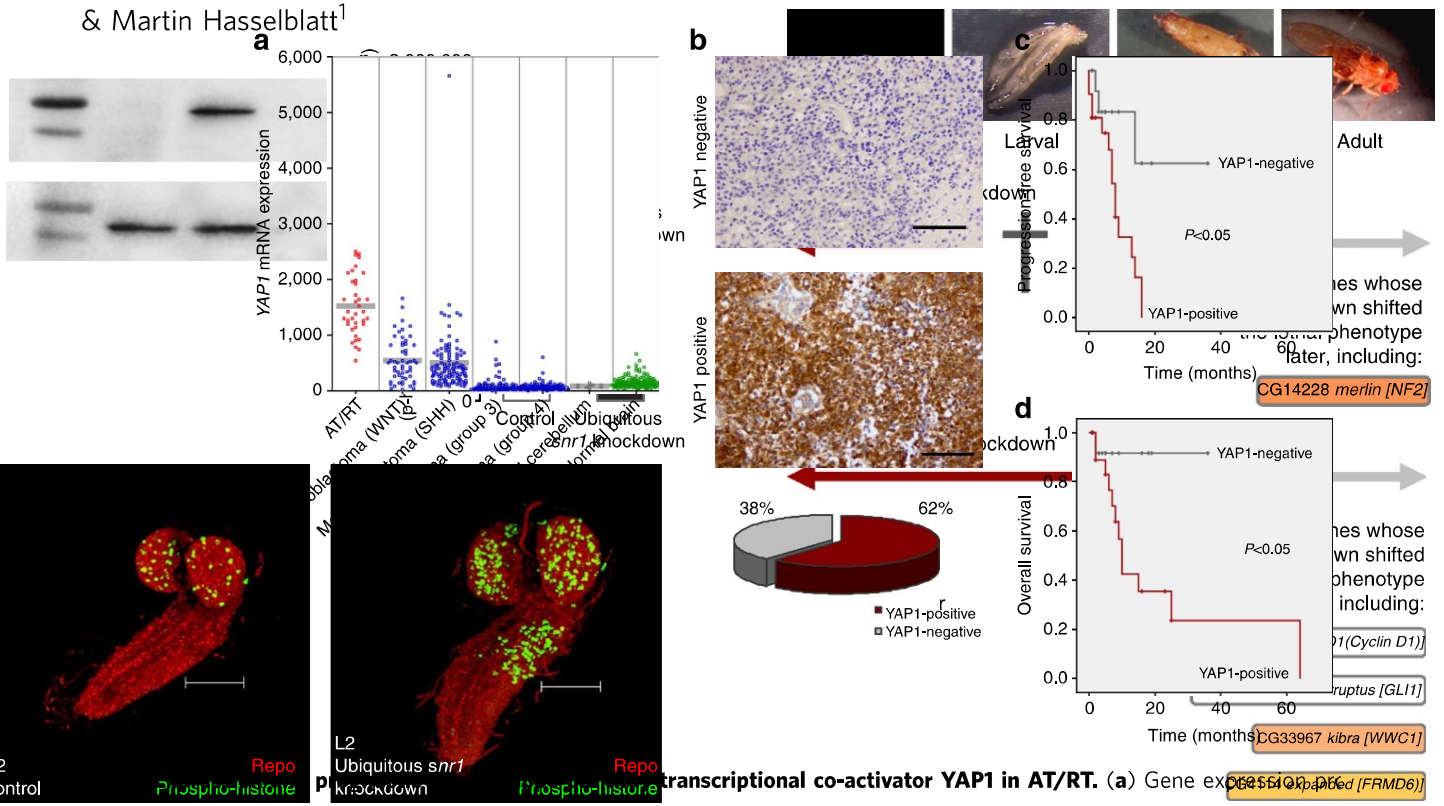
ARTICLE

Received 20 Nov 2013 | Accepted 29 Apr 2014 | Published 3 Jun 2014

DOI: 10.1038/ncomms5005

Identification of genes involved in the biology of atypical teratoid/rhabdoid tumours using *Drosophila melanogaster*

Astrid Jeibmann[1,*], Kristin Eikmeier[1,*], Anna Linge[1], Marcel Kool[2], Björn Koos[3], Jacqueline Schulz[1], Stefanie Albrecht[1], Kerstin Bartelheim[4], Michael C. Frühwald[4], Stefan M. Pfister[2], Werner Paulus[1] & Martin Hasselblatt[1]



p transcriptional co-activator YAP1 in AT/RT. (**a**) Gene ex

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Genomic Landscape of AT/RTs … There Is More Than SMARCB1

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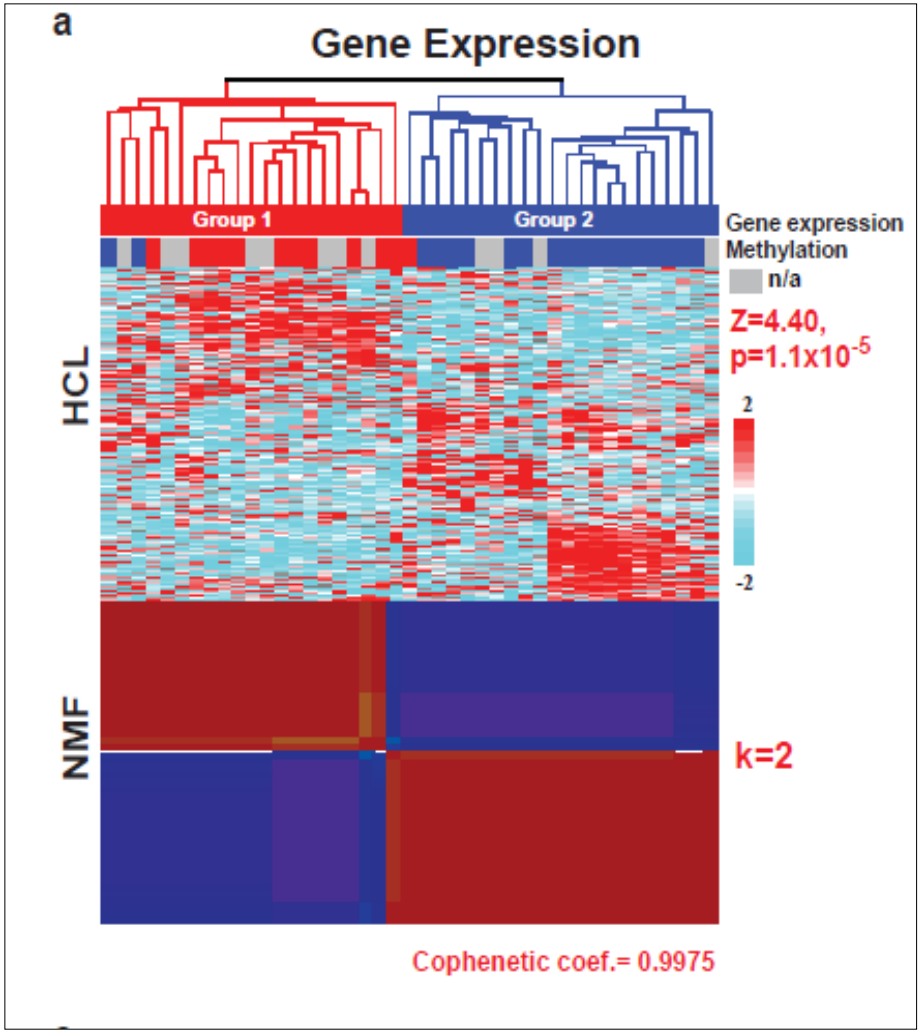
Annie Huang, Hospital for Sick Children, Toronto

AT/RTs Comprise At Least Two Molecular Classes



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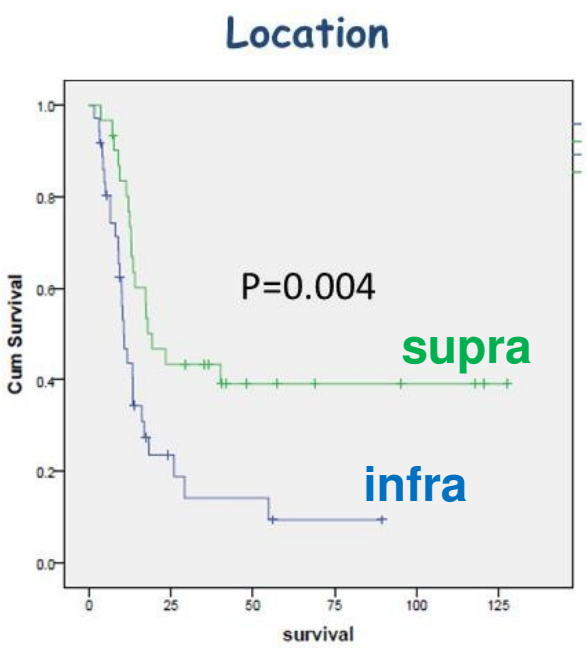
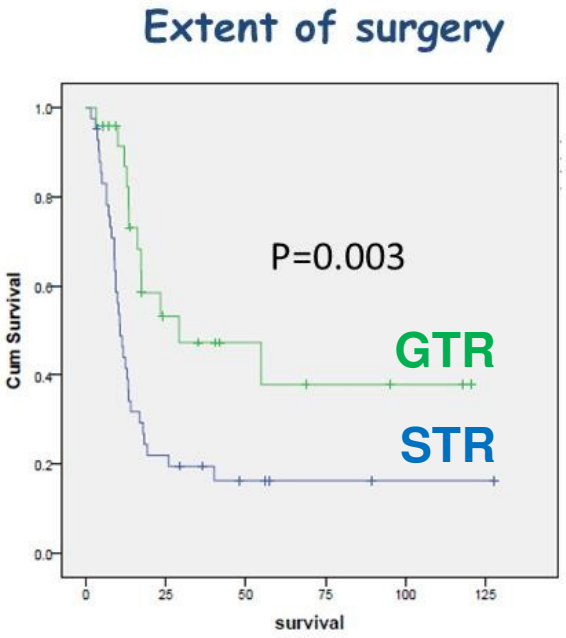
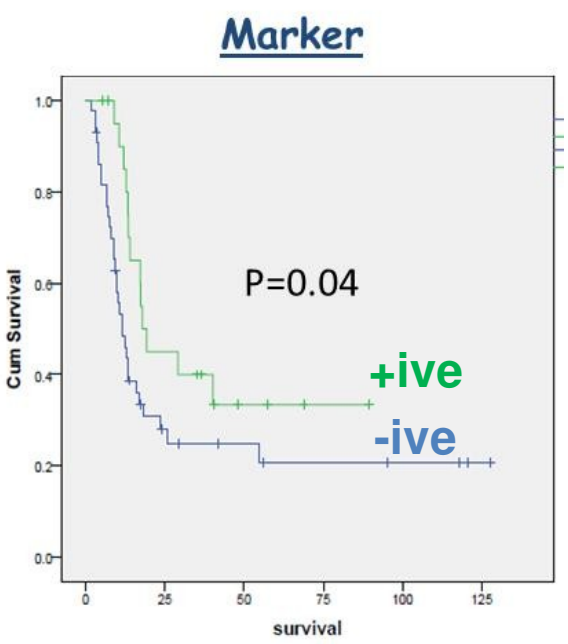
Annie Huang, Hospital for Sick Children

Risk Stratification of AT/RT

- Clinical risk factors: location & extent of surg



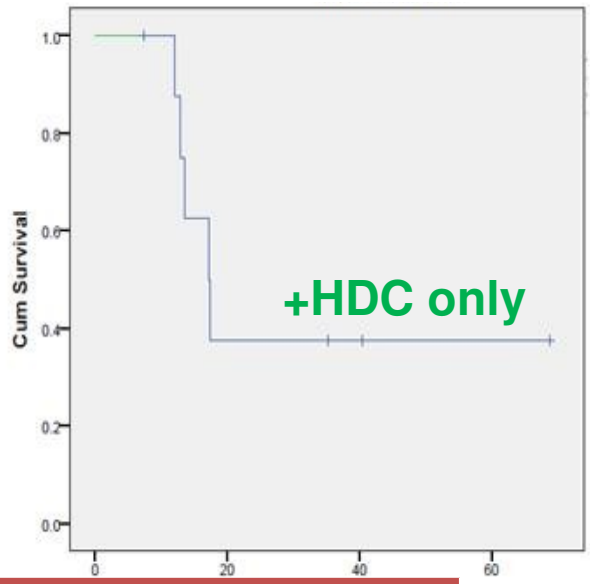


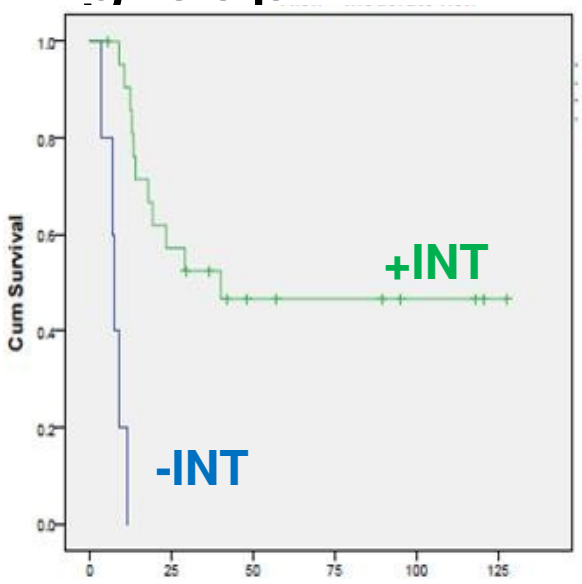


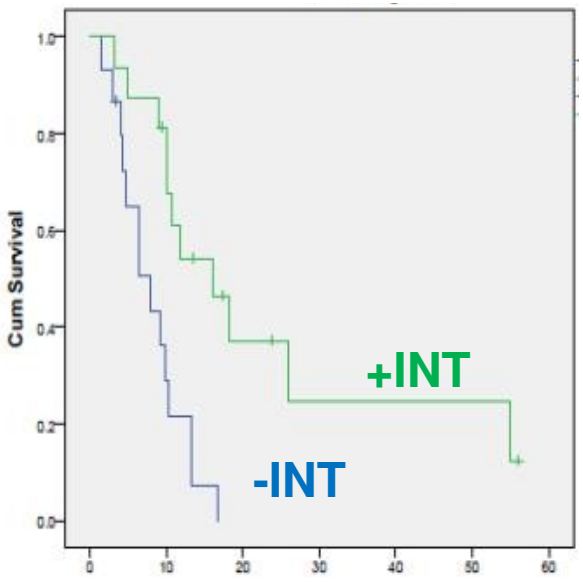
Annie Huang, Hospital for Sick Children

Risk Stratification of AT/RT

- AT/RT can be classified into low, moderate and high risk groups
- Treatment intensification showed differential effect predominately in moderate risk group







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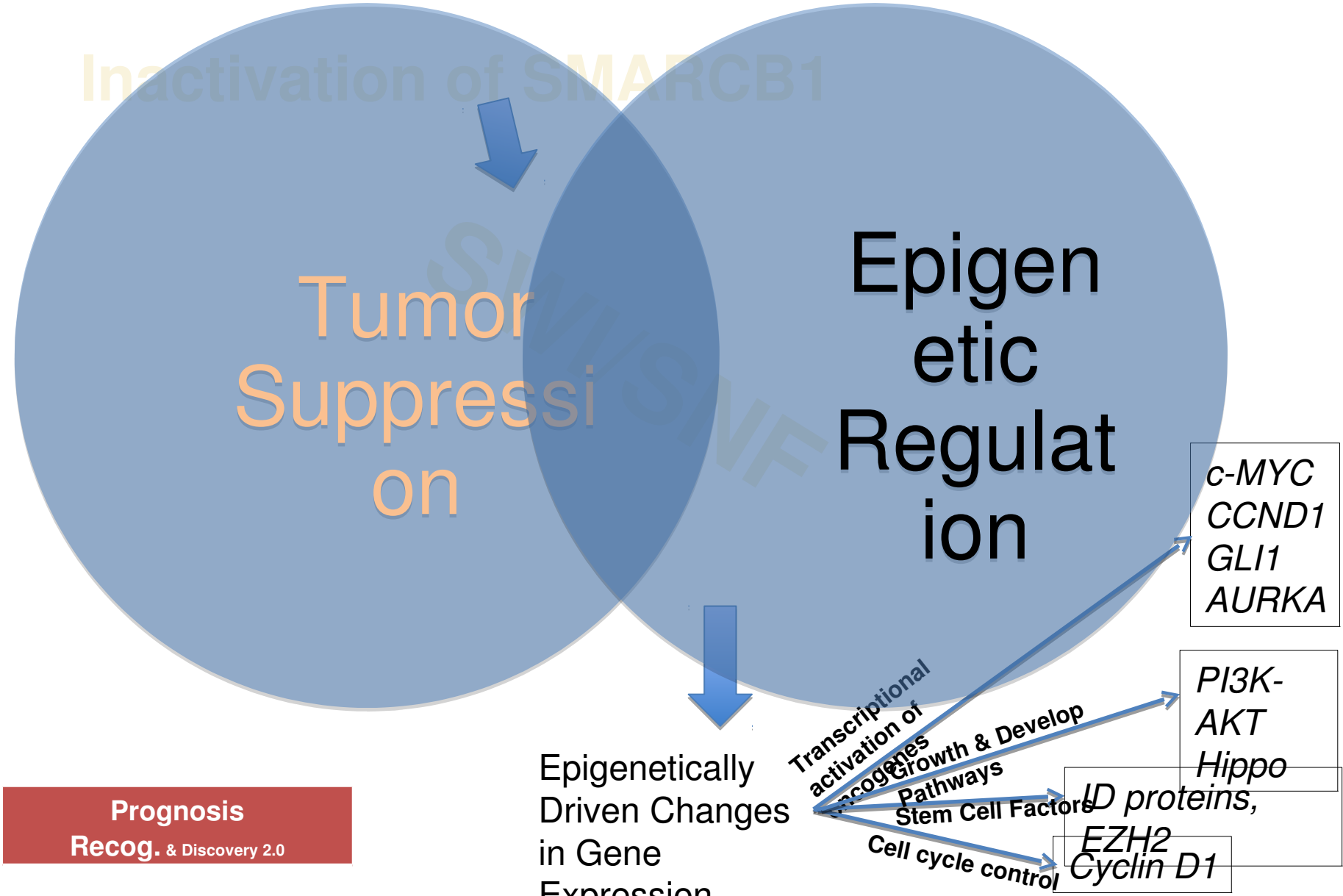
"A Remarkably Genetically Simple … But Not Quite That Simple … Disease"



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Treatment

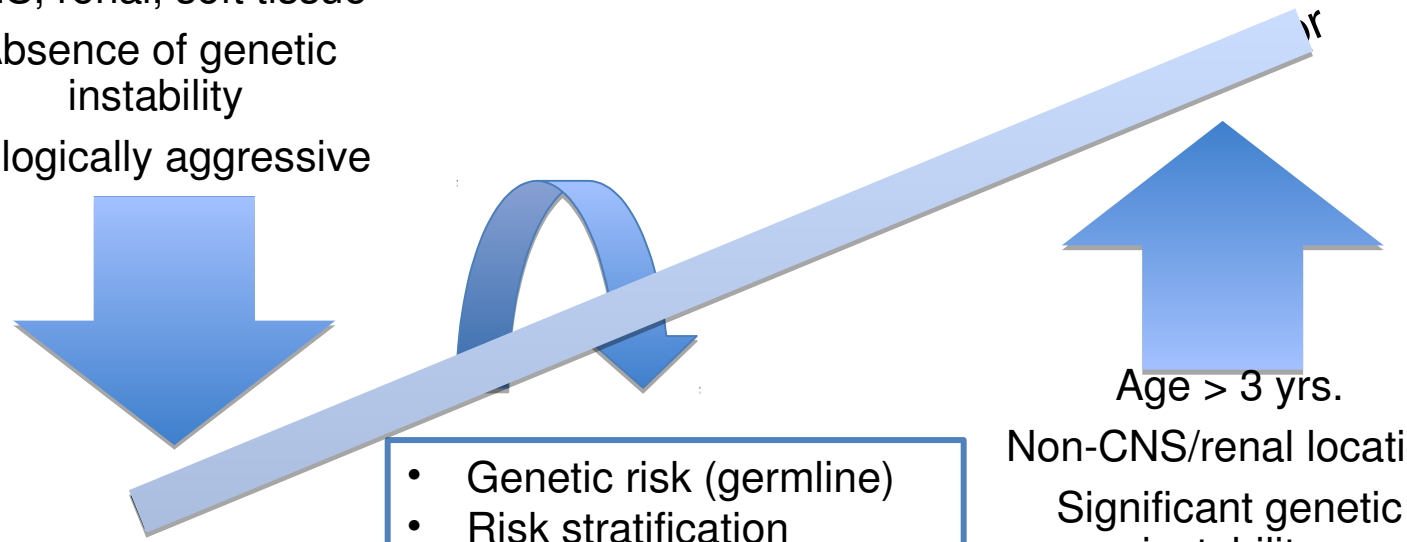
What does it mean when you have a newly diagnosed patient with SMARCB1 inactivation?"

Age < 3 yrs.

CNS, renal, soft tissue

Absence of genetic instability

Biologically aggressive



- Genetic risk (germline)
- Risk stratification
- Novel Agents (HDAC inhibitors, IGF-1R)
- Targeted therapies (Aurora Kinase A, EZH2, PI3K/Akt, Hippo,

Age > 3 yrs.

Non-CNS/renal location

Significant genetic instability

Biologically less aggressive or associated with a lower grade tumor

Treatment