Solid Pseudopapillary Neoplasm
Key Histopathologic and Genetic Features

Stefano La Rosa, MD
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Stefano La Rosa does not have relevant financial relationships
Historical background

Frantz V. Papillary tumors of the pancreas: benign or malignant?
Washington DC: US Armed Forces Institute of Pathology, 32-3, 1959

Synonyms
- Frantz’s Tumor
- Hamoudi’s tumor
- Solid-pseudopapillary tumor
- Papillary epithelial neoplasm
- Papillary and solid neoplasm
- Papillary-cystic carcinoma
- Solid-cystic tumor
- Papillary-cystic tumor

Virginia Kneeland Frantz (1896 -1967)
WHO definition
A low-grade malignant tumor composed of poorly cohesive monomorphic epithelial cells forming solid and pseudopapillary structures

Diagnosis (cytology-histology)
Genetic features

Open issues
✓ Prognostic markers
✓ Pathogenesis
Epidemiology

- 0.9 to 2.7% of all exocrine pancreatic neoplasms
- 5% of cystic neoplasms
- 30% of pancreatic neoplasms <40 years
- No apparent ethnic predilection
- More frequent in young women
- Mean age: 28 years
- Rarer in men, 5-10 years older than women
- Pediatric cases

8-17% of pancreatic neoplasms
More frequent in the head
Macroscopy
Cytology

- Richly cellular
- Branching capillaries surrounded by neoplastic cells
- Background clean or hemorrhagic
- Discohesive small and monomorphic neoplastic cells
- Sometimes with indented or grooved nuclear membrane
- Naked nuclei are also present
- Foamy histiocytes and multinucleated giant cells

Courtesy from Prof. Bongiovanni, University of Lausanne, Switzerland
Histology

Solid areas

✓ Uniform polygonal cells
✓ Numerous delicate capillary-sized blood vessels
Pseudopapillary areas
Loosely cohesive cells surrounding capillary-sized blood vessels
Additional features

Intra-cytoplasmic hyaline globules
PAS-D stained
α1-antichymotrypsin positive

Foamy macrophages

Cholesterol crystals
Hemorrhage
Variants

Pigmented

Lipofusin

Melanin
Clear cell

Courtesy from Prof. Sessa, University of Insubria, Varese, Italy

β-catenin
Differential diagnosis of pancreatic neoplasms with clear cells
Do MiNENs composed of SPN and NEN exist?

Solid Pseudopapillary Neoplasm Collides With a Well-Differentiated Pancreatic Endocrine Neoplasm in an Adult Man

Case Report and Review of Histogenesis

Shirley X. Yan, MD,1 Carol F. Adair, MD,2 Jyoti Balani, MD,1 John C. Mansour, MD,3 and Seifik T. Gokaslan, MD1

Am J Clin Pathol 2015;143:283-287

Glucagon

β-catenin

 Probably they are not MiNENs. By definition, in MiNENs the two components are presumed to be clonally related. Additional studies are needed to solve this issue.
Role of immunohistochemistry
Traditional markers

β-cat

CD10

Vim

PgR

Cyclin D1

Syn
Additional proposed markers

**E-cadherin** (membrane loss or nuclear expression)


**CD99** (dot-like)


Glutamine synthetase (GLUL)

P504s
TFE3
Jiang Y, et al. *Hum Pathol* 81:166-75, 2018

SOX11
CD138
Handra-Luca A. J Clin Pathol 2018

CD200
Lawlor RT, et al. Virchows Arch 474:105-9, 2019
The sensitivity and specificity of immunohistochemistry is increased using a panel.
Proposed panel

**Positive**
- β-catenin
- Vimentin
- CD99 (dot-like)
- P504s
- TFE3
- CD10

**Negative**
- PDX1
- CK7
- Trypsin
- BCL10
- Chromogranin
- Loss membrane e-cadherin

AR
PgR
Nuclear e-cadherin
Synaptophysin
Diagnostic algorithm

Circumscribed nodule in pancreas

Histology: Pseudopapilla; discohesive cells with nuclear grooves.
- Or Cytology: Branching capillary with attached discohesive cells; “coffee-bean” nuclei; cercariform cells and large cytoplasmic vacuoles.

Histology: Lacks papillary or pseudopapillary structure; nests of polygonal cells with granular chromatin.
- Or Cytology: Loosely cohesive groups/cords of monotonously uniform plasmacytoid cells; round nuclei.

Histology: Mixture of acini, squamoid corpuscles, and sometimes endocrine features; very cellular, uniform epithelial cells in sheets and nests with acini/ducts.

Histology: Solid, nesting, glandular or acinar patterns with sharp luminal space outlines; highly cellular with minimal stroma and no desmoplasia: monotonous, uniform polarized cells with abundant eosinophilic granular cytoplasm.
- Or Cytology: Hypercellular with both epithelial (acinar or undifferentiated) and immature mesenchymal cells.

Histology: Cystic spaces lined by cuboidal epithelial cells, and with clear cytoplasm (glycogen); minimal mucin; myoepithelial layer present; round hyperchromatic nuclei; islets between lobules (radiating pattern); central stellate scar.

Histology: Cystic spaces lined by cuboidal epithelial cells, and with clear cytoplasm (glycogen); minimal mucin; myoepithelial layer present; round hyperchromatic nuclei; islets between lobules (radiating pattern); central stellate scar.

CD99 (dot-like) P504s TFE3

Order β-catenin (N+), CD10 (+), vimentin (+), synaptophysin (partially +), keratin (variably +).

Order synaptophysin, chromogranin, and keratin (all diffusely +).

Elevated pancreatic enzymes; order α1-antichymotrypsin and alpha-fetoprotein (diffusely +), CA and mucin (diffusely + in luminal secretions of small acini), vimentin (+).

Highly elevated pancreatic enzymes; order CK7 and CK19 (+), BCL10 (+), PAS (+, diastase resistant) for granules, trypsin and chymotrypsin (+ in 90%), β-catenin (abnormal nuclear positivity).

Cytology: Prominent acinar formation with numerous single cells; prominent nuclei.

Cytology: Rondoval nuclei; no mitotic figures.

Order EMA (+), low-molecular-weight keratin (+), PAS without diastase (+).

Serous cystadenoma

Pancreatoblastoma

Acinar cell carcinoma

Dinarvand, 2017
Considering the morphology of these two BCL10 and trypsin negative tumors, which IHC panel do you favor for the differential diagnosis?

A. CD99, β-catenin, chromogranin A, p504s
B. CD200, PgR, synaptophysin, CD56
C. Cyclin D1, β-catenin, TFE3, CD200
Poll: Considering the morphology of these two BCL10 and trypsin negative tumors, which IHC panel do you favor for the differential diagnosis?
A. CD99, β-catenin, p504s

B. CD200, PgR, synaptophysin, CD56

C. Cyclin D1, β-catenin, TFE3, CD200

- Lawlor RT, et al. Virchows Arch 474:105-9, 2019
Risk factors for recurrence and prognostic markers

Criteria for malignancy? All SPNs are considered low-grade malignant tumors

Background

➢ With surgical resection 85-90% of patients have excellent prognosis
➢ About 19% of SPNs are metastatic
➢ Metastatic behavior cannot be predicted by traditional morphological parameters of aggressiveness
➢ 3-9% of recurrence after surgery
➢ Long disease-free period for both localized, metastatic and recurrent disease
➢ Metastasis itself does not seem to be strongly correlated with poor outcome
➢ Mostly of few patients who have died of a metastasizing SPN had tumors harbored an undifferentiated component.
Proposed prognostic markers

➢ Age >60
➢ Size >5 cm

No prognostic markers

➢ Gender
➢ Margin status
➢ Site
➢ Symptoms
➢ Histologic parameters
Clinically Aggressive Solid Pseudopapillary Tumors of the Pancreas
A Report of Two Cases With Components of Undifferentiated Carcinoma and a Comparative Clinicopathologic Analysis of 34 Conventional Cases

Leona H. Tong, MD, PhD,* Hakan Aydin, MD,* Murray F. Brennan, MD,† and David S. Klimstra, MD*

Ki67 proliferative index

Ki67 >5% predictor of recurrent disease
No data on survival

✓ Promising marker to be validated
✓ To standardize the method for Ki67 counting

Prognostic value of Ki-67 in solid pseudopapillary tumor of the pancreas: Huashan experience and systematic review of the literature

Feng Yang, PhD, MD, a Xinzhe Yu, MD, a Yun Bao, MD, b Zunguo Du, MD, b Chen Jin, PhD, MD, a and Deliang Fu, PhD, MD, a Shanghai, China

Etiology

Long-Term Follow-Up of Patients With Familial Adenomatous Polyposis Undergoing Pancreaticoduodenal Surgery

Leyo Ruo, M.D., Daniel G. Coit, M.D., Murray F. Brennan, M.D., Jose G. Guillen, M.D., M.P.H.


- Female
- 43-year-old
- Diameter: not reported
- Deceased for CRC metastases after 71 months

Solid Pseudopapillary Neoplasm of the Pancreas Associated with Familial Adenomatous Polyposis

Tadahisa Inoue¹, Yuiji Nishi¹, Fumihiro Okamura¹, Takashi Mizushima¹, Hirotada Nishie¹, Hiroyasu Iwasaki¹, Kaiki Anbe¹, Takanori Ozeki¹, Kenta Kashi¹, Shigeki Fukusada¹, Yuta Suzuki¹, Akira Mizuno², Masaki Kajikawa², Kazuko Watanabe³ and Hitoshi Sano¹


- Male
- In his thirties
- Diameter: 12x10 mm
- Follow-up not reported
Pathogenesis

The pathogenesis is still largely unknown

- Female prevalence
- PgR expression
- AR expression
- Regression of some cases after menopause (Kurokawa 2015)
- Ovarian and testicular cases with identical morphology of SPN
- Lack of pancreatic marker (i.e. PDX1; GCG and PPY2 genes)

**Hypothesis:**

SPN may derive from pluripotent stem cells from the genital ridges that become attached to the pancreas during embryogenesis
Molecular features

- Lack of RAS, TP53, P16/CDKN2A, SMAD4 alterations

\(\beta\)-catenin

- In 90% of SPNs cytoplasmic/nuclear \(\beta\)-catenin expression is related to mutation of exon 3 of CTNNB1
- In 10% of SPN the cause of cytoplasmic/nuclear \(\beta\)-catenin expression is unclear
- \(\beta\)-catenin escapes intracytoplasmic phosphorylation and translocates into the nucleus where activates the transcription of oncogenes c-myc and cyclin D1, and activates the Wnt/\(\beta\)-catenin signaling pathway.

However, there is a very low proliferation rate probably related to an unexplained and not clear overexpression of p21 and p27.
Mutation in \textit{CTNNB1} gene explains:

- Cyclin D1 overexpression
- Glutamine synthetase

Alterations in the Wnt pathway may explain:

- TFE3 expression, because it contains GSK3 phosphorylation site. It cannot be phosphorylated by GSK3 when the Wnt pathway is activated

\begin{center}
\includegraphics[width=\textwidth]{image}
\end{center}
CD138 and the Wnt pathway


Handra-Luca A. *J Clin Pathol* 2018
Additional molecular alterations

Possible sensitivity to afatinib or osimertinib
Additional molecular alterations

Gene expression profiling provides insights into the pathways involved in solid pseudopapillary neoplasm of the pancreas

Catherine Caussé1,2, Anne Audibert3, Francis Letoumeau1,2, Virginie Aubert1,2, Frédéric Bavot1,2, Nicolo Cagnard1,2, Brigitte Redrenn1,2, Pascal Viel1,2, Marie-Claire Victor-Lemus1,2, Christine Ferrel1,2 and Benoît Trémolières1,2

Table 1. List of Wnt/ß-catenin-related genes with altered expression in SPN

<table>
<thead>
<tr>
<th>Official symbol</th>
<th>Gene name</th>
<th>Fold change in SPN vs. normal pancreas</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP1</td>
<td>WNT inhibitory factor 1</td>
<td>56.92</td>
<td>1.22E-08</td>
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<td>EDN3</td>
<td>Endothelin 3</td>
<td>52.20</td>
<td>9.98E-09</td>
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<td>TBK3</td>
<td>T-box 2 (T-cell specific, HMG-box)</td>
<td>35.09</td>
<td>3.86E-08</td>
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<td>SPS</td>
<td>Spalt transcription factor</td>
<td>31.56</td>
<td>3.02E-07</td>
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<td>FZD10</td>
<td>Frizzled homologue 10 (Drosophila)</td>
<td>18.42</td>
<td>6.52E-05</td>
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<tr>
<td>DHX4</td>
<td>Diklopf homologue 4 (Drosophila)</td>
<td>13.01</td>
<td>9.86E-06</td>
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<tr>
<td>AKX2</td>
<td>Avian (Drosophila)</td>
<td>12.79</td>
<td>1.98E-05</td>
</tr>
<tr>
<td>TCF7</td>
<td>Transcription factor 7 (T cell-specific, HMG-box)</td>
<td>6.74</td>
<td>0.000633</td>
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<tr>
<td>Fzd7</td>
<td>Frizzled homologue 7 (Drosophila)</td>
<td>6.11</td>
<td>0.000243</td>
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<td>JAG1</td>
<td>Jagged 1 (Alagille syndrome)</td>
<td>4.82</td>
<td>0.000099</td>
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<tr>
<td>CSG2</td>
<td>Versican</td>
<td>4.67</td>
<td>0.000533</td>
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<td>NOTUM</td>
<td>Notum (Drosophila)</td>
<td>3.90</td>
<td>0.00164</td>
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<tr>
<td>Ctnnb1</td>
<td>Catenin (Drosophila-associated protein, A1, B1, K42a)</td>
<td>3.20</td>
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<tr>
<td>Dvl2</td>
<td>Dishevelled, dsh homologue 2 (Drosophila)</td>
<td>2.78</td>
<td>0.0083</td>
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Table 2. List of Notch-related genes with altered expression in SPN

<table>
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<th>Official symbol</th>
<th>Gene name</th>
<th>Fold change in SPN vs. normal pancreas</th>
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</thead>
<tbody>
<tr>
<td>HEY1</td>
<td>hairy-enhancer-of-split related with YRPW motif 1</td>
<td>47.27</td>
<td>3.44E-07</td>
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<td>JAG1</td>
<td>Jagged 1 (Alagille syndrome)</td>
<td>4.82</td>
<td>0.000099</td>
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<tr>
<td>HEY2</td>
<td>hairy-enhancer-of-split related with YRPW motif 2</td>
<td>3.88</td>
<td>0.00114</td>
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<td>NOTCH2</td>
<td>Notch homologue 2 (Drosophila)</td>
<td>3.80</td>
<td>0.0171</td>
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<tr>
<td>DTX3</td>
<td>Delta 3 homologue (Drosophila)</td>
<td>2.52</td>
<td>0.00256</td>
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<td>LNX1</td>
<td>Lunatic fringe</td>
<td>0.15</td>
<td>0.0000349</td>
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<tr>
<td>SEL1</td>
<td>Seli-1 suppressor of lin-12-like (Ctenorhabditis elegans)</td>
<td>0.15</td>
<td>5.32E-05</td>
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</table>
mRNA

microRNA

Table 2. List of Wnt(beta-catenin, H)

<table>
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<th>Official symbol</th>
<th>Gene name</th>
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<td>Wnt signaling pathway</td>
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<td>DKK4</td>
<td>dickkopf hom</td>
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<tr>
<td>WIF1</td>
<td>WNT inhibitor</td>
</tr>
<tr>
<td>NKD1</td>
<td>naked cuticle</td>
</tr>
<tr>
<td>AXIN2</td>
<td>axin 2</td>
</tr>
<tr>
<td>FZD7</td>
<td>frizzled hom</td>
</tr>
<tr>
<td>WNT2B</td>
<td>wingless-type</td>
</tr>
<tr>
<td>RUVBL1</td>
<td>RuvB-like 1</td>
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<tr>
<td>WNT3A</td>
<td>wingless-type</td>
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<tr>
<td>NKD2</td>
<td>naked cuticle</td>
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<td>MAPK7</td>
<td>mitogen-activated</td>
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<tr>
<td>TCF7</td>
<td>transcription factor</td>
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<tr>
<td>PPP1R3E</td>
<td>protein phosphatase</td>
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<td>FZD8</td>
<td>frizzled hom</td>
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<td>NFAT5</td>
<td>nuclear factor</td>
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<tr>
<td>CTNNB1</td>
<td>catenin (cad)</td>
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<td>CCND3</td>
<td>cyclin D3</td>
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<td>SMAD3</td>
<td>SMAD family</td>
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<td>SKP1</td>
<td>S-phase kinase</td>
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<td>SLIT4</td>
<td>seven in abs</td>
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<td>DVL2</td>
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<td>BTRC</td>
<td>beta-transducin</td>
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<td>NFAIC3</td>
<td>nuclear factor</td>
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<td>calcineurin</td>
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<td>Hedgehog signaling pathway</td>
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<td>BMP7</td>
<td>bone morpho</td>
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<td>ZIC2</td>
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<td>GLI2</td>
<td>GLI family z</td>
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<tr>
<td>GLI3</td>
<td>GLI family z</td>
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<td>Shh</td>
<td>suppressor c</td>
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<td>Androgen receptor signaling path</td>
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<td>AR</td>
<td>androgen receptor</td>
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<td>MED10</td>
<td>mediator c</td>
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<td>MED17</td>
<td>mediator c</td>
</tr>
<tr>
<td>DAXX</td>
<td>death-domain</td>
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<tr>
<td>THRAP3</td>
<td>thyroid hormone</td>
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Validation

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<th>qRT-PCR</th>
<th>WB</th>
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Abbreviations: HED, Hedgehog; AR, androgen receptor.
Molecular alterations associated with metastases of solid pseudopapillary neoplasms of the pancreas

Mutation legend:
- Missense
- Frame-shift
- P = Primary SPN
- L = Liver metastasis

B

CTNNB1
KDCA6A
BAP1
TET1
SMAD4
TP63
FLT1
FGFR3

P | L
P | L
P | L
P | L
P | L
P | L
P | L

C

Number of alterations

\( m = 1 \)  \( m = 2 \)  \( m = 3 \)  \( m = 1 \)

SPN11  SPN12  SPN13  SPN14  SPN56

\( m = \) metastasis
- Progresor
- Founder

\( m = 1 \)  \( m = 2 \)  \( m = 3 \)

SPN11  SPN12  SPN13  SPN14  SPN56

\( m = \) metastasis
- Progresor
- Founder
Why SPNs are poorly cohesive?

Mechanisms underlying abnormal cell-cell junctions:

- Mutation of \textit{CTNNB1} with loss of \( \beta \)-catenin membrane location
- Loss of e-cadherin membrane expression probably mediated by p120 catenin alteration

Proteomic Analysis of Solid Pseudopapillary Tumor of the Pancreas Reveals Dysfunction of the Endoplasmic Reticulum Protein Processing Pathway*

Yi Zhu, Hong Xu, Hao Chen, Junjie Xie, Minmin Shi, Baiyong Shen, Xiaoxing Deng, Chao Liu, Xi Zhan, and Chenghong Peng

<table>
<thead>
<tr>
<th>Protein ID</th>
<th>Gene</th>
<th>Protein</th>
<th>Fold change (N/T)</th>
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<tbody>
<tr>
<td>Q4QZC0</td>
<td>HLA-A</td>
<td>MHC class I antigen (Fragment)</td>
<td>0.47</td>
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<tr>
<td>E6WV9</td>
<td>HLA-B</td>
<td>MHC class I antigen (Fragment)</td>
<td>0.52</td>
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<tr>
<td>K7FP40</td>
<td>CLDN7</td>
<td>Claudin-7 (Fragment)</td>
<td>2.10</td>
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<tr>
<td>D6R3526</td>
<td>VCAN</td>
<td>Versican core protein (Fragment)</td>
<td>0.32</td>
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<tr>
<td>O00501</td>
<td>CLDN5</td>
<td>Claudin-5</td>
<td>0.24</td>
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<td>H7FDX6</td>
<td>NCAM1</td>
<td>Neural cell adhesion molecule 1</td>
<td>0.59</td>
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<td>Q19897</td>
<td>HDPAD2</td>
<td>Hla-dedeha partial alpha 2 domain (extracellular domain)</td>
<td>0.64</td>
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<td>1.96</td>
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<td>Q9Y5Z2</td>
<td>JAM</td>
<td>Junction adhesion molecule</td>
<td>1.81</td>
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<td>B3GN61</td>
<td>CDH1</td>
<td>Truncated E-cadherin</td>
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<td>AMN8W1</td>
<td>CD99</td>
<td>CD99 antigen</td>
<td>1.78</td>
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<td>B4D5E1</td>
<td>SDC</td>
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<td>Myosin-1</td>
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<td>P63096</td>
<td>GNA11</td>
<td>Guanine nucleotide-binding protein G(i) subunit alpha-1</td>
<td>0.59</td>
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<td>Q6P2M7</td>
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<td>Gcinlin</td>
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<td>Ras-related protein Rab-3B</td>
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<td>P13955</td>
<td>MYH8</td>
<td>Myosin-8</td>
<td>0.63</td>
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<tr>
<td>B4DH56</td>
<td>MPOZD</td>
<td>cDNA FLJ54707, highly similar to Multiple PDZ domain protein</td>
<td>1.66</td>
</tr>
</tbody>
</table>
Take home messages

- Rare neoplasm but increasing in incidence
- Pediatric cases
- More frequent in young women
- Typical cyto-histological features
- Differential diagnosis with NET and ACC
- IHC: β-catenin, CD10, vimentin, CD99, P504s, TFE3
- Wnt pathway
- New molecular markers involving NOTCH, Hedgehog, and AR pathways