Korean Pathologists Association of North America
(KOPANA)
2024 Virtual Spring Seminar

# Beyond the surface: Exploring Head and neck cancer through molecular pathology

Seoul National University Hospital
Seoul National University College of Medicine
Jiwon Koh

SNUH

Education:

- Medical School: Seoul National University
- Residency: Seoul National University Hospital
- Fellowship: Seoul National University Hospital

Current Position & Institution:

Clinical Assistant Professor

Department of Pathology

Seoul National University Hospital

Subspecialty area:

Breast, Head and Neck, Cardiovascular pathology

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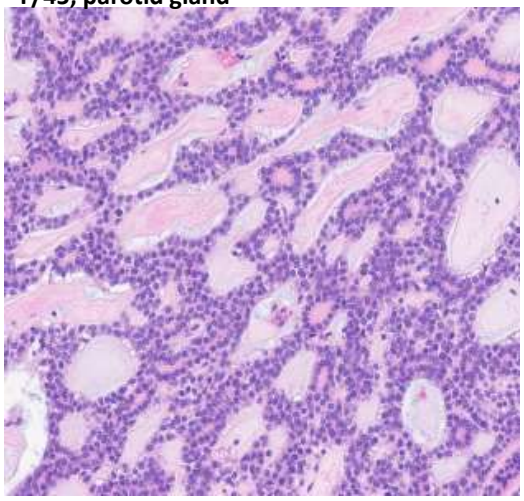
Histopathology
Molecular pathology

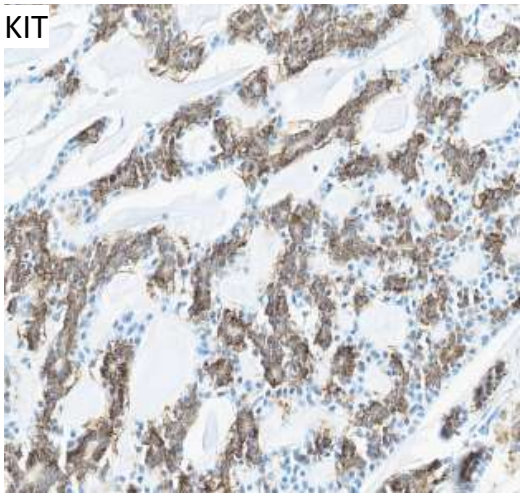
- Adenoid cystic carcinoma
- Mucoepidermoid carcinoma
- Salivary duct carcinoma
- Acinic cell carcinoma
- Secretory carcinoma
- Basal cell adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Carcinoma ex pleomorphic adenoma
- Myoepithelial carcinoma
- Hyalinizing clear cell carcinoma

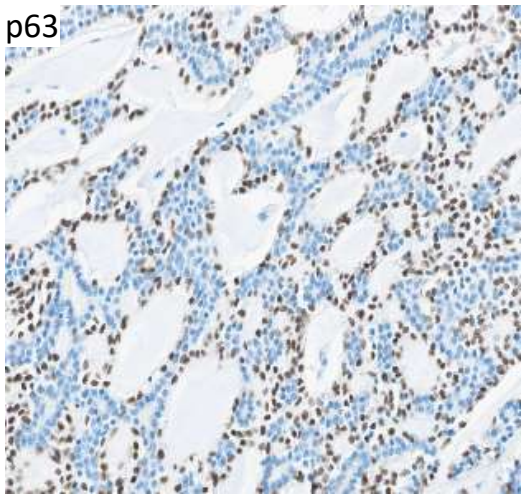
# Adenoid cystic carcinoma (AdCC)

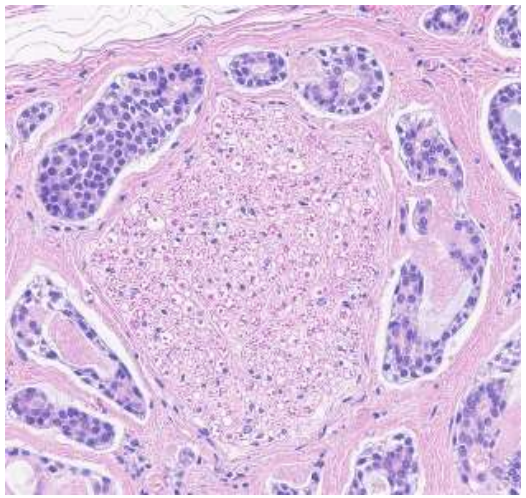
- **Clinical features**
  - 25% of all primary salivary carcinomas; median age of 60 years
  - 60% in major salivary gland (parotid, submandibular); 30% in minor salivary gland (palate)
  - Neural symptoms are common
  - Prolonged clinical course with frequent local recurrences, late onset of metastases
    - Median OS after distant metastasis : 36 months
- **Histopathology**
  - Two cell component
    - Ductal cells: eosinophilic cytoplasm and uniform round nuclei (CK7+, KIT+)
    - Myoepithelial cells: clear cytoplasm and hyperchromatic angular nuclei (p63+, p40+, calponin+, α-SMA+)

F/45; parotid gland



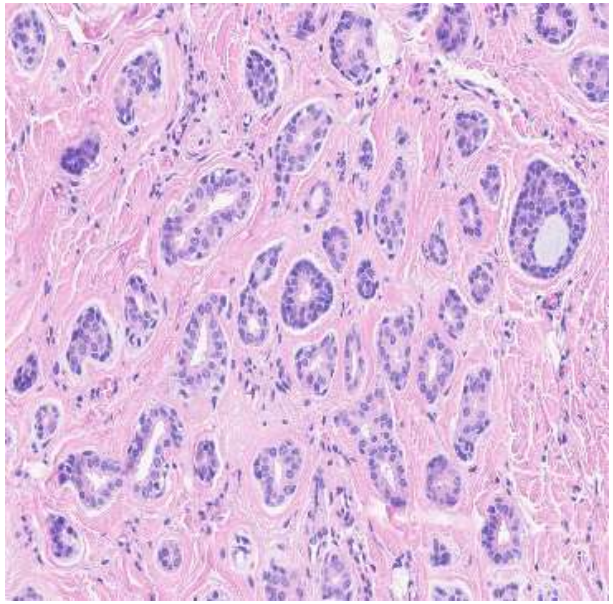


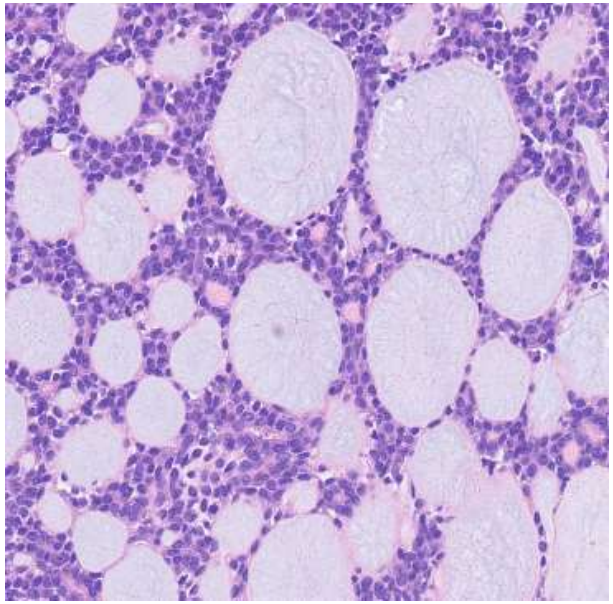



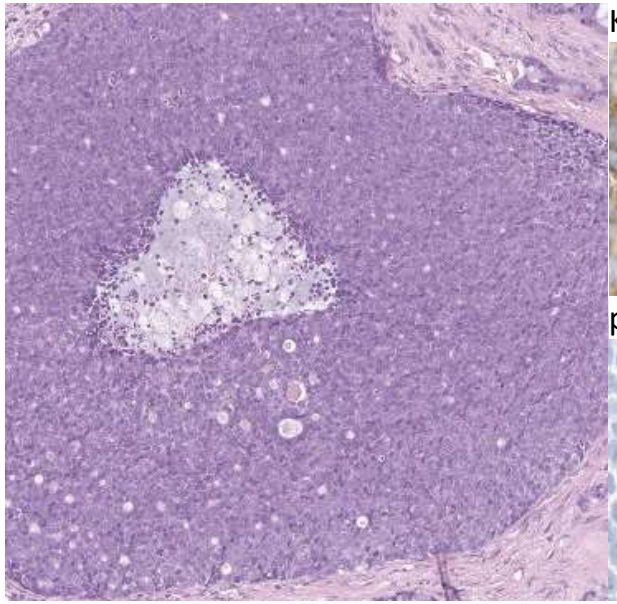



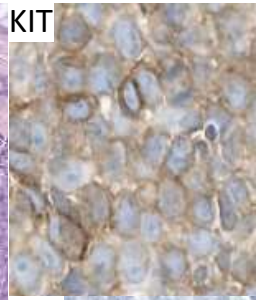
# Adenoid cystic carcinoma (AdCC)

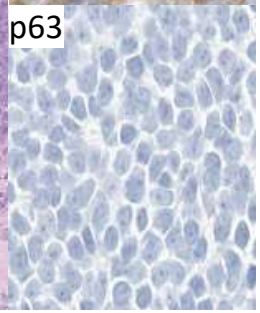
- **Histopathology**
  - Growth patterns
    - Tubular: well-formed ducts and tubules lined with luminal ductal and abluminal myoepithelial cells
    - Cribriform: most frequent; nests of tumor cells with microcystic spaces, filled with hyaline/basophilic material
    - Solid: tumour sheets composed of basaloid cells lacking tubular or cribriform
      - >30% solid component → more aggressive clinical course
  - High-grade transformation
    - Pleomorphic, mitotically active high-grade carcinoma component → negative for myoepithelial markers





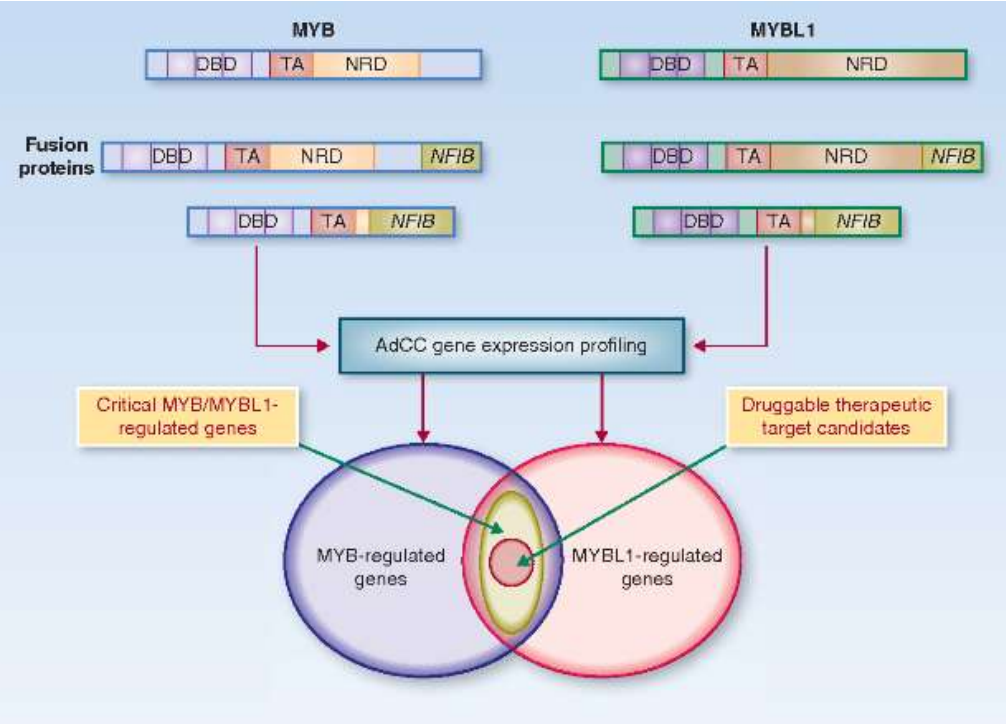




# Adenoid cystic carcinoma (AdCC)

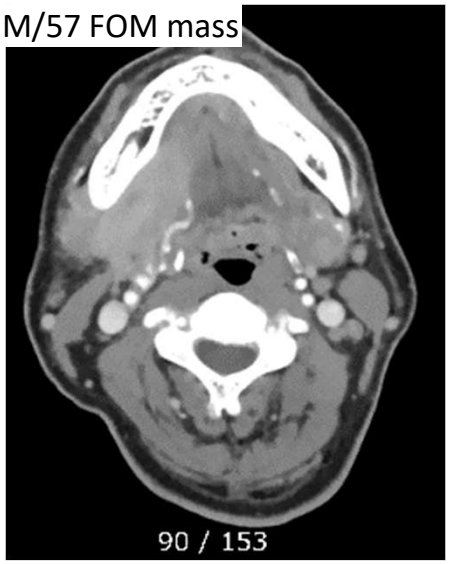
- **Molecular pathology**
  - *MYB*::*NFIB* fusion (29-86%); *MYBL1*::*NFIB* fusion (9-14%) → each mutually exclusive
    - *MYB*: transcription factor regulating proliferation and differentiation of hematopoietic, colonic, and neural progenitor cells
    - *NFIB*: transcription factor nuclear factor I/B protein → key regulator of hematopoietic and epithelial cells
    - *MYB*::*NFIB* → overexpression of truncated MYB protein d/t loss of negative regulatory elements
  - Rarer fusions including *MYB::PDCD1LG2, MYB::EFR3A, MYBL1::RAD51B, MYBL1::YTHDF3, NFIB::AIG1* fusions

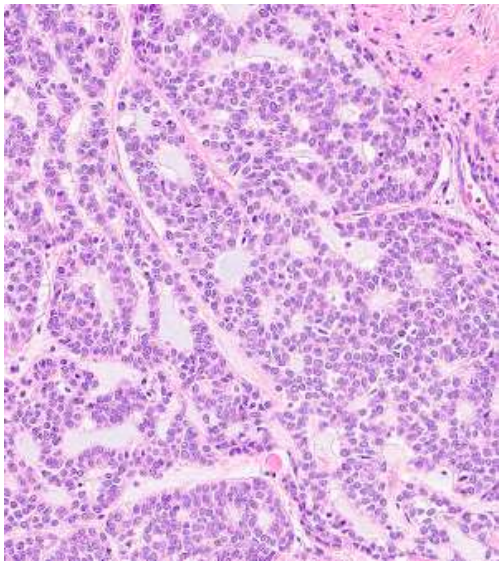



Gonda, Cancer Discov. 2016

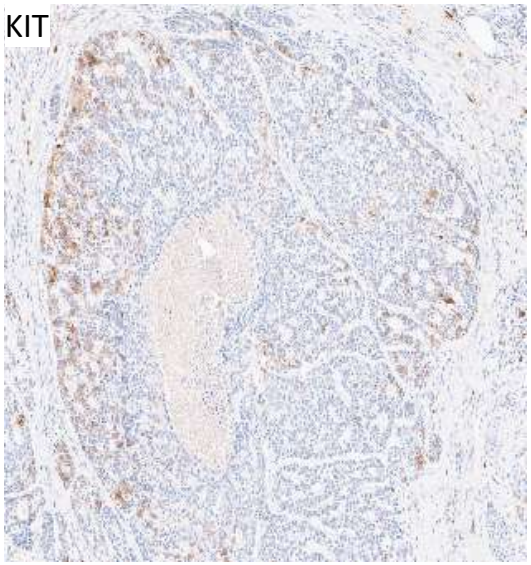
# Adenoid cystic carcinoma (AdCC)

M/57 FOM mass

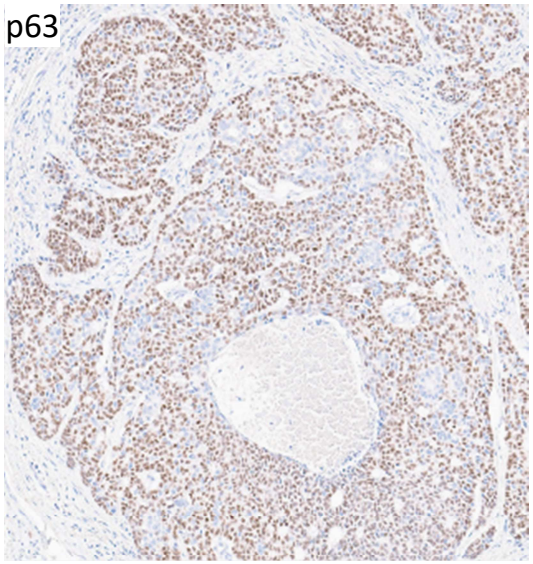


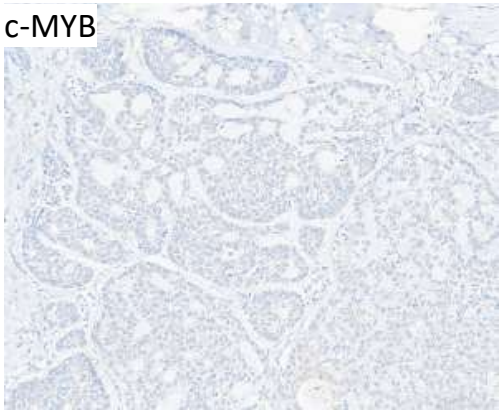
KIT



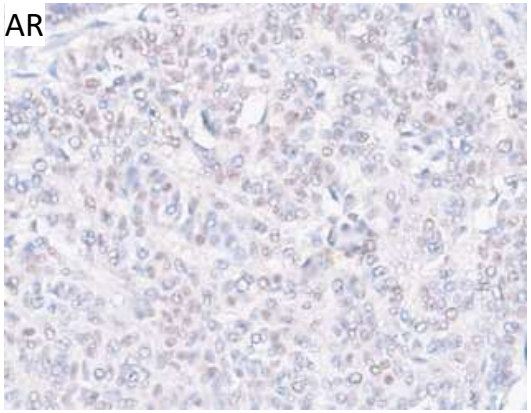
p63



c-MYB



AR



# Adenoid cystic carcinoma (AdCC)

SNUH 서울대학교병원

## Cancer panel - Report

FIRST-Cancer Panel / Molecular Genetic Testing

FiRST CANCER PANEL

**▣ Result of Actionable Gene Mutation Analysis**

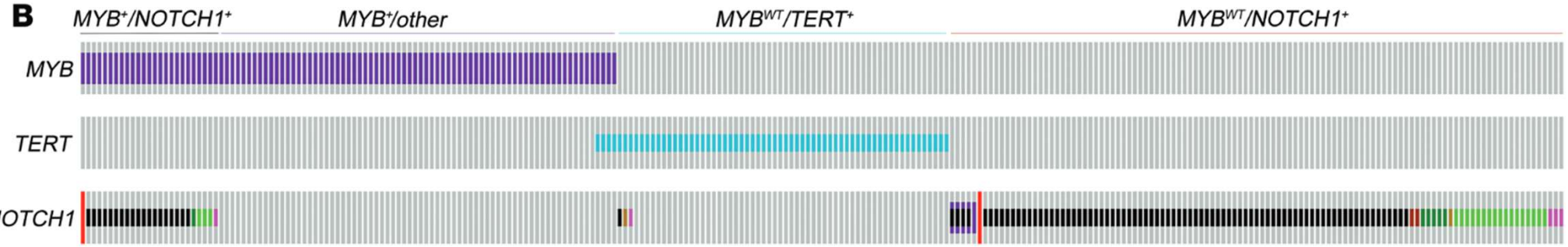
-SNV/INDEL

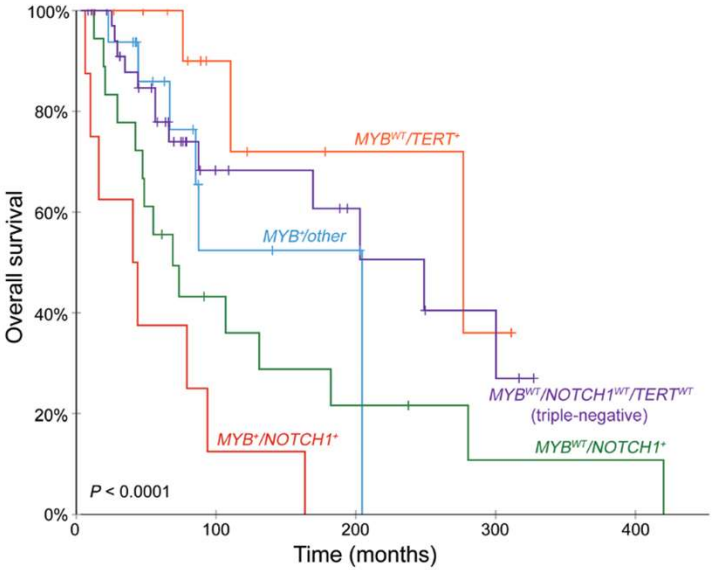
| Gene | Chr | Position | Refseq | Exon | AA | CDS | %VAF | Alt | Total | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| Not detected | | | | | | | | | | |

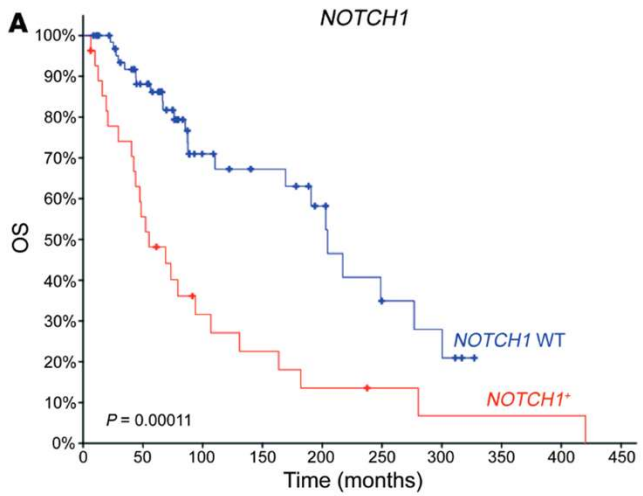
- Fusion

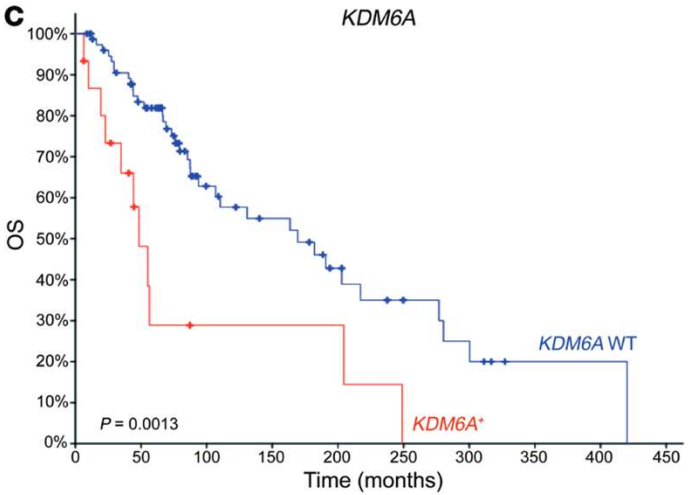
| Fusion Gene | Cytoband1 | Cytoband2 | DNA.Evidence (Span/Split) | RNA.Evidence (Span/Split) | Transcript1 | Transcript2 | Last Observed | First Observed | Tier |
|---|---|---|---|---|---|---|---|---|---|
| MYB->NFIB | 6q23.3 | 9p23-p22.3 | 0/0 | 0/107 | NM_005375 | NM_005596 | EXON_14 | EXON_9 | D |

# Adenoid cystic carcinoma (AdCC)



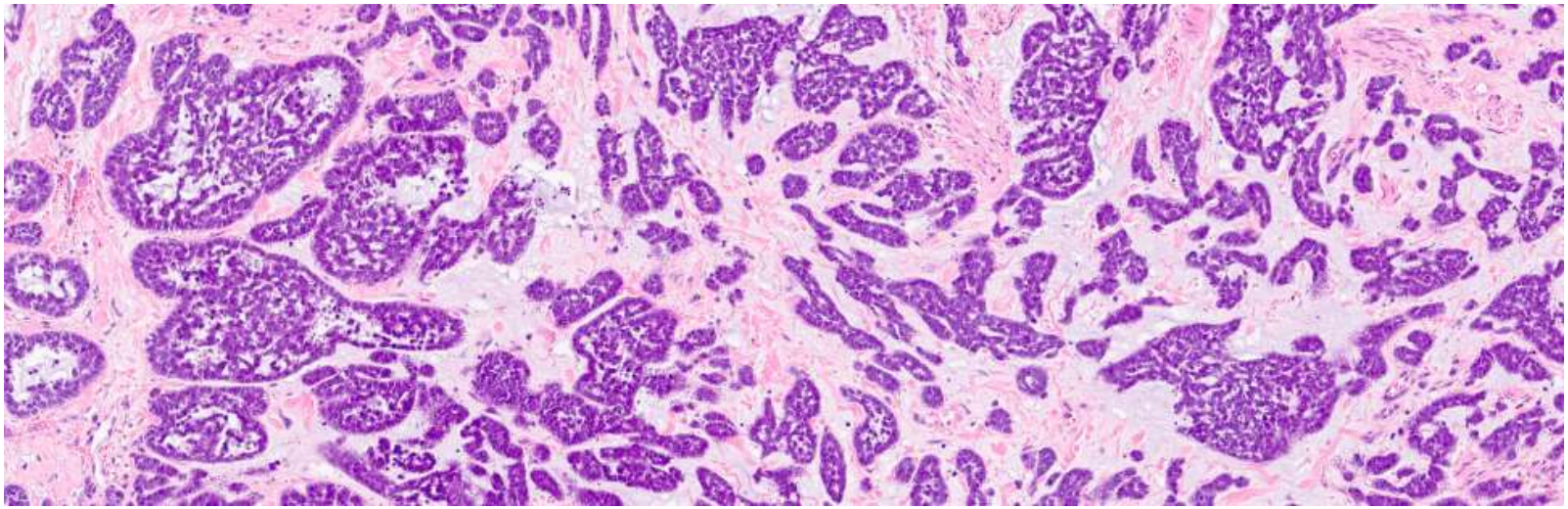




Ho, J Clin Invest. 2019

# Adenoid cystic carcinoma (AdCC)

F/39; lacrimal gland



-SNV/INDEL

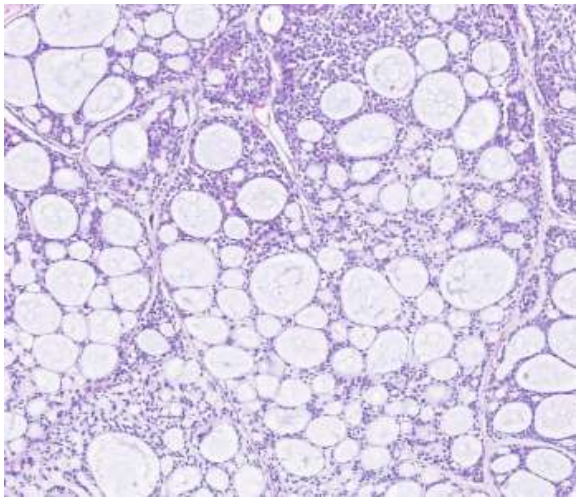
| Gene | Chr | Position | Refseq | Exon | AA | CDS | %VAF | Alt | Total | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| NOTCH1 | chr9 | 139390793 | NM_017617.3 | 34 | p.Ser2467fs | c.7363_7397dupACTATTCTGCCCCAGGAGAGCCCCGCCCTGCCCAC | 24.50 | 172 | 702 | D |
| NOTCH1 | chr9 | 139401189 | NM_017617.3 | 23 | p.Glu1294fs | c.3857_3879dupAGCGCGTCAATGACTTCCACTGC | 11.54 | 239 | 2071 | D |
| CREBBP | chr16 | 3817868 | NM_004380.2 | 16 | p.Glu1035* | c.3103G>T | 33.59 | 174 | 518 | D |

- Fusion

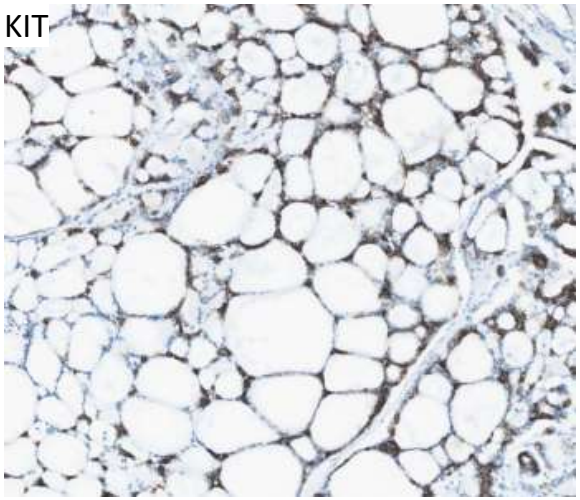
| Fusion Gene | Cytoband1 | Cytoband2 | DNA.Evidence (Span/Split) | RNA.Evidence (Span/Split) | Transcript1 | Transcript2 | Last Observed | First Observed | Tier |
|---|---|---|---|---|---|---|---|---|---|
| MYB->NFIB | 6q23.3 | 9p23-p22.3 | 0/0 | 9/777 | NM_005375 | NM_001369461 | EXON 14 | EXON 10 | D |

# Adenoid cystic carcinoma (AdCC)

M/65
FOM mass



KIT



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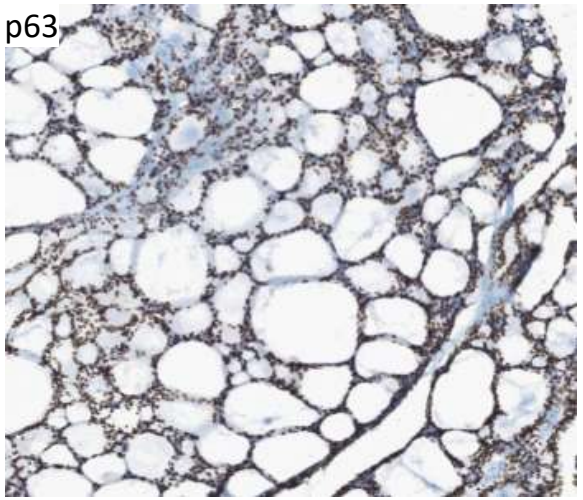


-SNV/INDEL

| Gene | Chr | Position | Refseq | Exon | AA | CDS | %VAF | Alt | Total | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| Not detected | | | | | | | | | | |

- Fusion

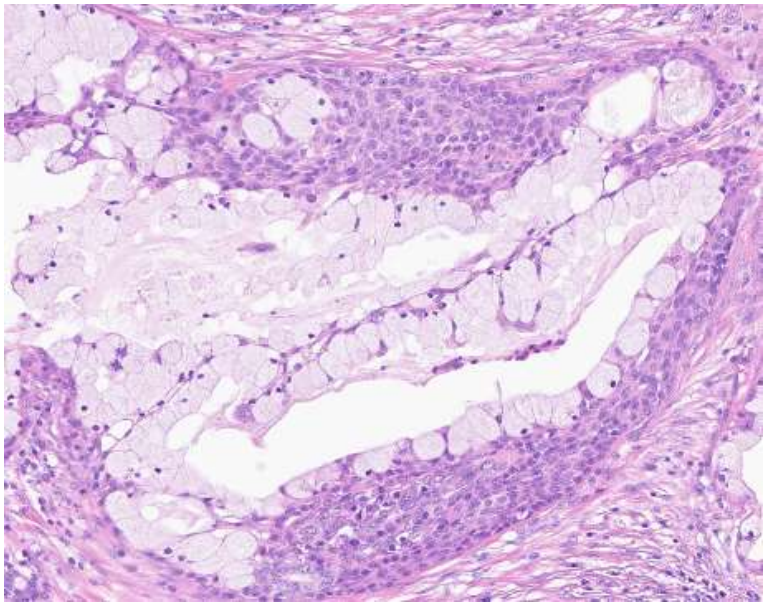
| Fusion Gene | Cytoband1 | Cytoband2 | DNA.Evidence (Span/Split) | RNA.Evidence (Span/Split) | Transcript1 | Transcript2 | Last Observed | First Observed | Tier |
|---|---|---|---|---|---|---|---|---|---|
| Not detected | | | | | | | | | |

-CNV

| Gene | Chr | Start | End | CNV | AvgL2R | DelR | NeutralR | AmpR | CN | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| PDGFRA | chr4 | 55124713 | 55161605 | Amplification | 1.957 | 0.0 | 0.0 | 1.0 | 11 | D |
| KIT | chr4 | 55523974 | 55604878 | Amplification | 2.112 | 0.0 | 0.0 | 1.0 | 11 | D |
| KDR | chr4 | 55945938 | 55991666 | Amplification | 2.081 | 0.0 | 0.0 | 1.0 | 10 | D |

# Mucoepidermoid carcinoma (MEC)

- **Clinical features**
  - Childhood to elderly (median age of 45) / M:F 1:1.1-1.5
  - About 50% in major salivary gland (parotid > submandibular gland > sublingual gland)
- **Histopathology**
  - Malignant salivary gland neoplasm characterized by mucous, intermediate and epidermoid (squamoid) tumor cells forming cystic and solid growth patterns
    - Mucous cells: lining cystic spaces; intracytoplasmic mucicarmine or PAS staining with diastase resistance
    - Overt keratinization is rare

# Mucoepidermoid carcinoma (MEC)

- **Histopathology – grading**

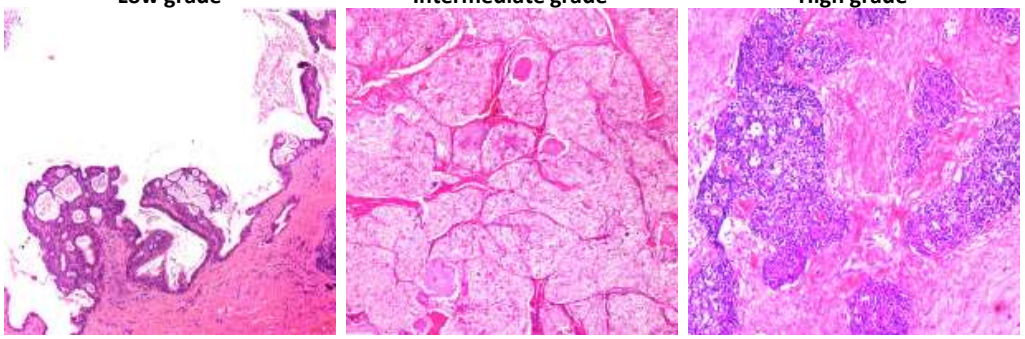
**Table 1.** AFIP, Brandwein, and modified Healy grading systems (modified from Seethala)[5]

| AFIP | | Brandwein | | Modified Healy |
|---|---|---|---|---|
| Intracystic component <20% | +2 | Intracystic component <25% | +2 | Low grade:<br>• Macrocysts and microcysts<br>• Differentiated mucin with 1/1 mucin/epidermoid with minimal to moderate intermediate cells<br>• Absent to minimal pleomorphism and rare mitoses<br>• Broad front or circumscribed borders<br>• Pools of extravasated mucin |
| Neural invasion | +2 | Neural invasion | +2 | |
| | | Tumour invades in small nests | +2 | |
| Mitosis (≥4/10HPFs) | +3 | Mitosis (≥4/10HPFs) | +3 | |
| Necrosis | +3 | Necrosis | +3 | Intermediate grade:<br>• Solid nests, few microcysts, no macrocysts<br>• Mild to moderate pleomorphism, few mitoses, prominent nuclei and nucleoli<br>• Invasive, well defined and uncircumscribed with fibrosis separating tumour nests<br>Peripheral chronic inflammation |
| | | Vascular invasion | +3 | |
| Anaplasia | +4 | Nuclear atypia | +3 | |
| | | Bone invasion | +3 | |
| Grade | Score | Grade | Score | High grade:<br>• Predominately solid with no macrocysts<br>• Tumour cells range from poorly differentiated to epidermoid and intermediate cells to ductal cells adenocarcinoma<br>• Marked pleomorphism and easily found mitoses<br>• Perineural and vascular invasions, soft tissue invasion, and desmoplasia<br>• Less common peripheral chronic inflammation |
| Low grade | 0–4 | Low grade | 0 | |
| Intermediate grade | 5–6 | Intermediate grade | 2–3 | |
| High grade | ≥7 | High grade | ≥4 | |

**Table 2.** Our own (Memorial Sloan-Kettering Cancer Center) grading system

| | Low grade | Intermediate grade | High grade |
|---|---|---|---|
| Predominant growth pattern | Cystic | Predominantly solid | Any (usually solid) |
| Infiltration | Well circumscribed borders | Well circumscribed or infiltrative borders | Any (usually infiltrative borders) |
| Mitosis | 0–1/10 HPF | <4/10 HPFs | ≥4/10 HPFs |
| Tumour necrosis | Absent | Absent | Present |

**Low grade** | **Intermediate grade** | **High grade**



Circumscribed
Cystic
Groups of mucous cells

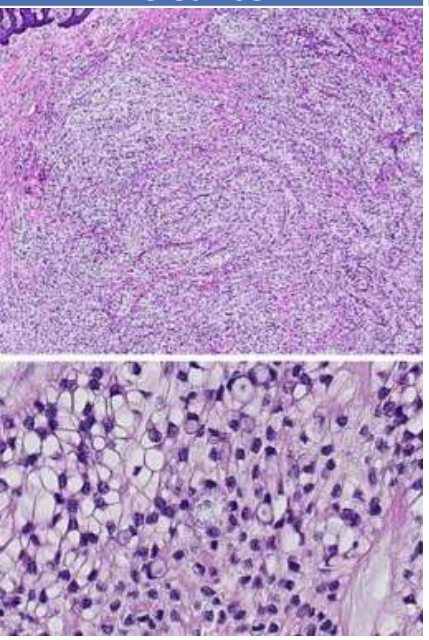
Solid
Fewer mucous cells
Pleomorphic, mitosis, necrosis
Perineural, LVI, bony invasion

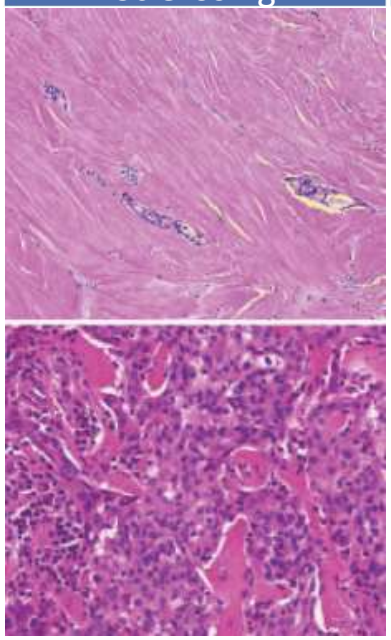
Katabi, Histopathology, 2014

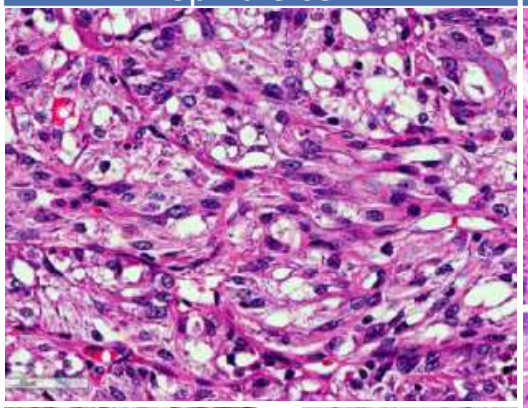
# Mucoepidermoid carcinoma (MEC)

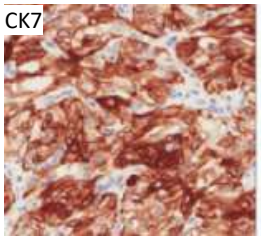
- **Histopathology – variants**

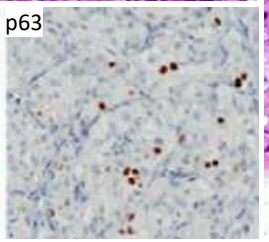
| Clear cell | Sclerosing | Spindle cell | Ciliated | Warthin-like |
|---|---|---|---|---|

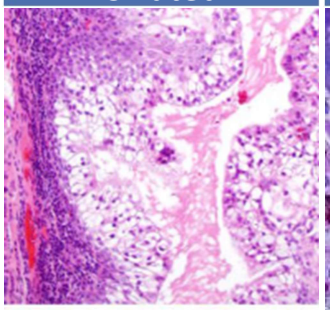


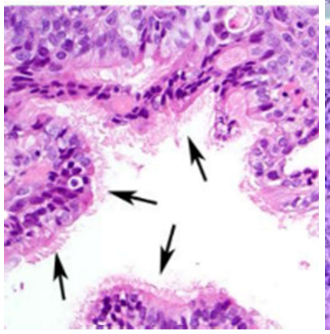


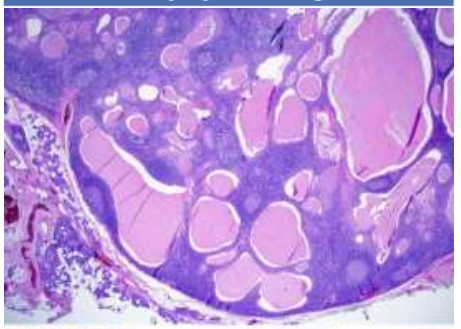


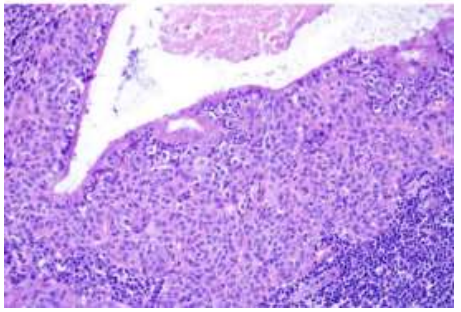




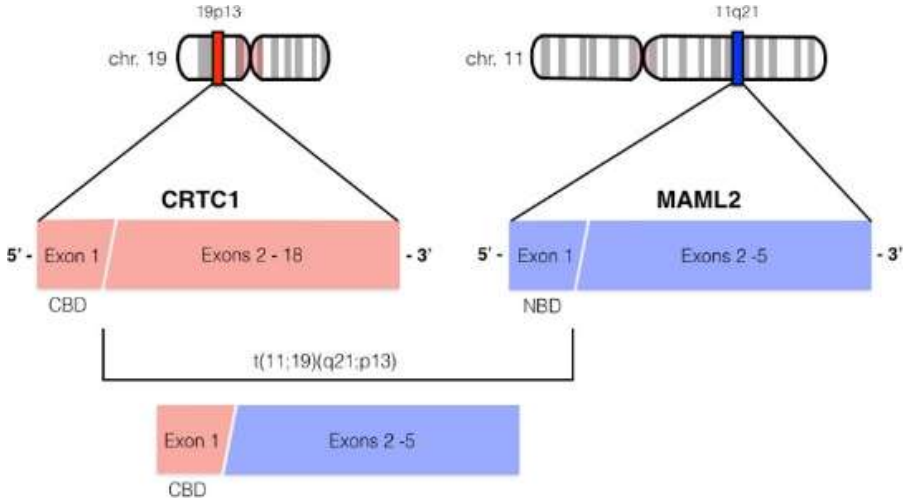





Tajima, Med Mol Morphol. 2015
Goh, Int J Surg Pathol. 2017
Yabuki, Int J Surg Pathol. 2017
Bishop, Am J Surg Pathol JSP, 2019
Skalova, Am J Surg Pathol. 2020

# Mucoepidermoid carcinoma (MEC)

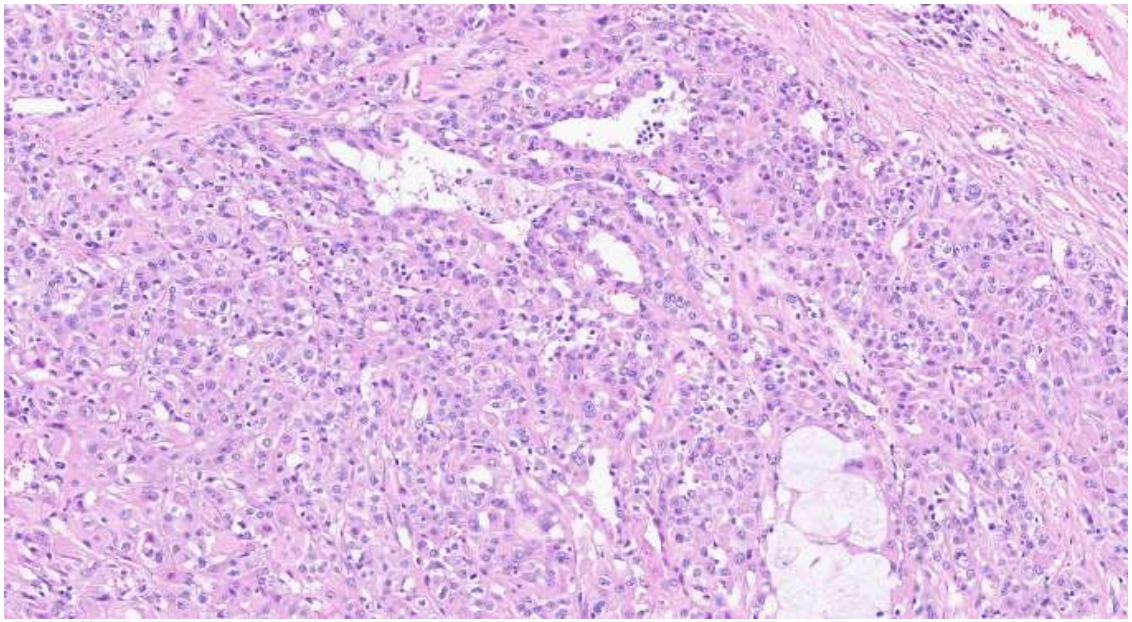
- **Molecular pathology**
  - t(11;19)(q21;p13) *CRTC1::MAML2* fusion
    - Present in 55-88% of MECs
    - *CRTC1* exon 1 ~ *MAML2* exon 2 to 5
    - CREB-binding domain of *CRTC1* replace Notch-binding domain of *MAML2*
  - Minor fusions including *CRTC1::MAML2; EWSR1::POU5F1*
  - ***CRTC1/3-MAML2* as prognostic biomarker**
    - Favorable prognosis
    - Mostly seen in younger patients with low-intermediate grade MEC

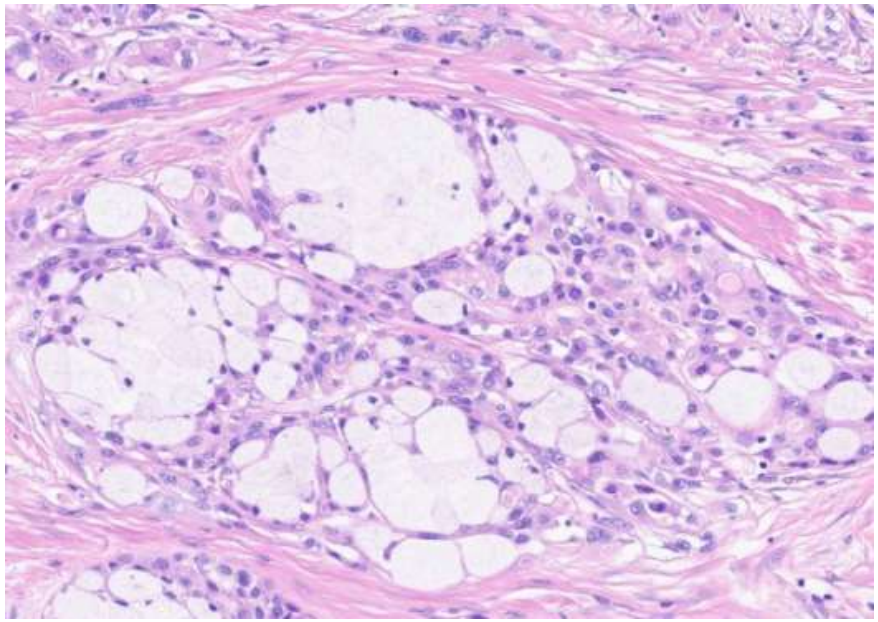



Perez-de-Oliveira, J Oral Pathol Med. 2020

# Mucoepidermoid carcinoma (MEC)

F/72; Tongue





-SNV/INDEL

| Gene | Chr | Position | Refseq | Exon | AA | CDS | %VAF | Alt | Total | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| BAP1 | chr3 | 52437795 | NM_004656.3 | 13 | p.Gln456* | c.1366C>T | 5.11 | 97 | 1900 | D |

- Fusion

| Fusion Gene | Cytoband1 | Cytoband2 | DNA.Evidence (Span/Split) | RNA.Evidence (Span/Split) | Transcript1 | Transcript2 | Last Observed | First Observed | Tier |
|---|---|---|---|---|---|---|---|---|---|
| CRTC1->MAML2 | 19p13.11 | 11q21 | 0/0 | 1/14 | NM_001098482 | NM_032427 | EXON_1 | EXON_2 | D |

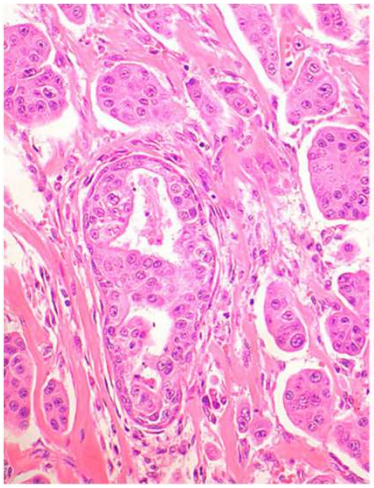
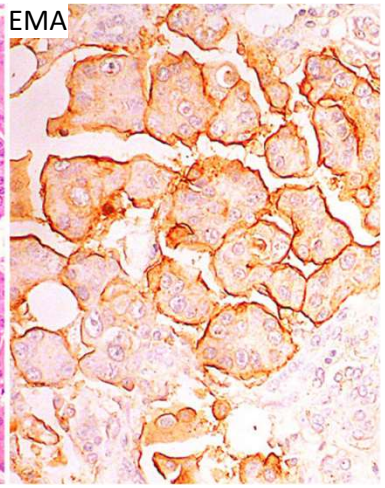
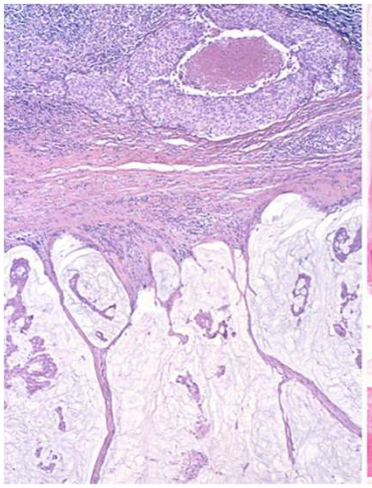
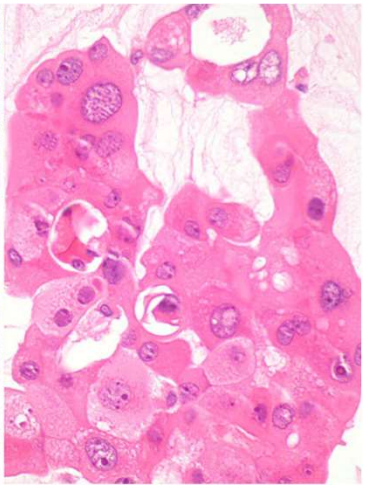
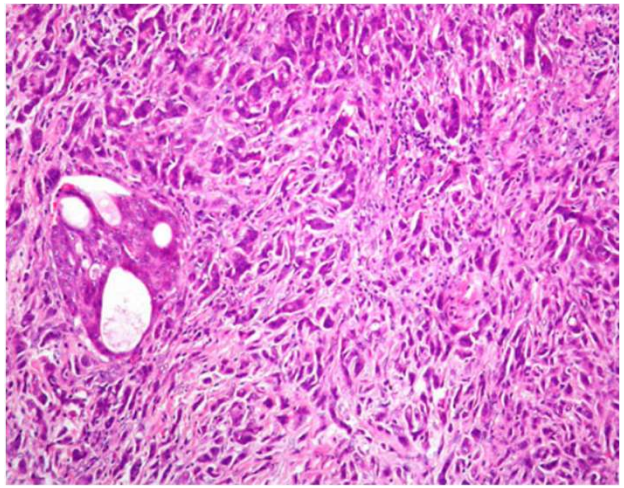
# Salivary duct carcinoma (SDC)

- **Clinical features**
  - Rapidly growing high-grade tumor, mostly involving major salivary gland
  - Distinct male predilection with peak incidence in the fifth to seventh decades of life

- **Histopathology**
  - Complex solid, cribriform, and papillary-cystic architecture with frequent comedo-necrosis
  - Large pleomorphic nuclei with coarse chromatin and prominent nucleoli
  - Abundant eosinophilic, typically apocrine cytoplasm
  - Lymphovascular and perineural invasion are common
  - IHC
    - AR expression in 90%
    - Diffuse and strong immunoreactivity for ERBB2/HER2 is identified in about 30%
    - CK7+, S100-, SOX10-

# Salivary duct carcinoma (SDC)

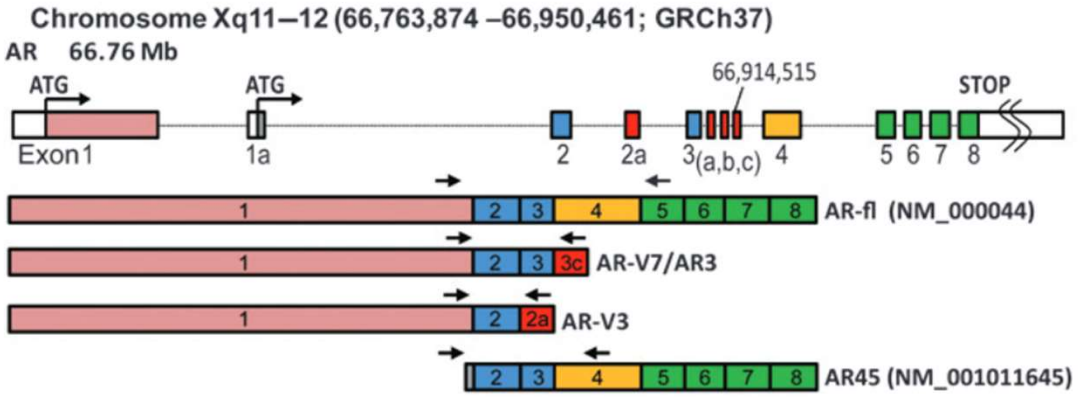
- **Histopathology – variants**

| Micropapillary | | Mucin-rich | | Mucin-rich |
|---|---|---|---|---|
|  |  EMA |  |  |  |

Simpson, Head Neck Pathol. 2013

# Salivary duct carcinoma (SDC)

- **Molecular pathology**
  - AR
    - chromosome Xq11-12
    - Copy number gain, mutation, alternative splicing




- Others

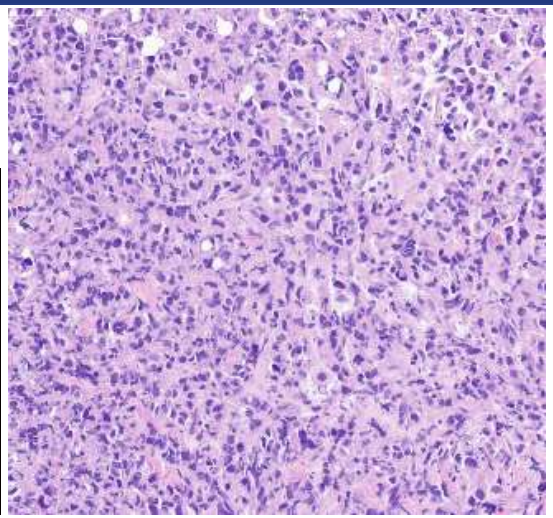
**TABLE 4.** Key Gene Mutations in Salivary Duct Carcinoma

| Genetic alterations | Frequency (%) |
|---|---|
| *AR* alteration | 40-70 |
| *TP53* mutation | 55-68 |
| *ERBB2* amplifications | 29-35 |
| *PIK3CA* mutation | 18-37 |
| *PTEN* mutation | 10-50 |
| *NF1* mutation | 16-21 |
| *HRAS* mutation | 4-27 |
| *KMT2C* mutation | 11 |
| *EGFR* mutation | 9 |
| *ALK* mutation | 7 |
| *CDKN2A* mutation | 7 |
| *NOTCH1* mutation | 7 |
| *KDM5C* mutation | 7 |
| *NRAS* mutation | 4 |
| *BRAF* mutation | 3-7 |
| *AKT* mutation | 2 |

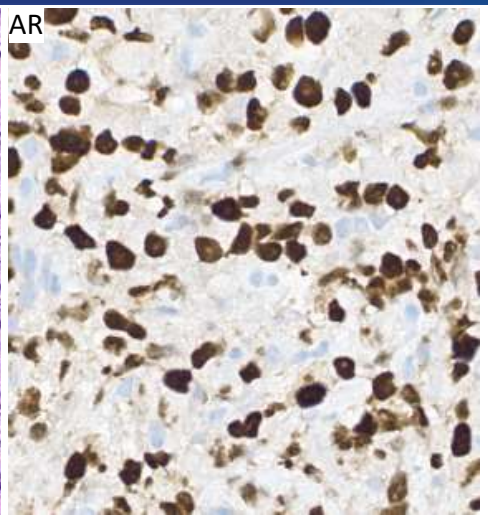
Mitani, Clin Cancer Res. 2014
Skálová, Am J Surg Pathol. 2018

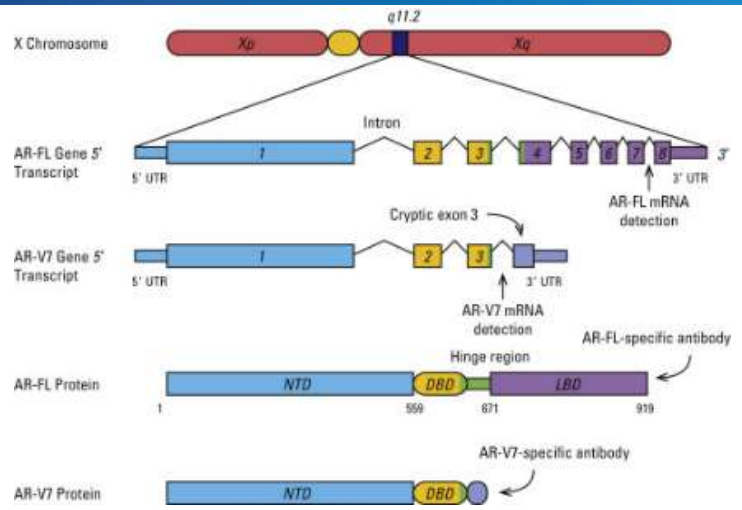
# Salivary duct carcinoma (SDC)

M/67
Parotid mass
M/LN, brain



AR






**AR-V7**
Splice variant of the androgen receptor mRNA resulting in the truncation of the ligand-binding domain

**▣ Result of Actionable Gene Mutation Analysis**

-SNV/INDEL

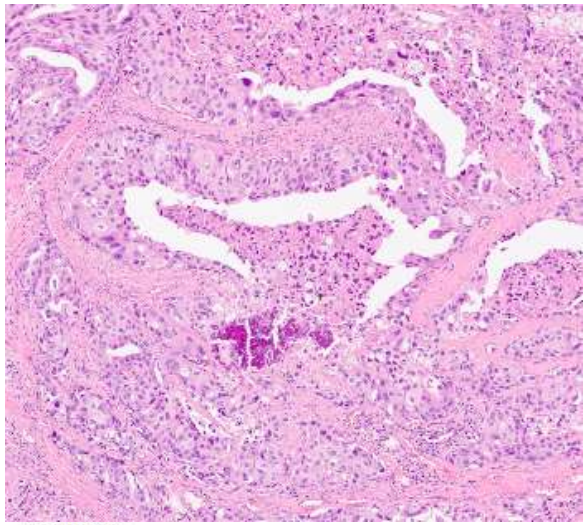
| Gene | Chr | Position | Refseq | Exon | AA | CDS | %VAF | Alt | Total | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| ERBB2 | chr17 | 37881000 | NM_004448.3 | 20 | p.Val777Leu | c.2329G>T | 53.94 | 1492 | 2766 | C |

- Fusion

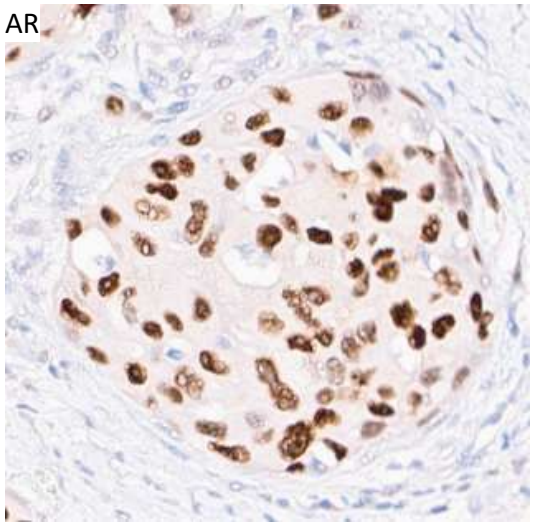
| Fusion Gene | Cytoband1 | Cytoband2 | DNA.Evidence (Span/Split) | RNA.Evidence (Span/Split) | Transcript1 | Transcript2 | Last Observed | First Observed | Tier |
|---|---|---|---|---|---|---|---|---|---|
| AR-V7 | Xq12 | Xq12 | 0/0 | 0/50 | NM_000044 | NM_000044 | EXON_3 | EXON_CE3 | D |

# Salivary duct carcinoma (SDC)

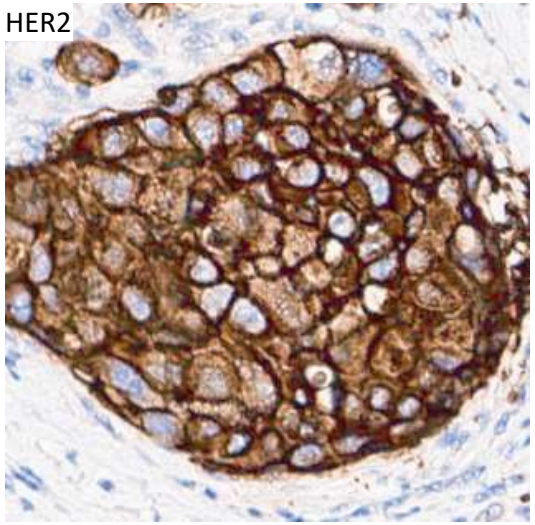
M/51
SMG mass



AR



HER2



-SNV/INDEL

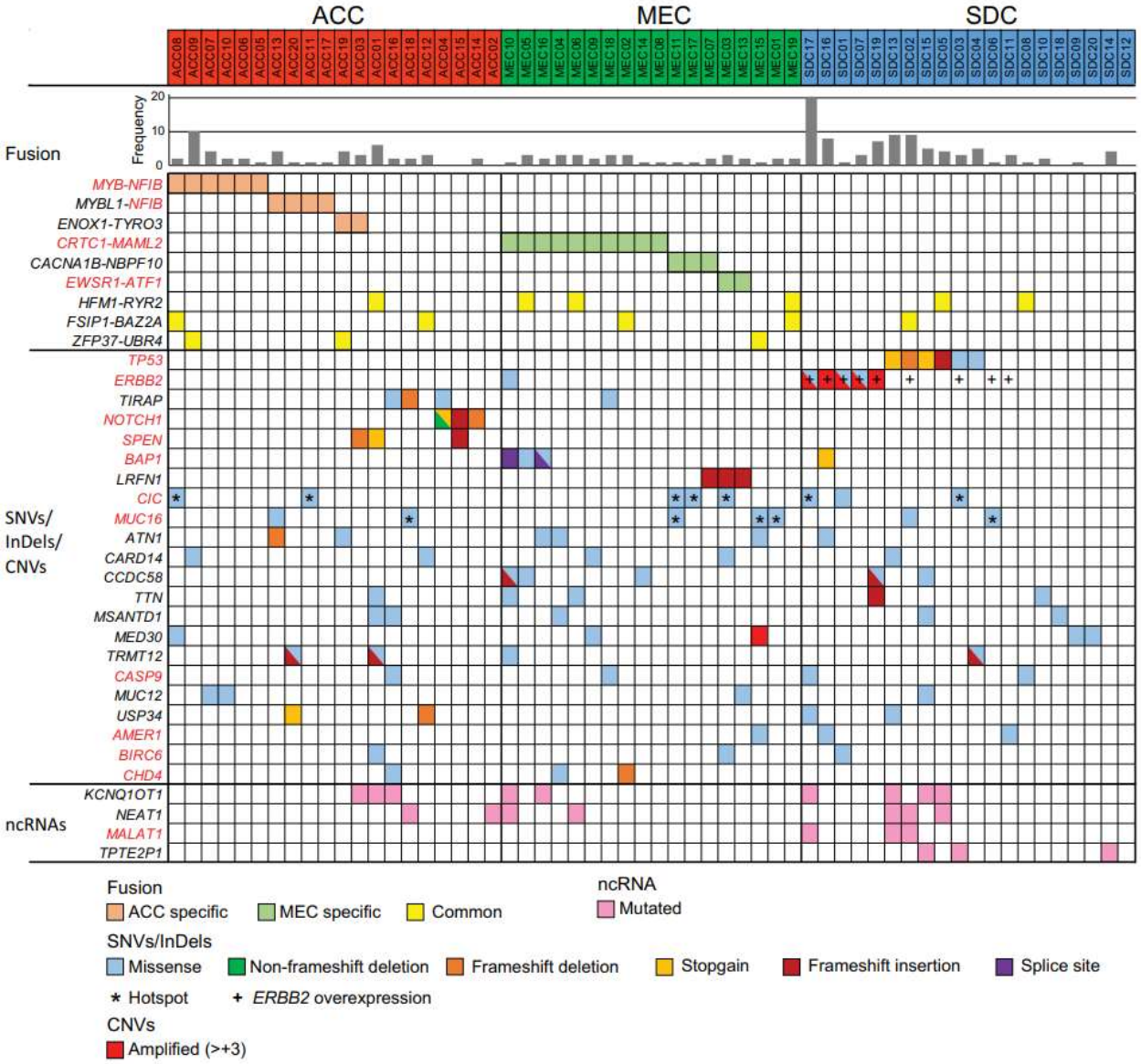
| Gene | Chr | Position | Refseq | Exon | AA | CDS | %VAF | Alt | Total | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| NRAS | chr1 | 115258744 | NM_002524.4 | 2 | p.Gly13Asp | c.38G>A | 1.27 | 26 | 2047 | C |
| PBRM1 | chr3 | 52668619 | NM_018313.4 | 12 | p.Arg434* | c.1300C>T | 18.98 | 26 | 137 | D |
| TP53 | chr17 | 7578553 | NM_000546.5 | 5 | p.Tyr126Cys | c.377A>G | 28.56 | 347 | 1215 | D |

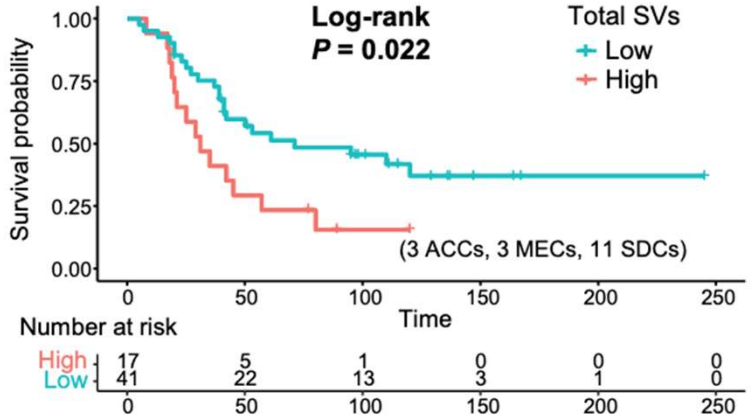
- Fusion

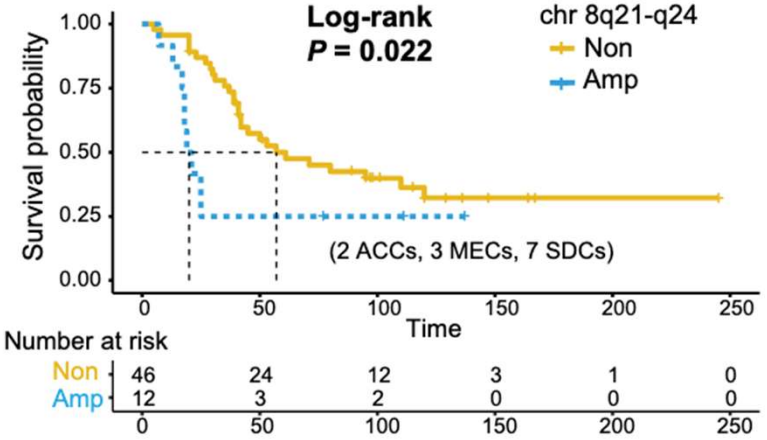
| Fusion Gene | Cytoband1 | Cytoband2 | DNA.Evidence (Span/Split) | RNA.Evidence (Span/Split) | Transcript1 | Transcript2 | Last Observed | First Observed | Tier |
|---|---|---|---|---|---|---|---|---|---|
| Not detected | | | | | | | | | |

-CNV

| Gene | Chr | Start | End | CNV | AvgL2R | DelR | NeutralR | AmpR | CN | Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| ERBB2 | chr17 | 37855608 | 37884459 | Amplification | 2.974 | 0.0 | 0.0 | 1.0 | 14 | C |




Karpinets, Clin Cancer Res. 2021

# Acinic cell carcinoma (AciCC)

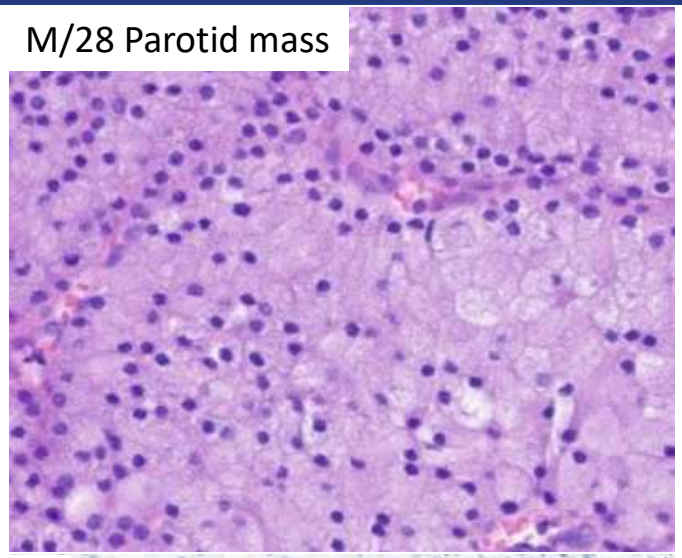
- **Clinical features**
  - 10% of all salivary gland malignancies; 90-95% of cases arise in the parotid gland; 18.7% of parotid carcinoma
  - 2nd most common salivary gland malignancy in children; wide age range (average 47.7 – 52)

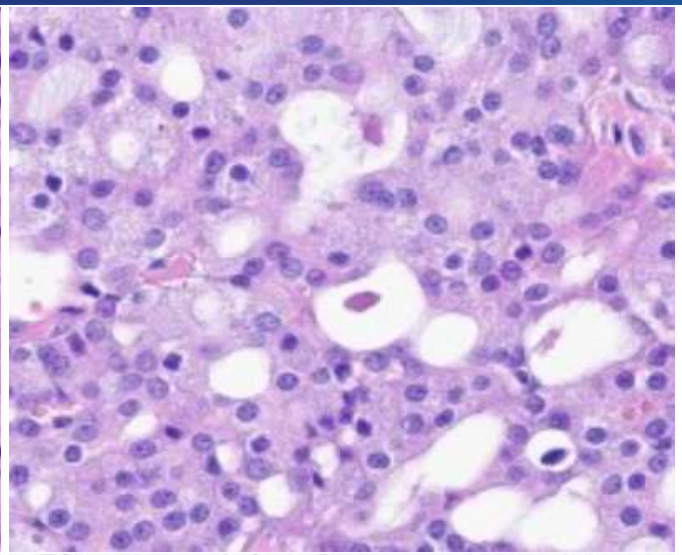
- **Histopathology**
  - Solid, microcystic, follicular, papillary-cystic architectures
  - Most commonly serous acinar cell proliferation
    → PAS-positive, diastase-resistant basophilic cytoplasmic zymogen granules
  - Variable intercalated duct-type, nonspecific glandular, vacuolated, oncocytic, and rarely clear cells
  - IHC
    - SOX10+, DOG1+ / p40-, p63-, mammaglobin-, S100-
  - High grade transformation
    → nuclear pleomorphism, coarse chromatin, necrosis, ↑mitotic activity/Ki-67 index, ↑ frequent perineural / LVI

# Acinic cell carcinoma (AciCC)

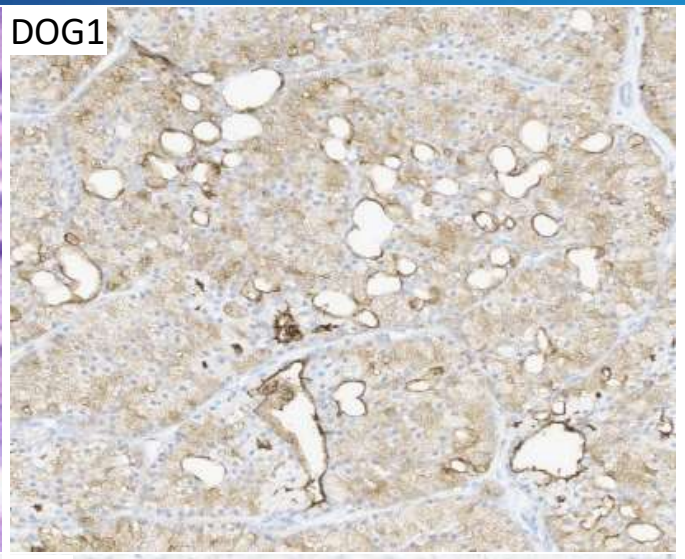
SNUH

M/28 Parotid mass

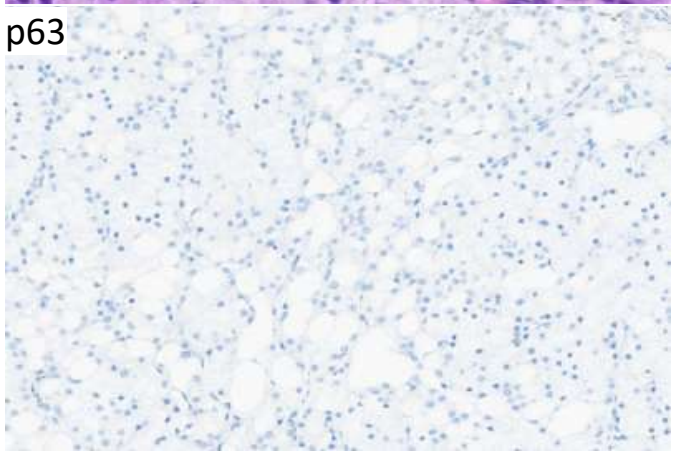




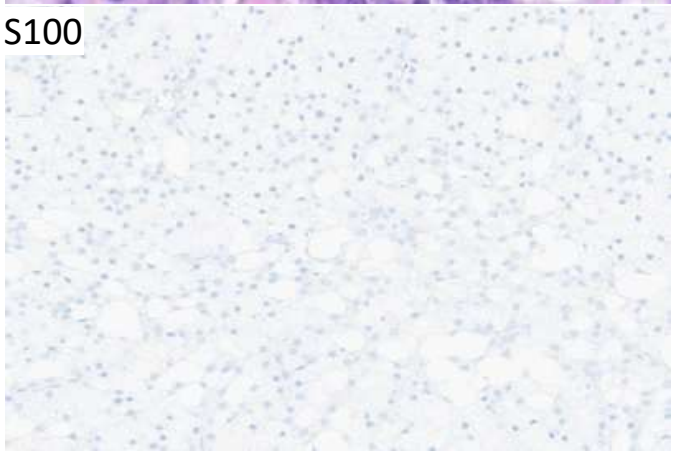
DOG1



p63



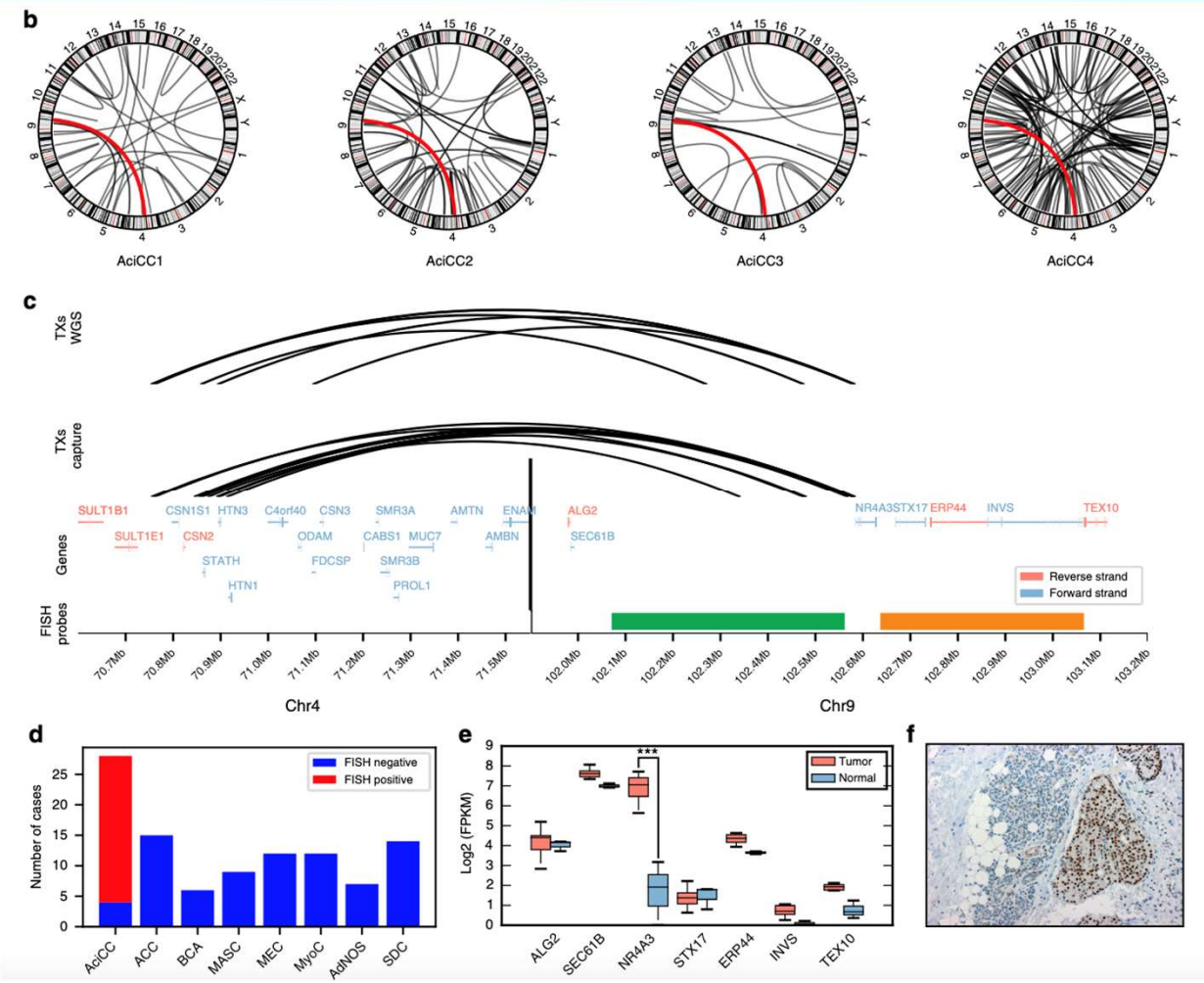
S100



TRK

# Acinic cell carcinoma (AciCC)

- **Molecular pathology**
  - t(4;9)(q13;q31) rearrangement
    - → Active enhancer of secretory Ca-binding phosphoprotein (SCPP) gene cluster at upstream of *NR4A3* gene
    - → Upregulation of *NR4A3* via enhancer hijacking
  - NR4A3 IHC
    - Sensitivity 94.4%; specificity 99%




Haller, Nat Commun. 2019
Haller, Am J Surg Pathol. 2019

# Secretory carcinoma (SC)

- **Clinical features**
  - Painless slowly growing mass; parotid gland (m/c) > oral cavity > submandibular gland
  - Mean patient age of 46.5 (range 10-86 years)

- **Histopathology**
  - Lobulated growth pattern separated by fibrous septa
  - Microcystic/solid, tubular, follicular, and papillary-cystic structures with distinctive luminal secretions
  - Low grade vesicular round-to-oval nuclei with finely granular chromatin and distinctive centrally located nucleoli
  - Granular to vacuolated pale, pink cytoplasm
  - Special stain/IHC
    - PAS, D-PAS, alcian-blue+ luminal secretions
    - CK7+ S100+, SOX10+, vimentin+, mammaglobin+
    - p63-, p40- DOG1-, NR4A3-

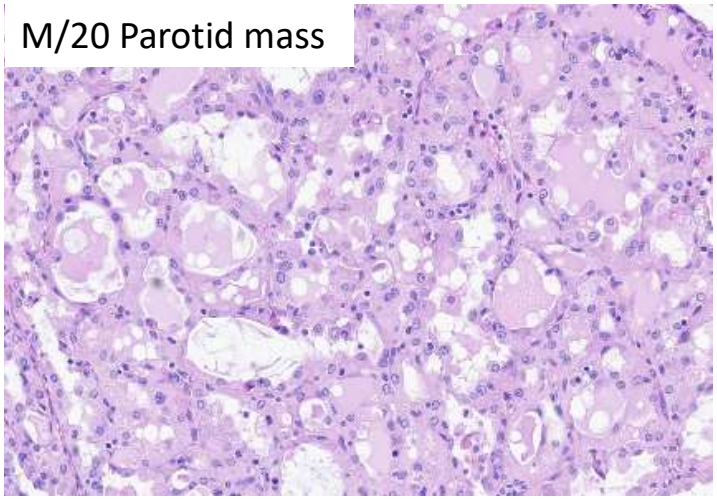
- **Molecular pathology**
  - 90% harbor t(12;15)(p13;q25) chromosomal rearrangement → *ETV6::NTRK3* fusion
  - Rarer rearrangements include *ETV6::RET, ETV6::MET, ETV6::MAML3, VIM::RET*

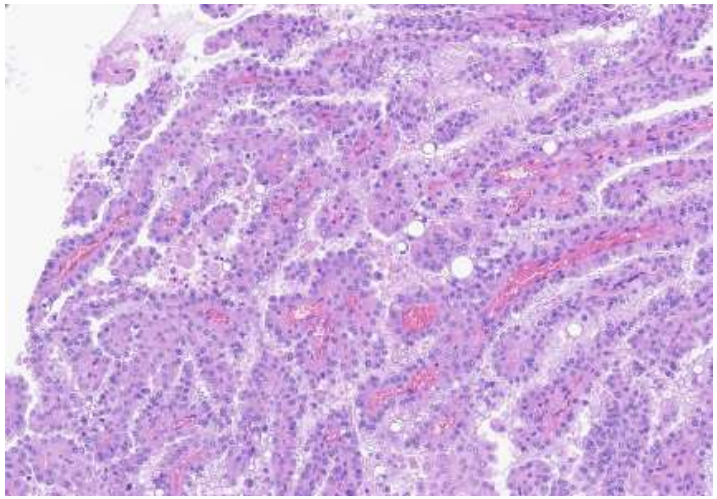
Skalova, Am J Surg Pathol. 2010
Skalova, Am J Surg Pathol. 2018
Skalova, Am J Surg Pathol. 2020

# Secretory carcinoma (SC)

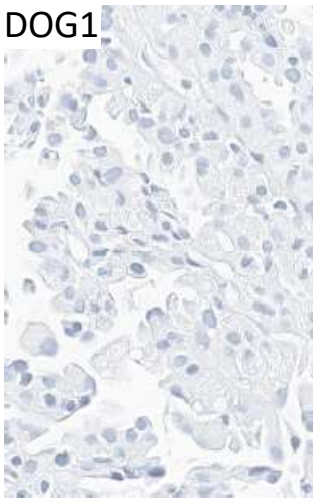
SNUH

M/20 Parotid mass

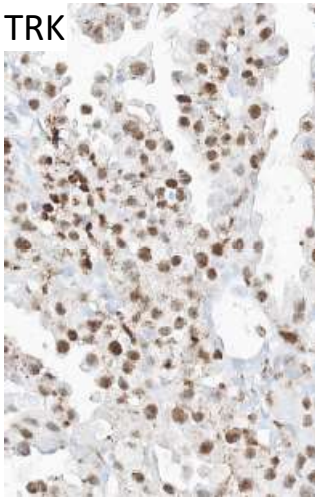




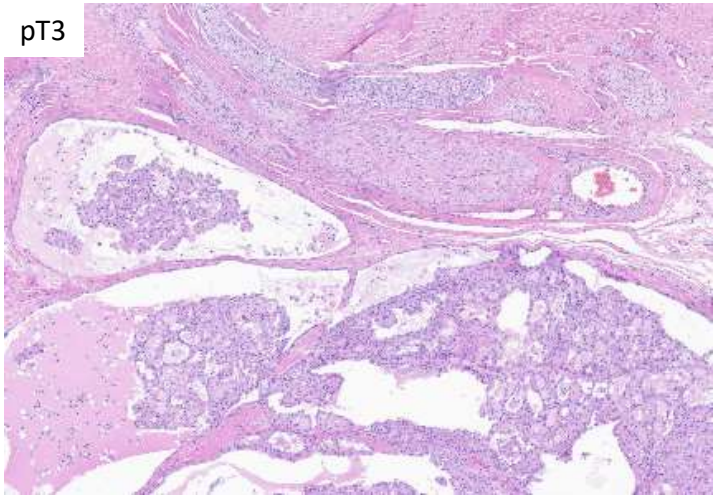
DOG1



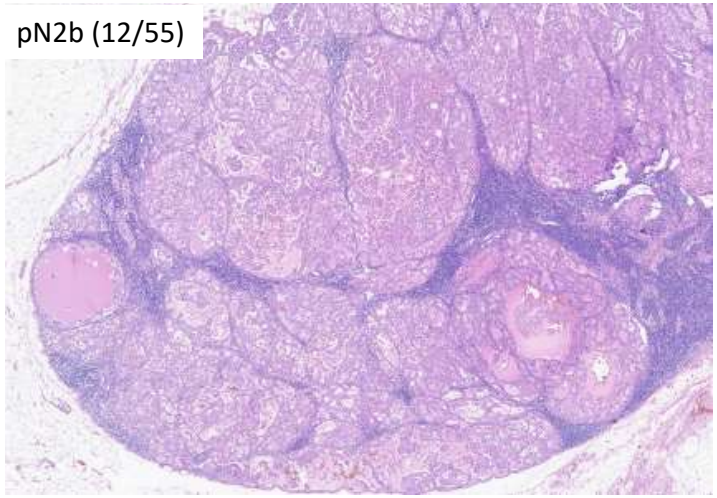
TRK



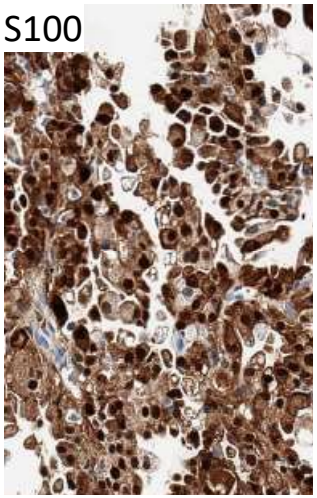
pT3



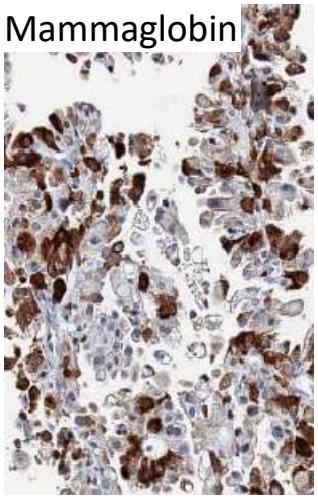
pN2b (12/55)



S100



Mammaglobin



# Basal cell adenocarcinoma (BCAC)

- **Clinical features**
  - Slow growing nodule in parotid gland (>90%) in 6$^{th}$–7$^{th}$ decades
  - About 15% occur in the setting of familial/multiple cylindromatosis syndromes
  - Complete surgical excision is curative in >90%
  - Regional lymph node and distant metastasis and disease related death are rare (<10%)

- **Histopathology**
  - Tubulo-trabecular, membranous, solid growth patterns
  - Tumor nests show peripheral palisading of dark cells with paler cells and centrally located ducts
  - DDx BCAC from basal cell adenoma (BCA)
    - Infiltration; necrosis; mitosis (>4 per 2mm$^2$)
  - IHC
    - Epithelial and myoepithelial markers highlights the dual cell components
    - Nuclear β-catenin immunoexpression: BCAC (66.7%-100%); BCA (70%-100%)

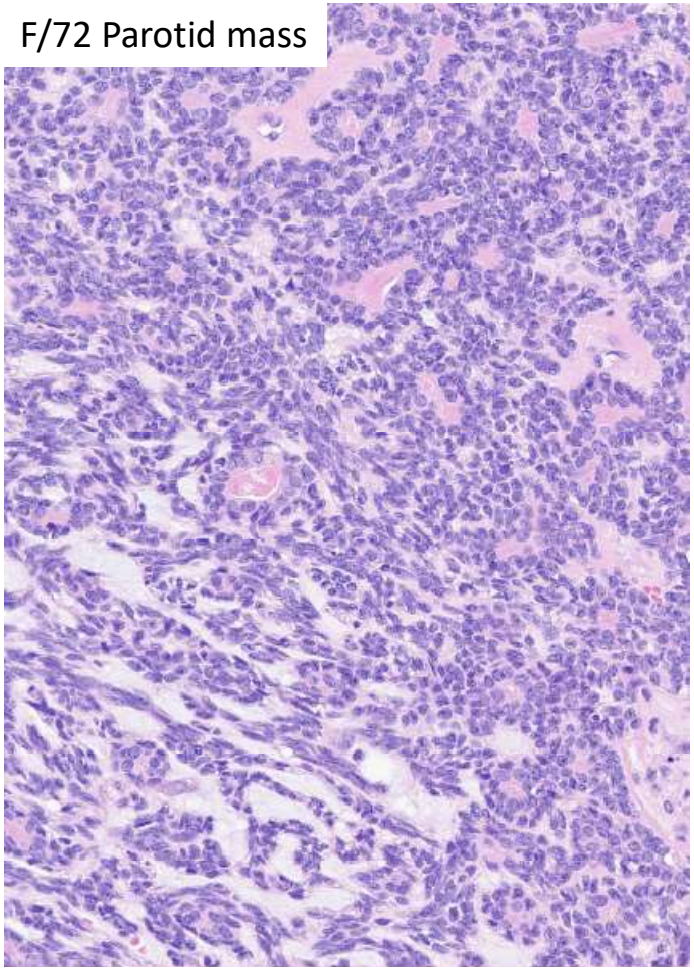
- **Molecular pathology**
  - Diagnostic feature: none
  - *CTNNB1* mutations: more common in BCA than BCAC
  - Other genetic profiles of BCAC
    - Activating mutations in *PIK3CA*, biallelic inactivation of *NFKBIA*, focal *CYLD* deletion

Jung, Diagn Pathol. 2013
Jo, Am J Surg Pathol. 2016

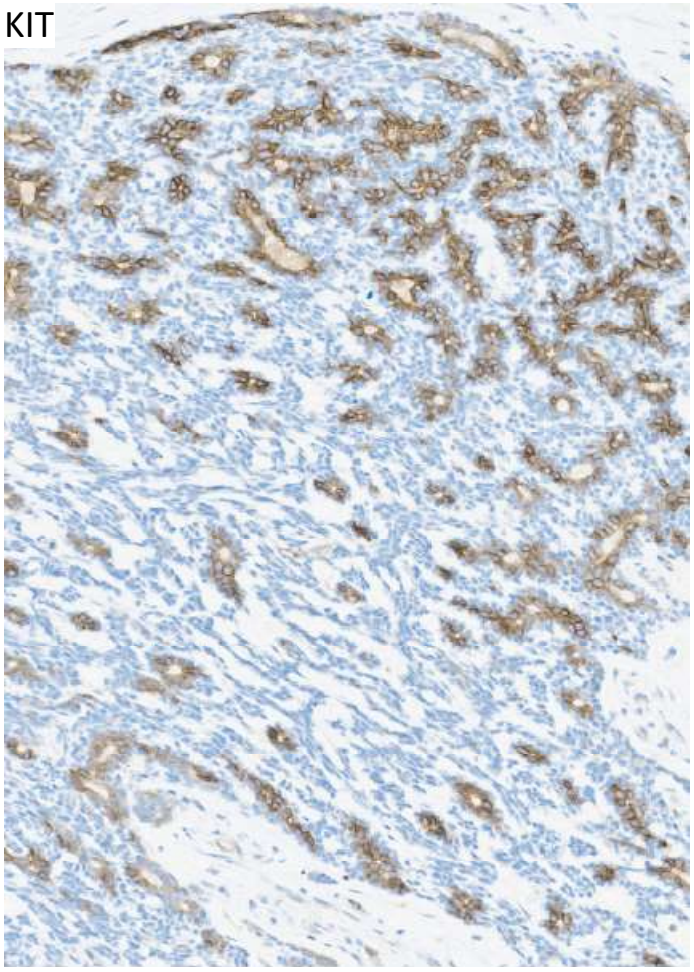
# Basal cell adenocarcinoma (BCAC)

SNUH

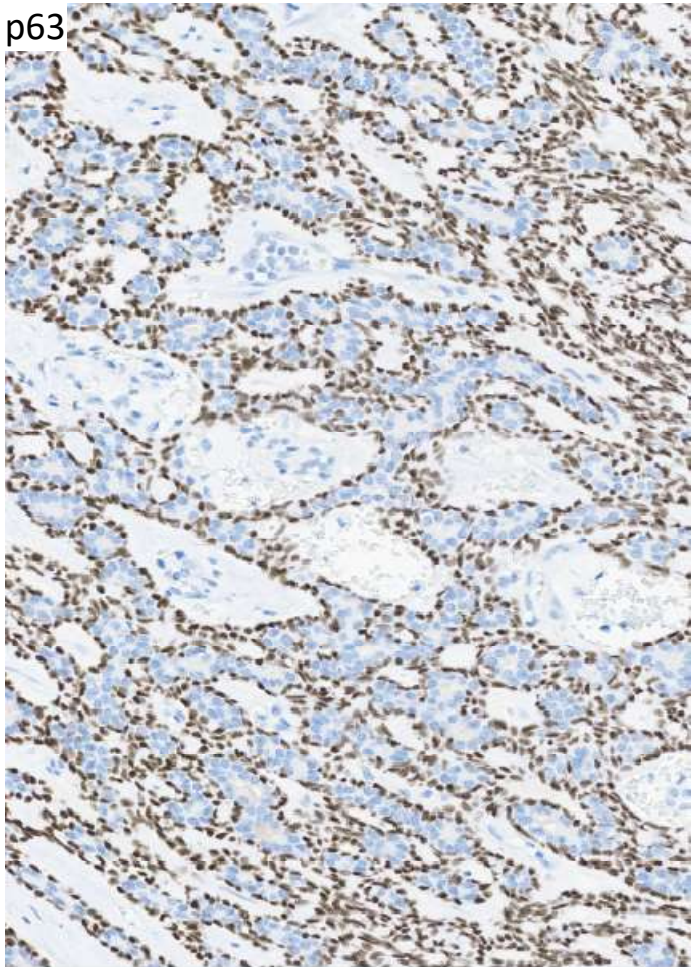
F/72 Parotid mass



KIT

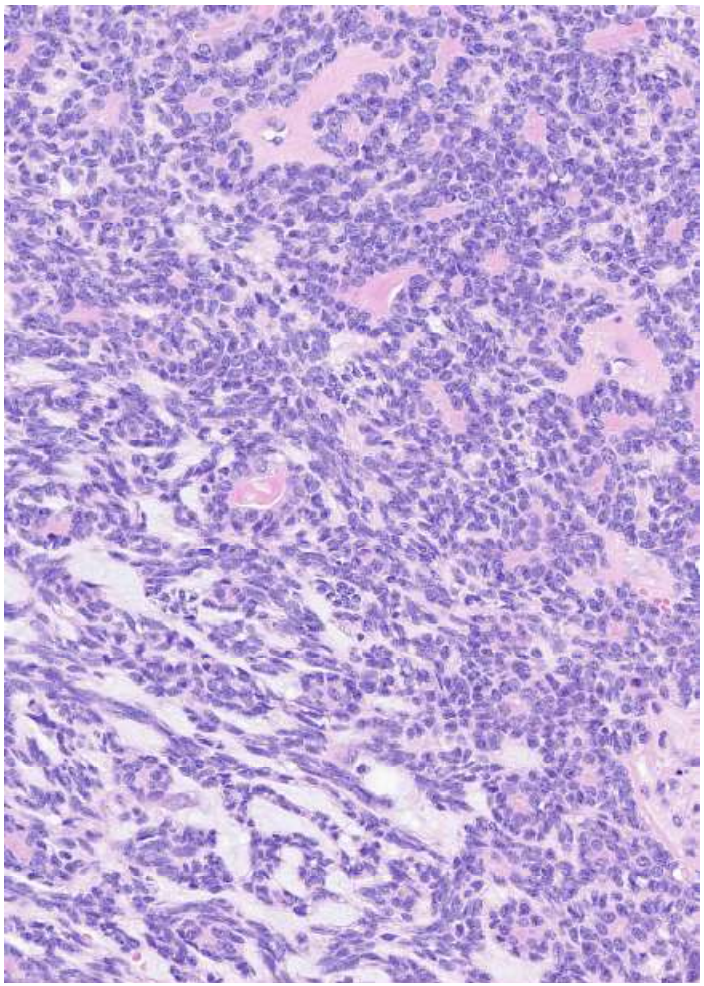


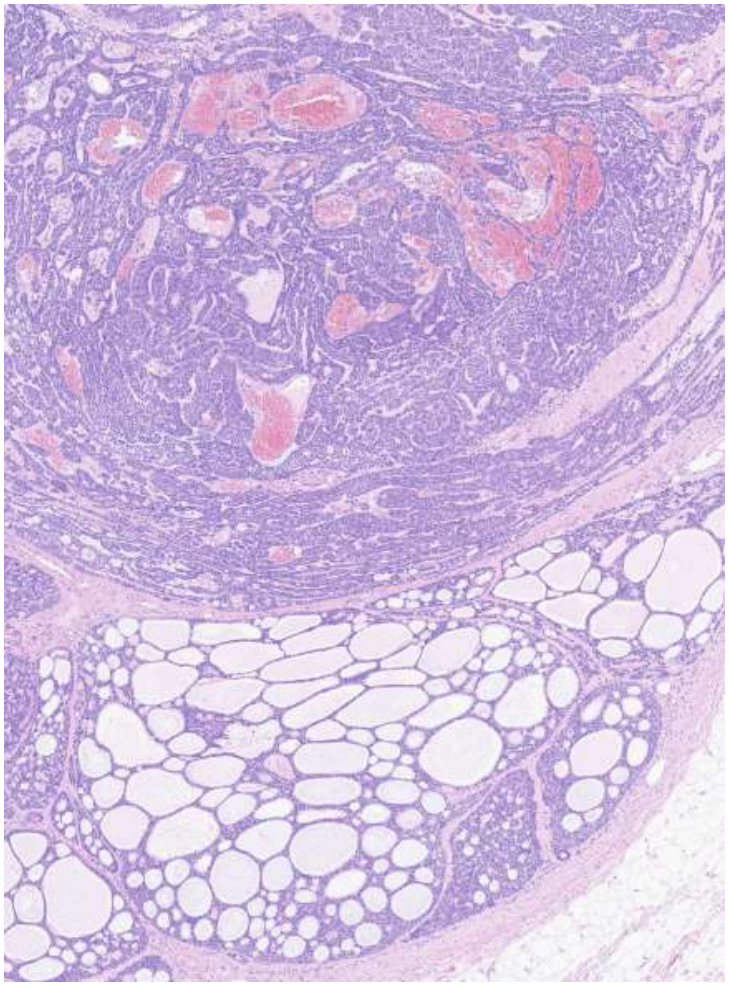
p63



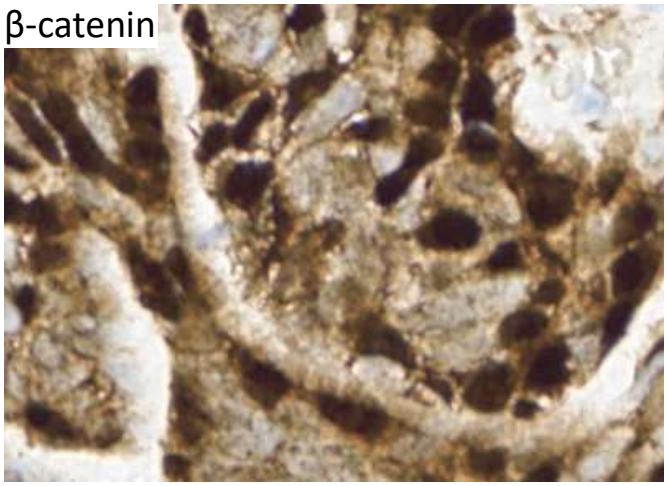
# Basal cell adenocarcinoma (BCAC)

SNUH



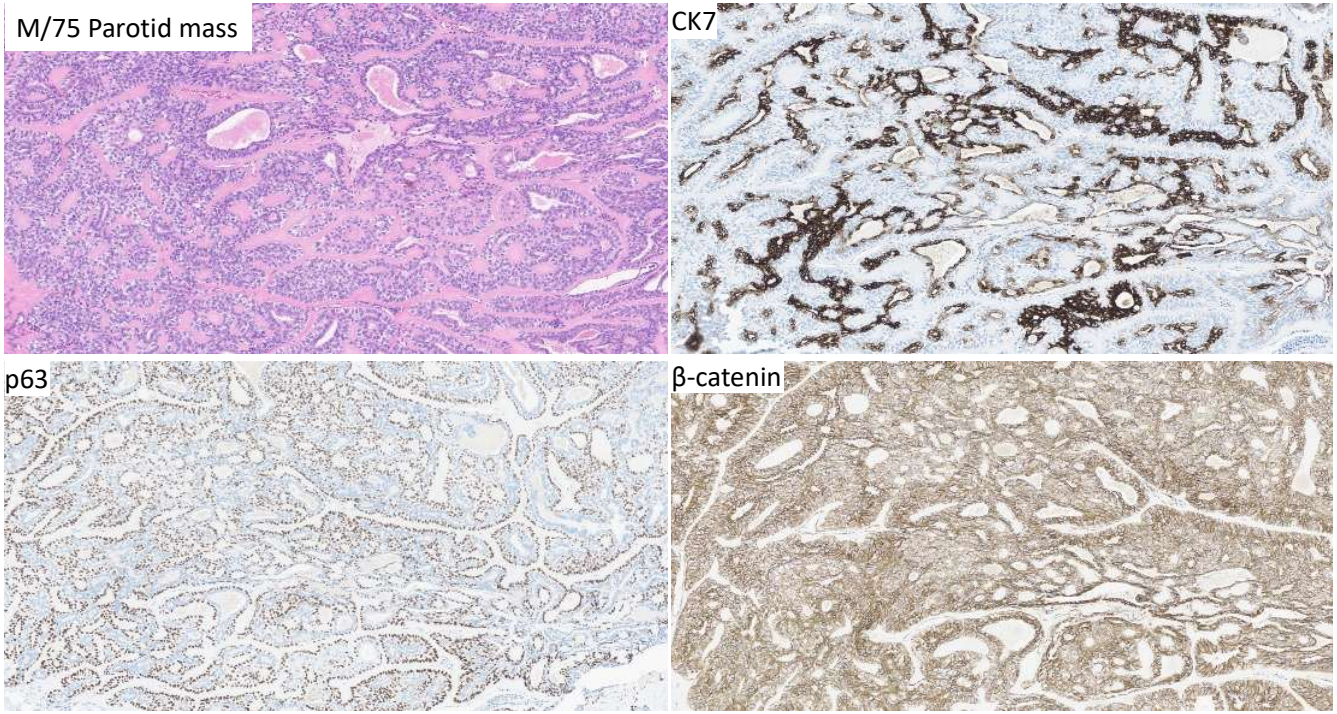


β-catenin



# Epithelial-myoepithelial carcinoma (EMC)

- **Clinical features**
  - 1% of all salivary gland tumors mostly affecting parotid gland in 6th-7th decades
- **Histopathology**
  - Biphasic tubules → tightly coupled inner eosinophilic ductal and prominent outer (often clear) myoepithelial cells
- **Molecular pathology**
  - *HRAS* codon 61 mutation in 82.7%; HRAS Q61R mutation-specific IHC positivity in 65%




Urano, Am J Surg Pathol. 2019
Nakaguro, Am J Surg Pathol. 2021

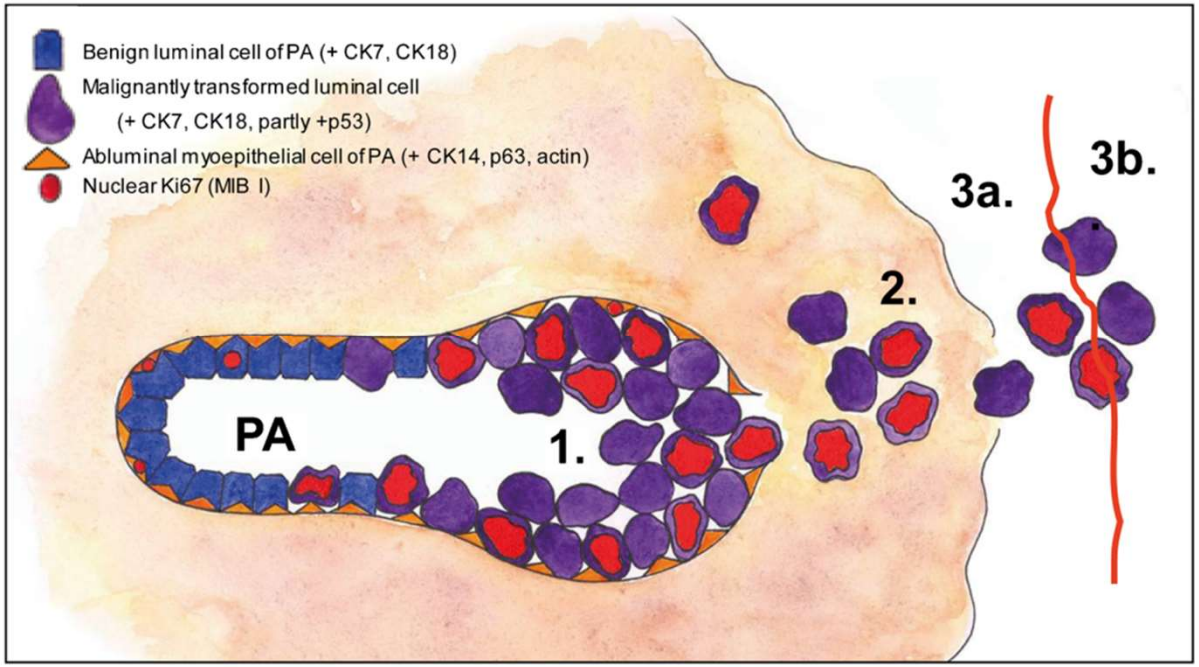
# Carcinoma ex pleomorphic adenoma (CXPA)

- **Clinical features**
  - Epithelial and/or myoepithelial malignancy in association with a primary or recurrent pleomorphic adenoma (PA), presenting at $6^{th}$-$7^{th}$ decades
  - Long-standing painless mass with recent rapid progression or of previous diagnosis of PA
  - Most commonly at parotid gland
  - Aggressive tumors with local and distant recurrence rates of 70%; 5-year survival from 25% to 75%
    - Poor prognostic factors: invasive CXPA, large size > 4 cm, multiple LN+, distant metastasis

- **Histopathology**
  - PA and carcinoma components can be intermixed or appear as discrete nodules
  - Histologic types of malignant components
    - Most commonly SDC > myoepithelial carcinoma > adenocarcinoma, NOS
    - Rarely carcinosarcoma : malignant epithelial and sarcomatous components arising in association with a PA

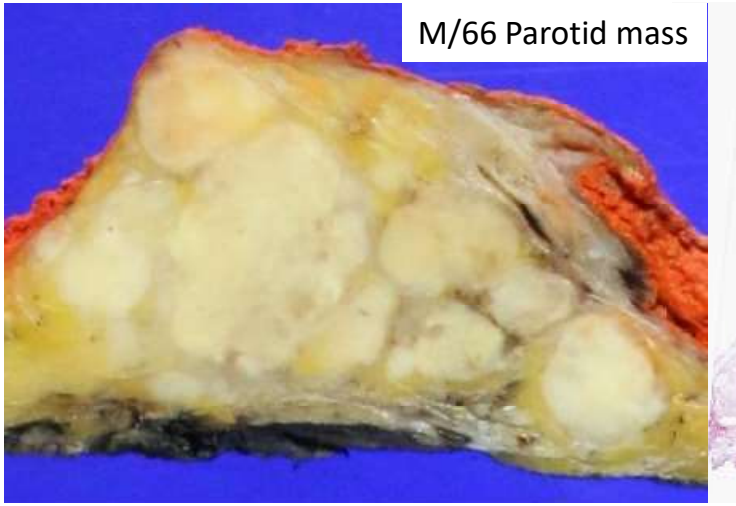
# Carcinoma ex pleomorphic adenoma (CXPA)

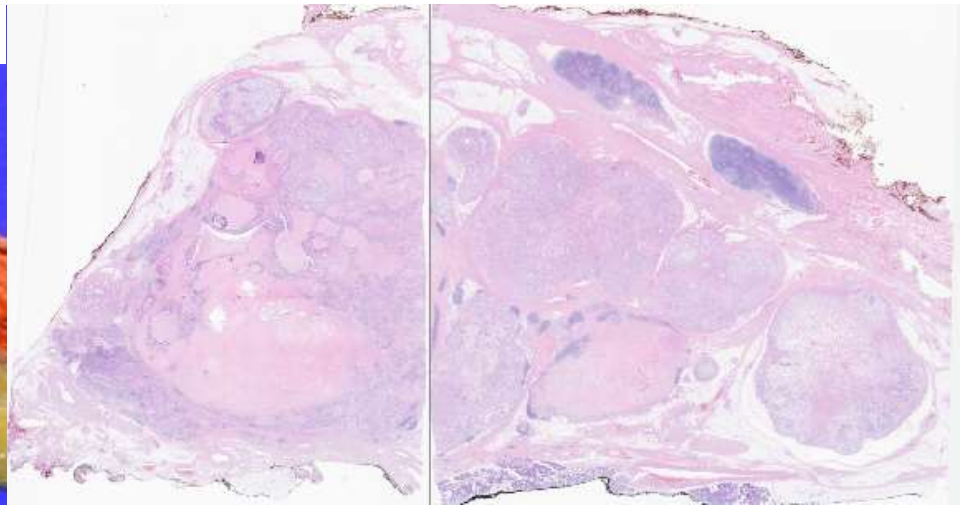
- **Histopathology – Subclassification**
  - Based on the extent of invasion beyond PA borders
    1) Intracapsular: carcinoma is confined within the PA capsule
       - In situ intracapsular when the malignant tumor cells replace ductal cells with an intact myoepithelial layer
    2) Minimally invasive: carcinoma invades < 4 - 6 mm beyond the PA borders
    3) Invasive: invasion beyond the PA capsule measures ≥ 6mm

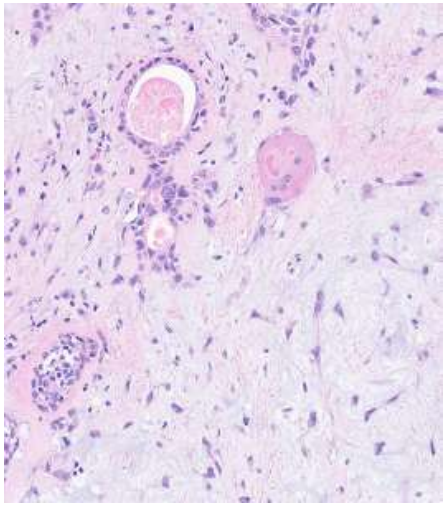


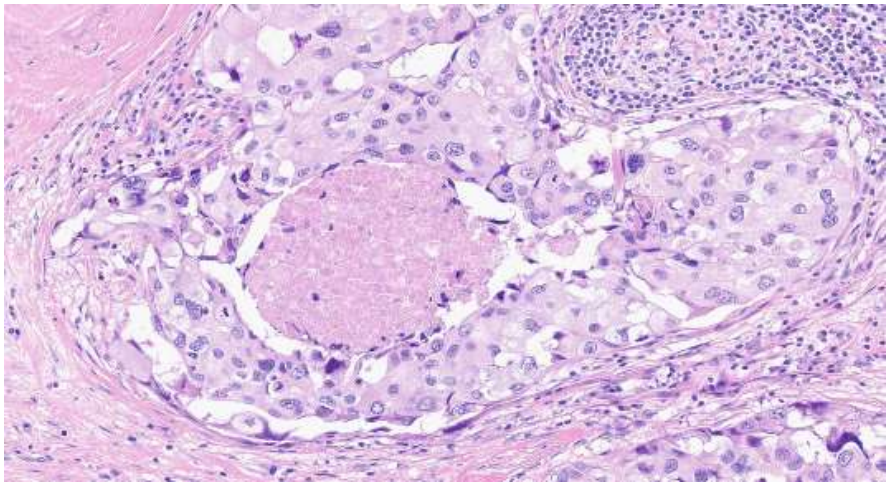

Ihrler, Virchows Arch. 2017

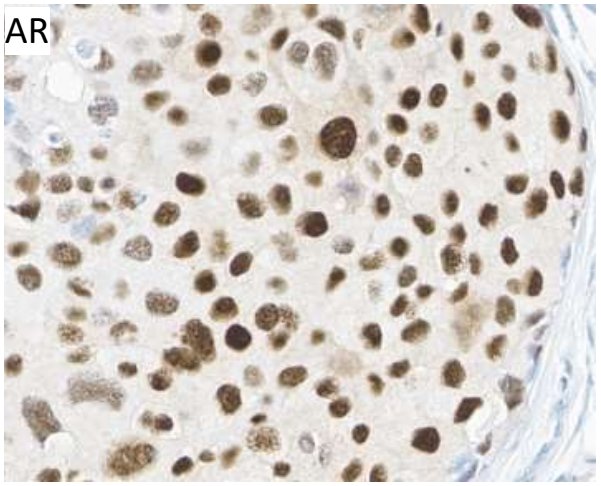
# Carcinoma ex pleomorphic adenoma (CXPA)

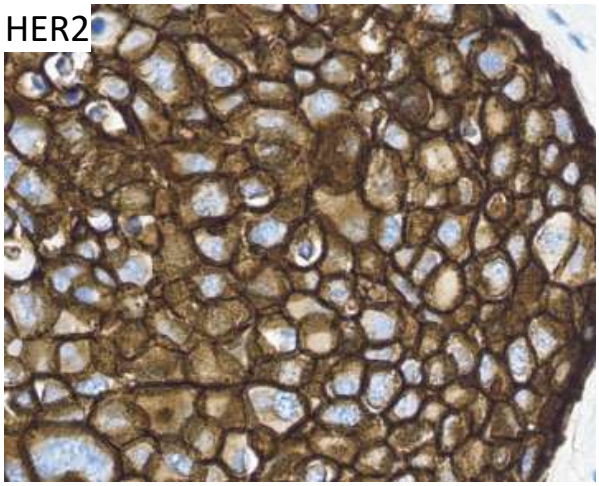


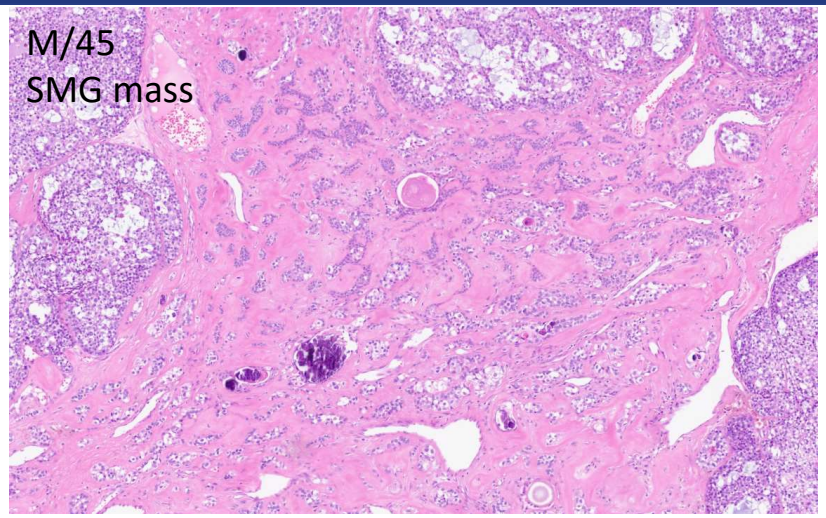


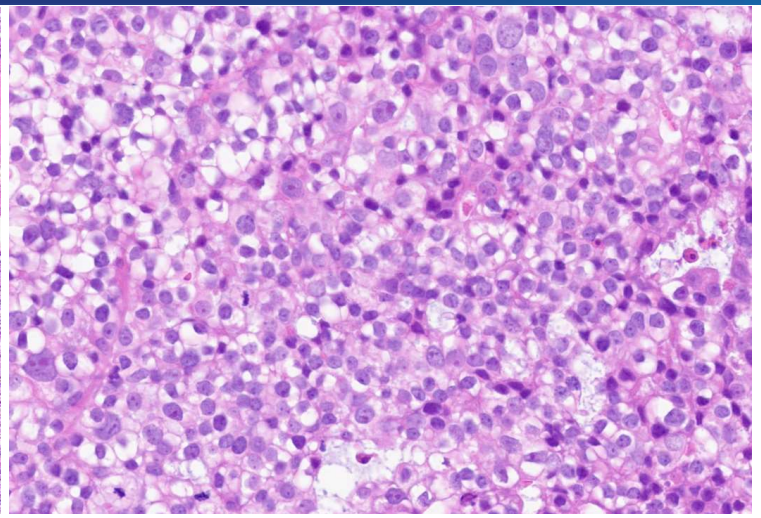


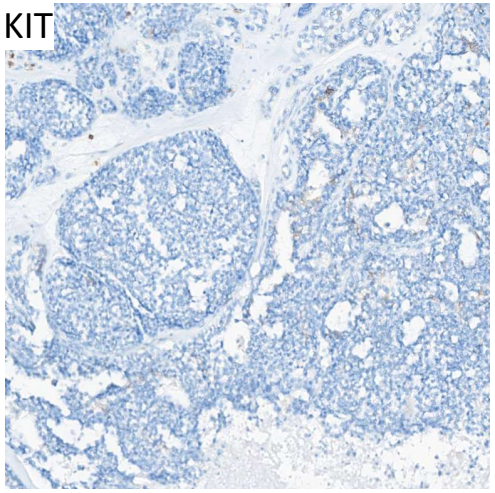


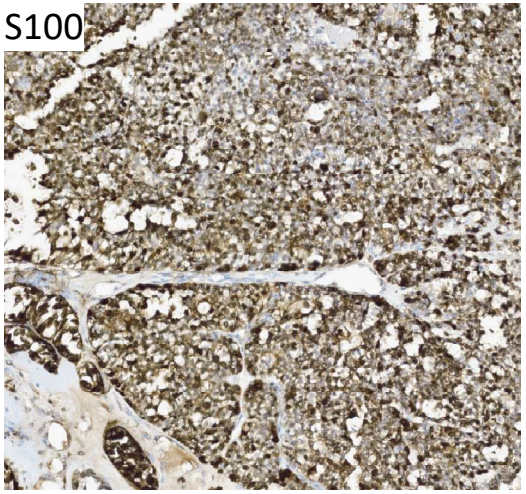



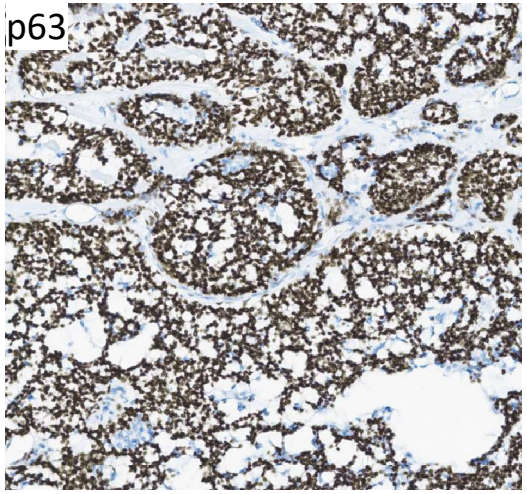
# Carcinoma ex pleomorphic adenoma (CXPA)



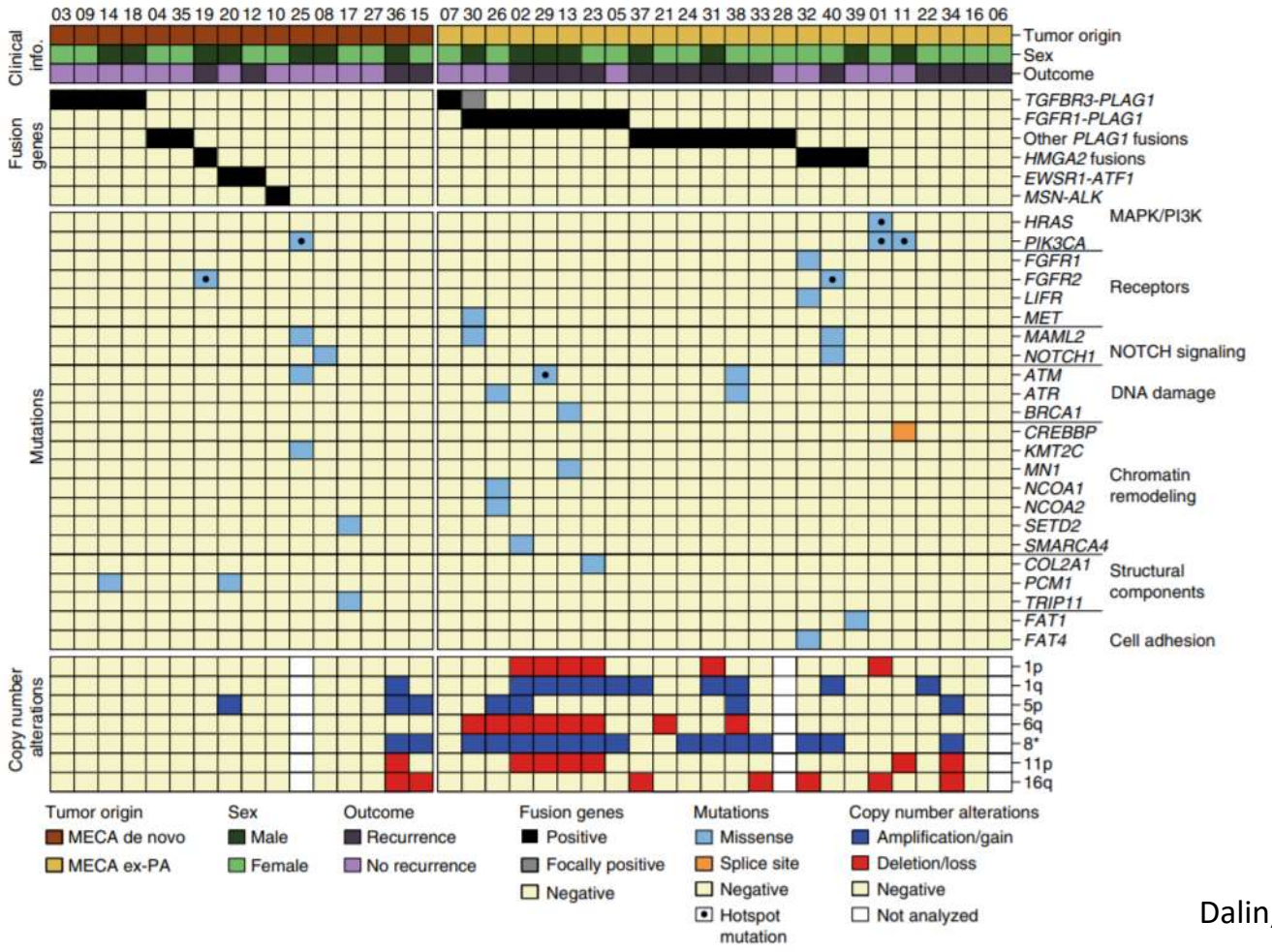


# Carcinoma ex pleomorphic adenoma (CXPA)

- **Molecular pathology**

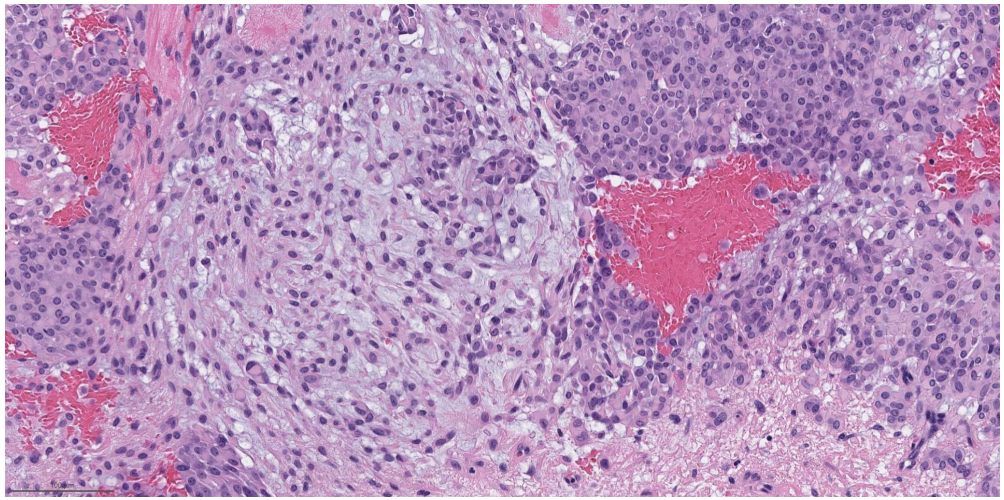



Dalin, Nat Commun. 2017

# Myoepithelial carcinoma (MC)

- **Clinical features**
  - Parotid gland followed by the palate, and the submandibular gland

- **Histopathology**
  - De novo or CXPA (2nd most common histologic subtype of CXPA)
  - Diverse cellular morphology including spindle, epithelioid, plasmacytoid, vacuolated, and clear cells
  - Solid, trabecular, and reticular growth patterns
  - Myxoid, myxochondroid or hyalinized stroma
  - IHC
    - SOX10+, S100+, CK+, myoepithelial markers+ (SMA, calponin, p63, p40)



# Hyalinizing clear cell carcinoma (HCCC)

- **Clinical features**
  - Mostly at oral minor salivary glands > oropharynx, nasopharynx, parotid, sinonasal tract, larynx, and hypopharynx
  - Median age at diagnosis of 56 years (range 23-87 years)

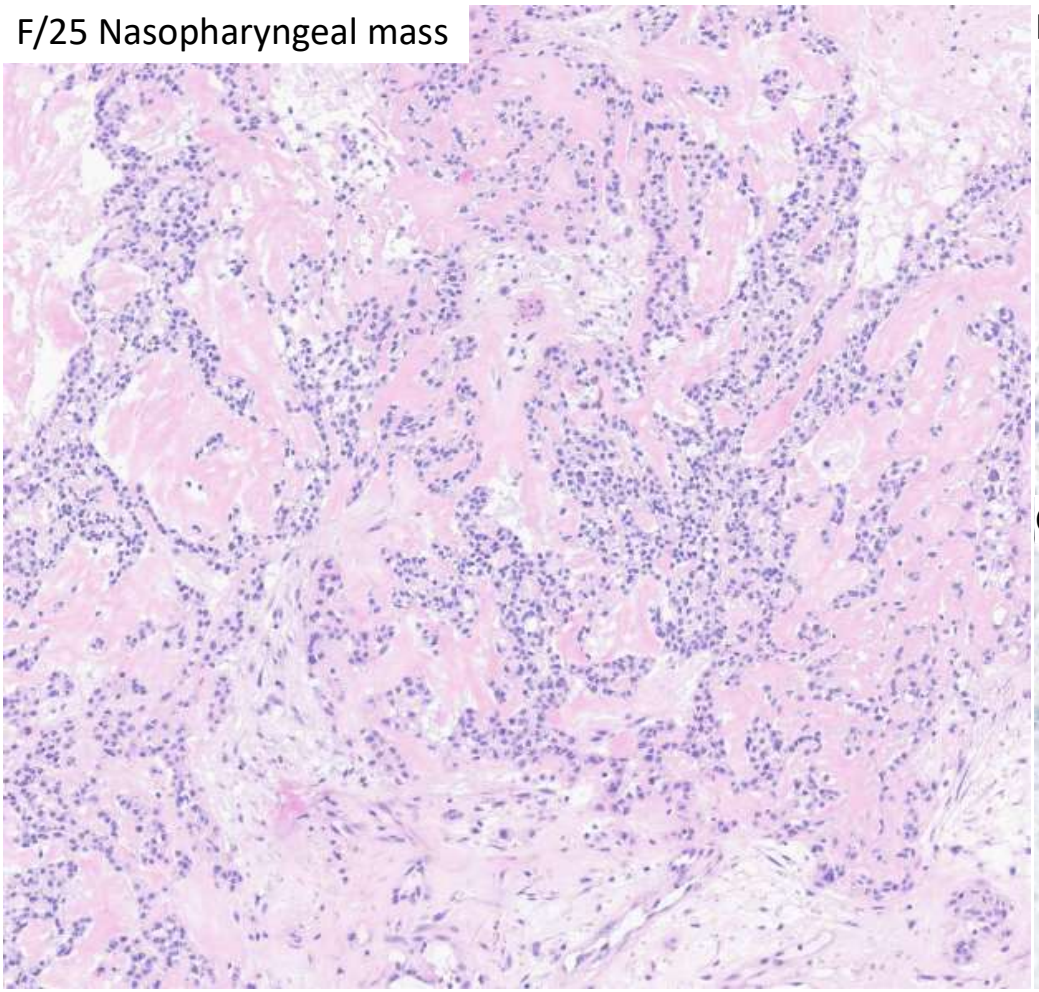
- **Histopathology**
  - Nests, cords and trabeculae composed of clear or eosinophilic cells
    - Some cases completely lack clear cells
  - Unencapsulated with cells infiltrating the surrounding tissue
  - Densely hyalinized basement membrane-like to desmoplastic or fibrocellular stroma
  - IHC
    - CK7+, CK19+, CK14+, EMA+
    - P63+, p40+, CK5/6+ → supporting squamous differentiation
    - Negative for myoepithelial markers (S100, SMA, calponin)

- **Molecular pathology**
  - *EWSR1::ATF1*; rarer fusion including *EWSR1::CREM*

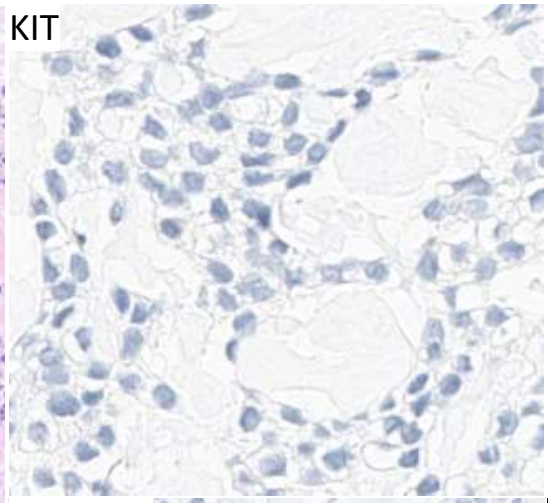
Antonescu, Genes Chromosomes Cancer. 2011

# Hyalinizing clear cell carcinoma (HCCC)

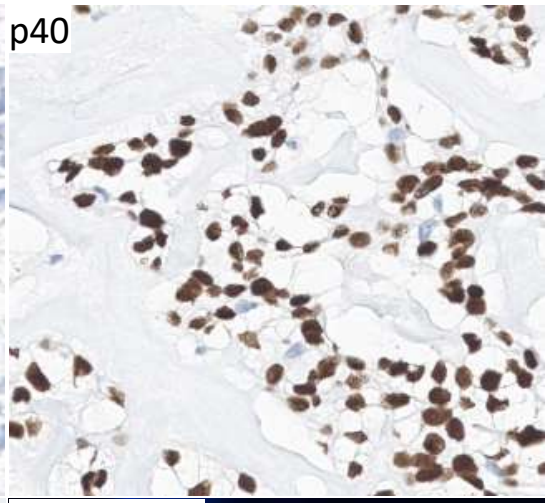
F/25 Nasopharyngeal mass



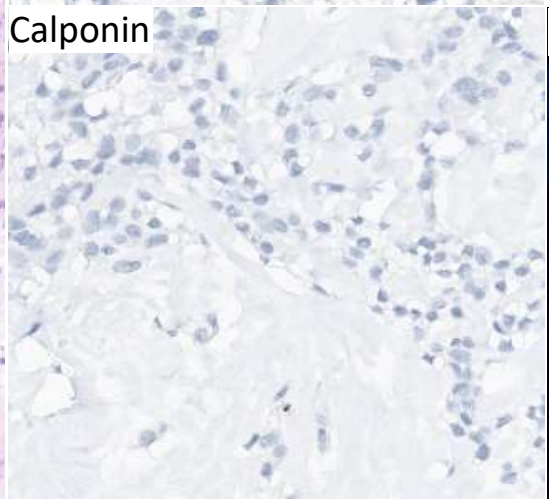
KIT



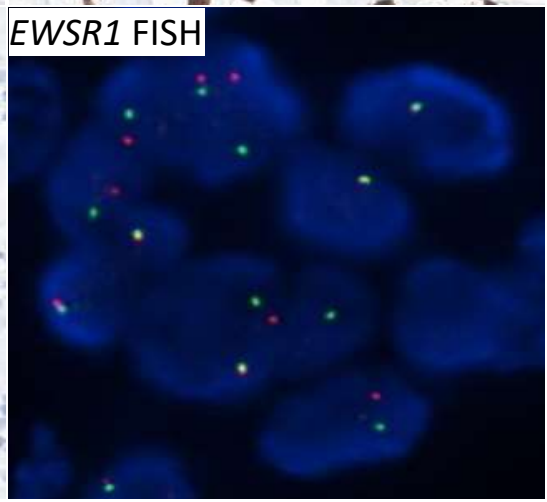
p40



Calponin



*EWSR1* FISH



# Summary

| | Gene and mechanism | Prevalence |
|---|---|---|
| AdCC | *MYB* fusion/activation/amplification | ~80% |
| | *MYBL1* fusion/activation/amplification | ~10% |
| | *NOTCH* mutations | 14% |
| MEC | *CRTC1::MAML2* | 40-90% |
| | *CRTC3::MAML2* | 6% |
| | *CDKN2A* deletion | 25% |
| SDC | *ERBB2* amplification | 31% |
| | *FGFR1* amplification | 10% |
| | *TP53* mutation | 56% |
| | *PIK3CA* mutation | 33% |
| | *HRAS* mutation | 33% |
| | *AR* copy gain | 35% |
| | *PTEN* loss | 38% |
| | *CDKN2A* loss | 10% |

| | Gene and mechanism | Prevalence |
|---|---|---|
| AciCC | *NR4A3* fusion/activation | 86% |
| | *MSANTD3* fusion/amplification | 4% |
| SC | *ETV6::NTRK3* fusion | > 90% |
| | *ETV6::RET* fusion | 2–5% |
| | *ETV6::MET* fusion | <1% |
| | *ETV6::MAML3* fusion | <1% |
| | *VIM::RET* fusion | <1% |
| BCAC | *CYLD* mutations | 29% |
| CXPA | *PLAG1* fusions/amplification | 73% |
| | *HMGA2* fusions/amplification | 14% |
| | *TP53* mutations | 60% |
| EMC | *HRAS* mutations | 78% |
| MC | *PLAG1* fusions | 38% |
| | *EWSR1::ATF1* fusions | 13% |
| HCCC | *EWSR1::ATF1* fusions | 93% |
| | *EWSR1::CREM fusions* | <5% |

# Thank you for your attention