Gene Expression Profiling of Head and Neck Tumors Identifies FOXP1 and SOX10 Expression as Useful for Distinguishing Ameloblastoma From Basaloid Salivary Gland Tumors

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汇报人：钱雪霞

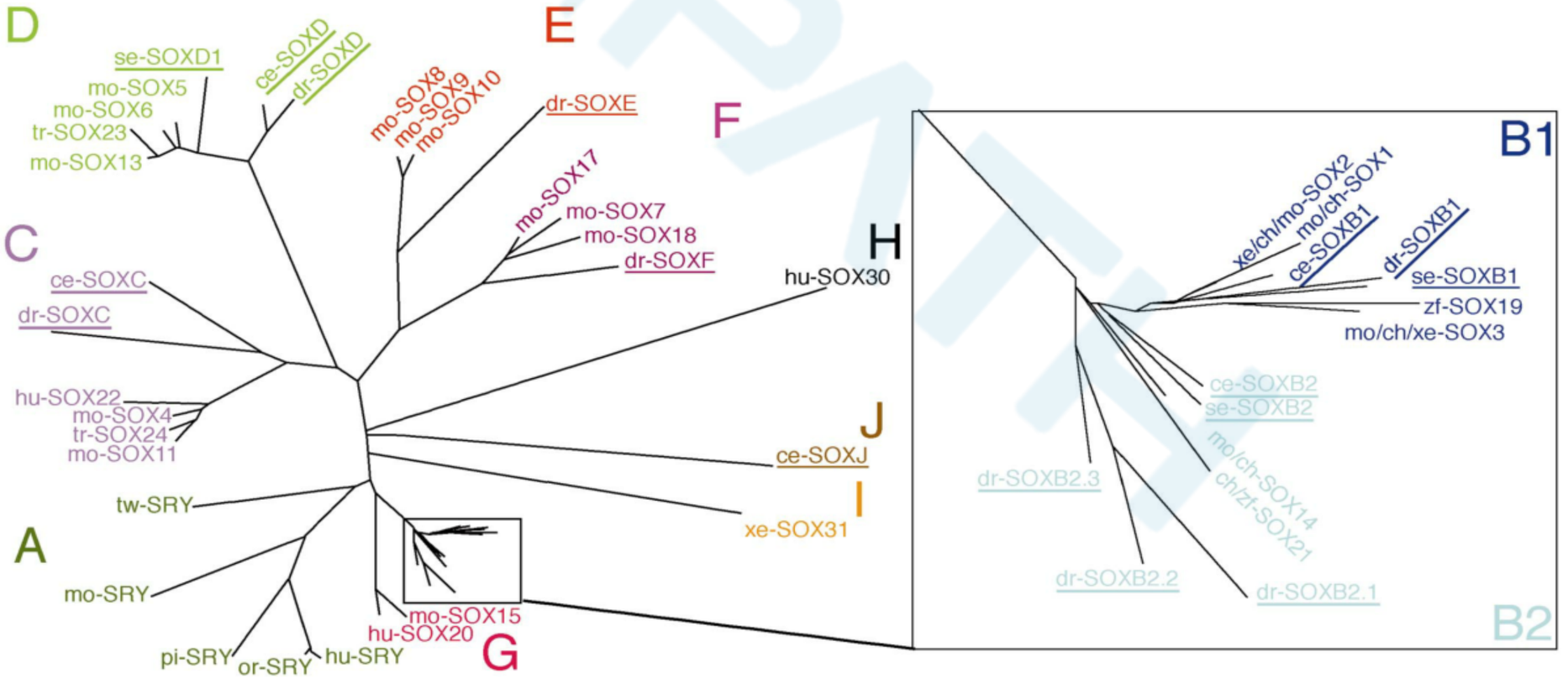
Part

01 背景知识

Background knowledge

背景知识
Background knowledge

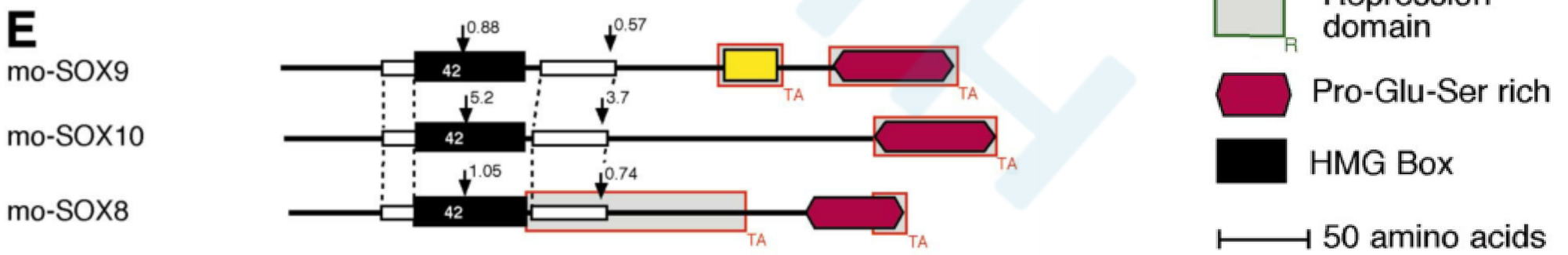
- SOX蛋白属于转录因子的HMG (high mobility group)结构域
- SOX-E是最早出现在神经板边缘的细胞亚群的标记物，产生神经嵴谱系细胞
- SOX10（ SRY-related HMG-box 10）是SOX-E家族成员之一，是各种神经嵴来源细胞正常发育所必需的。与其他SOX-E成员转录因子具有高度的序列同源性，调控和协调胚层形成、器官发育、细胞活性等多种发育过程。



Developmental Biology 227, 239 –255 (2000) doi:10.1006/dbio.2000.9883

背景知识
Background knowledge

- SOX10转录因子在Schwann细胞和黑素细胞系中均有表达，在其发育、成熟以及维持过程中起重要作用，可作为相应肿瘤的标志物而且相比于S100更敏感和特异
- SOX10也表达于乳腺、支气管黏膜下层和唾液腺的正常肌上皮细胞，以及软组织的肌上皮肿瘤和三阴性及化生乳腺癌。



Developmental Biology 227, 239 –255 (2000) doi:10.1006/dbio.2000.9883

背景知识
Background knowledge

MODERN PATHOLOGY (2013), 1–10

SOX10 is a novel marker of acinus and intercalated duct differentiation in salivary gland tumors: a clue to the histogenesis for tumor diagnosis

Rie Ohtomo[1,7], Taisuke Mori[2,7], Shinsuke Shibata[3], Koji Tsuta[1], Akiko M Maeshima[1], Chihiro Akazawa[4], Yukio Watabe[5], Kazufumi Honda[5], Tesshi Yamada[5], Seiichi Yoshimoto[6], Masao Asai[6], Hideyuki Okano[3], Yae Kanai[2] and Hitoshi Tsuda[1]

[1]Department of Pathology and Clinical Laboratory, National Cancer Center Hospital, Tokyo, Japan; [2]Division of Molecular Pathology, National Cancer Center Research Institute, Tokyo, Japan; [3]Department of Physiology, Keio University School of Medicine, Tokyo, Japan; [4]Department of Biochemistry and Biophysics, Graduate School of Health and Sciences, Tokyo Medical and Dental University, Tokyo, Japan; [5]Division of Chemotherapy and Clinical Research, National Cancer Center Research Institute, Tokyo, Japan and [6]Department of Head and Neck Oncology and Plastic Surgery, National Cancer Center Hospital, Tokyo, Japan

背景知识

Background knowledge

Table 1 Immunohistochemical profile of salivary gland tumors

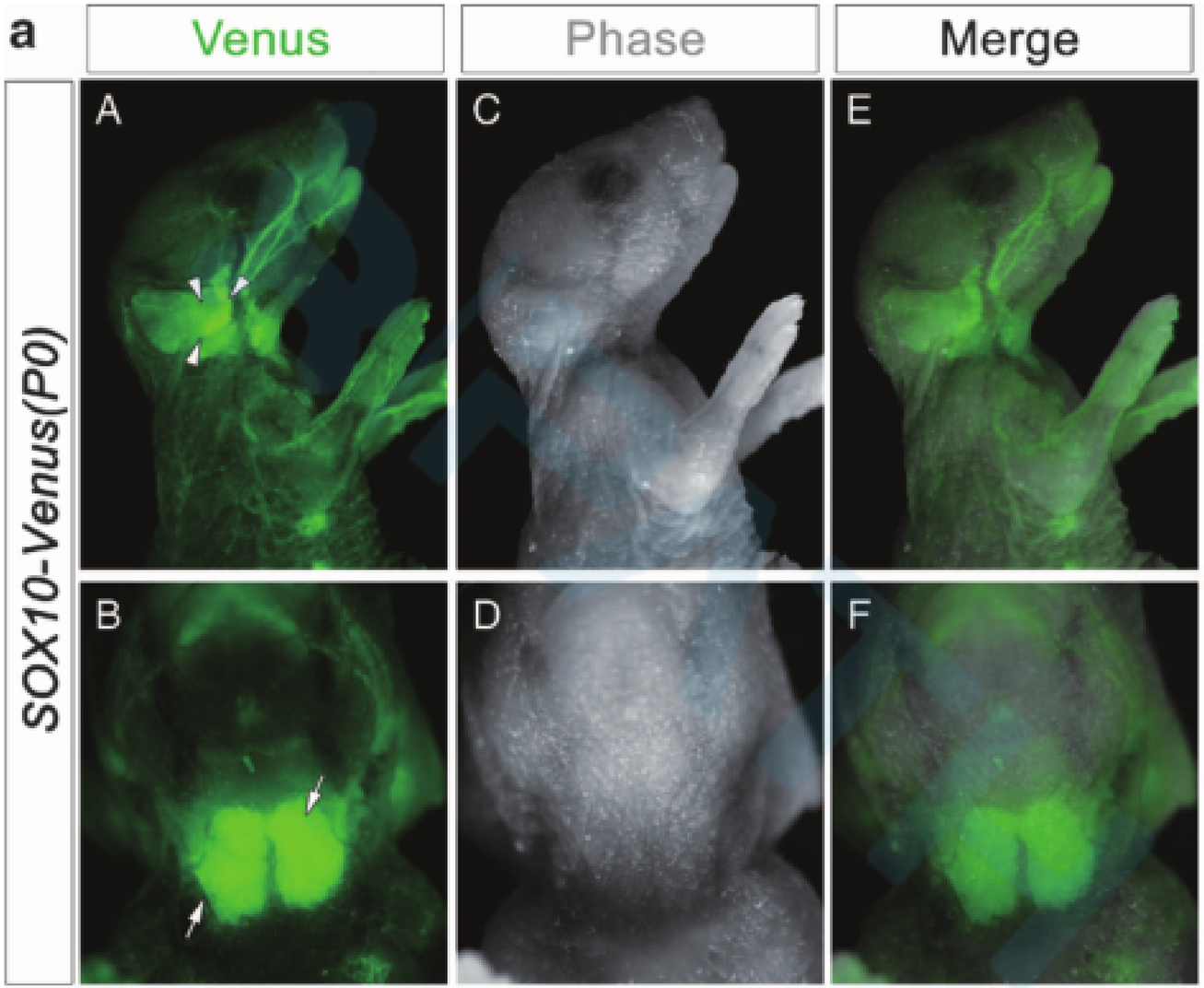
Histological diagnosis	*No. of positive cases (%)*						
	n	*SOX10*	*p63*	*SMA*	*Calponin*	*S100*	*GFAP*
Malignant							
ACC	23	22 (96)	21 (91)	21 (91)	18 (78)	21 (91)	5 (21)
AciCC	8	8 (100)	0	0	0	1(13)	0
SDC	6	0	0	0	0	1 (17)	3 (50)
MuEC	6	0	2 (33)	0	0	1 (17)	2 (33)
EMC	5	5 (100)	5 (100)	5 (100)	3 (60)	4 (80)	3 (60)
MyEC	1	1	1	1	0	0	0
OncCa	1	0	0	0	0	0	0
CaNOS[a]	22	5 (23)	10 (45)	0	4 (18)	9 (41)	5 (23)
Benign							
PA[b]	10	10 (100)	8 (80)	7 (70)	7 (70)	10 (100)	9 (90)
ME	4	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	3 (75)
Onc	2	0	2 (100)	0	0	0	1 (50)
WT	2	0	2 (100)	0	0	0	0

Abbreviations: ACC, adenoid cystic carcinoma; AciCC, acinic cell carcinoma; CaNOS, carcinoma not otherwise specified; EMC, epithelial-myoepithelial carcinoma; GFAP, glial fiburillary acidic protein; MuEC, mucoepidermoid carcinoma; MyEC, myoepithelial carcinoma; ME, myoepithelioma; Onc, Oncocytoma; OncCa, oncocytic carcinoma; PA, pleomorphic adenoma; SMA, smooth muscle actin; SDC, salivary duct carcinoma; WT, Warthin tumor.
When the case had >10% positive cells, it was counted as positive.
[a]Including CaNOS components of seven cases of carcinoma ex pleomorphic adenoma cases.
[b]Including PA components of four cases of carcinoma ex pleomorphic adenoma cases.

Modern Pathology advance online publication, 5 April 2013; doi:10.1038/modpathol.2013.54

背景知识

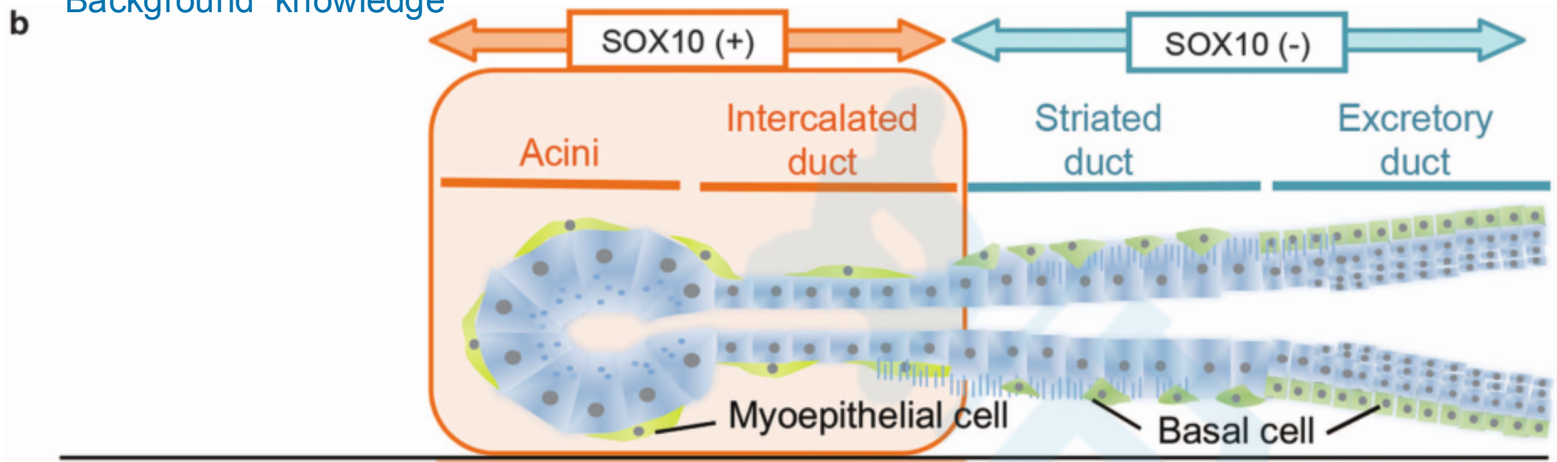
Background knowledge



Modern Pathology advance online publication, 5 April 2013; doi:10.1038/modpathol.2013.54

背景知识

Background knowledge



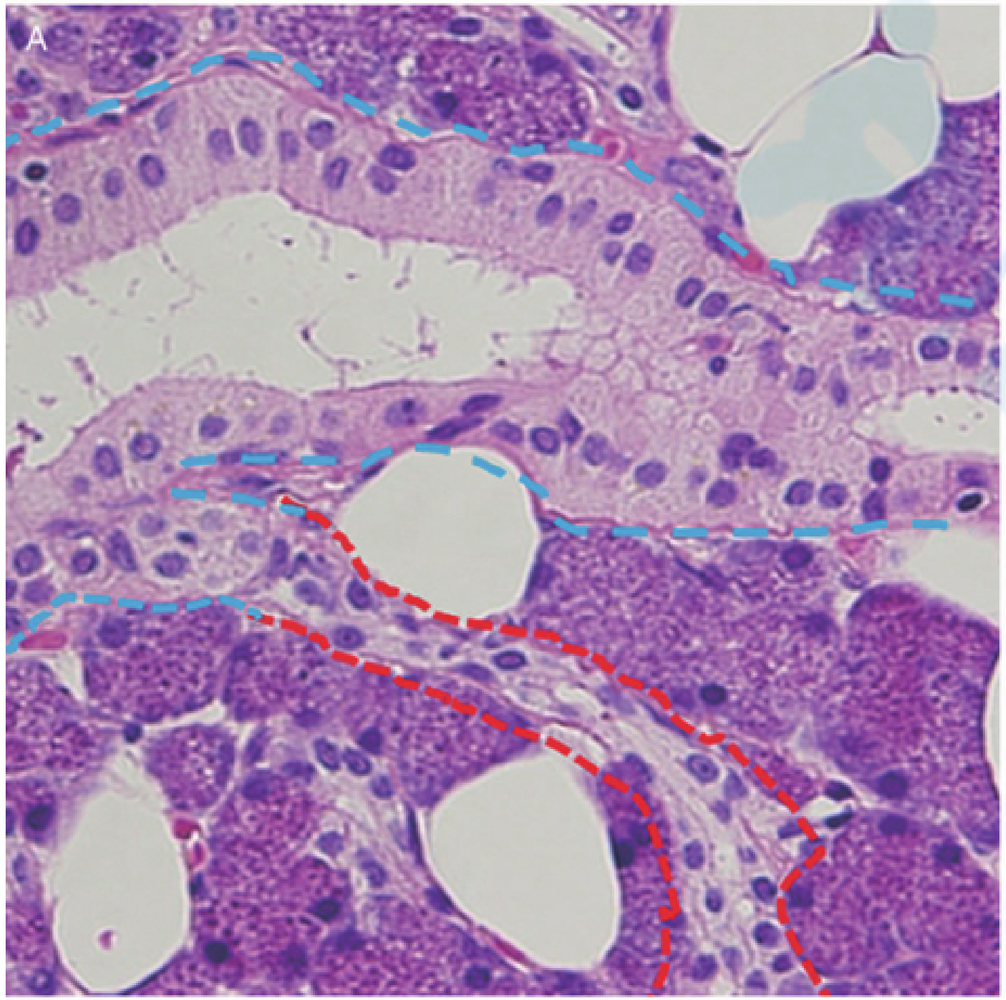
		Acini	Intercalated duct	Striated duct	Excretory duct
SOX10	luminal	++/H*	++/L	-	-
	abluminal	++/H	++/H	-	-
p63	luminal	-	-	-	-
	abluminal	++/H	++/H	++/H	++/H
SMA	luminal	-	-	-	-
	abluminal	++/H	++/H	-	-
Calponin	luminal	-	-	-	-
	abluminal	++/H	++/H	-	-
S100	luminal	-	-	-	-
	abluminal	++/H	++/H	-	-
GFAP	luminal	-	-	±	±
	abluminal	-	-	-	-

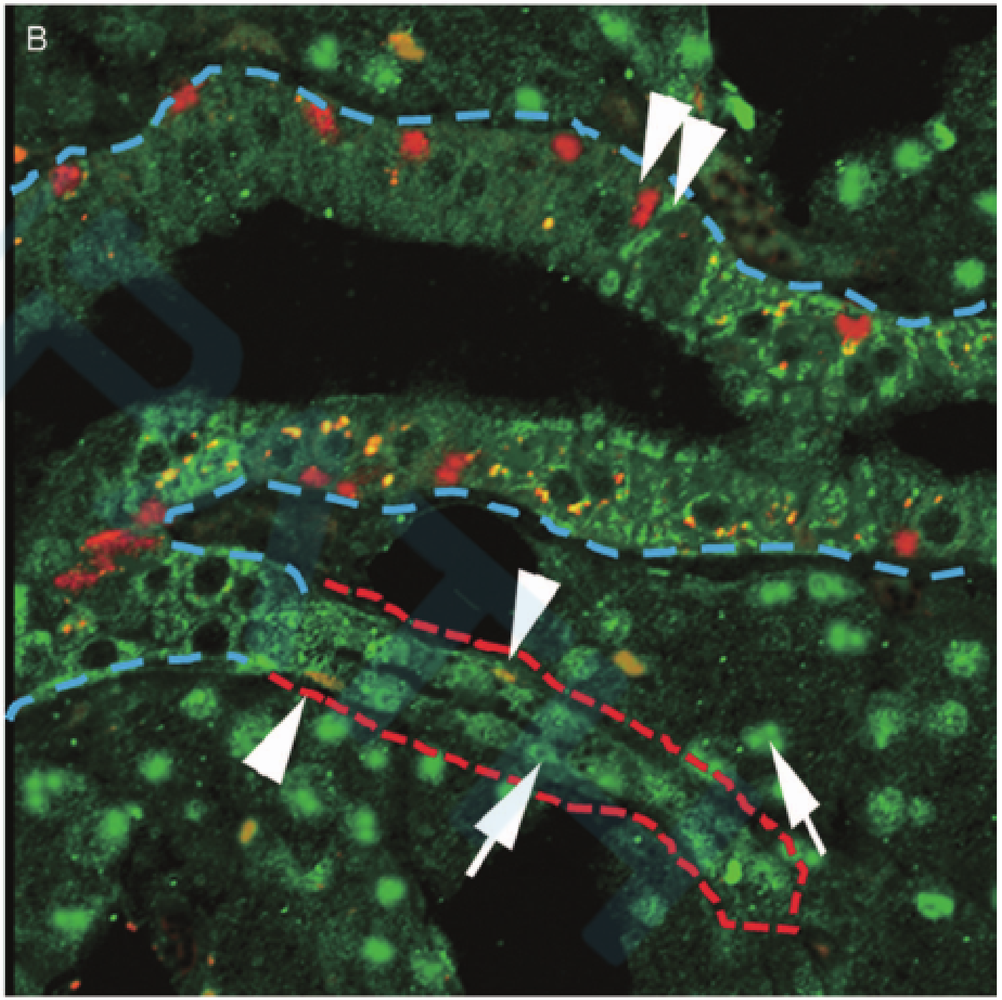
The proportion of positive cells : ++, >90% of positive cells; +, 11-90%; ±, 1-10%; -, negative.
The intensity of positive cells; H, high intensity; L, low intensity. * Serous(++)>Mucinous (+) acini luminal cell
SMA: Smooth muscle actin; GFAP: Glial fibrillary acidic protein

- SOX10在正常人唾液腺的几乎所有腺泡和闰管中均有表达。
- 表达模式与p63不同，p63在包括肌上皮细胞和基底细胞在内的管腔外细胞中表达，但在管腔细胞中不表达。
- 表达模式不同于SMA、calponin、S100和GFAP，后者常被用作肌上皮标志物。GFAP在正常的肌上皮细胞中不表达，但在肿瘤性肌上皮细胞中表达。
- SOX10在与腺泡和闰管相似的肿瘤（如腺泡细胞癌、腺样囊性癌、多形性腺瘤、上皮性肌上皮癌、肌上皮瘤和肌上皮癌）中高表达，在类似于纹状管和分泌导管的肿瘤(如黏液表皮样癌、涎腺导管癌和Warthin肿瘤)中不表达

Modern Pathology advance online publication, 5 April 2013; doi:10.1038/modpathol.2013.54

背景知识
Background knowledge



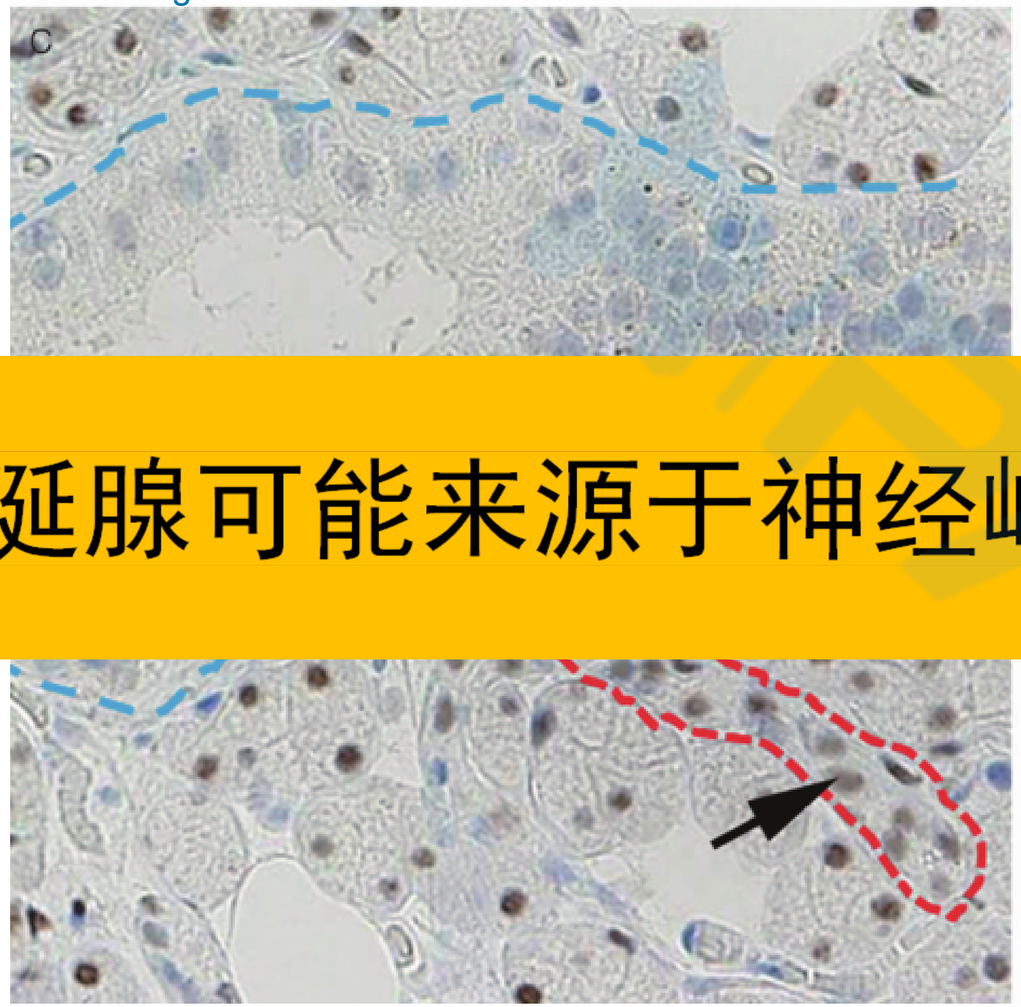


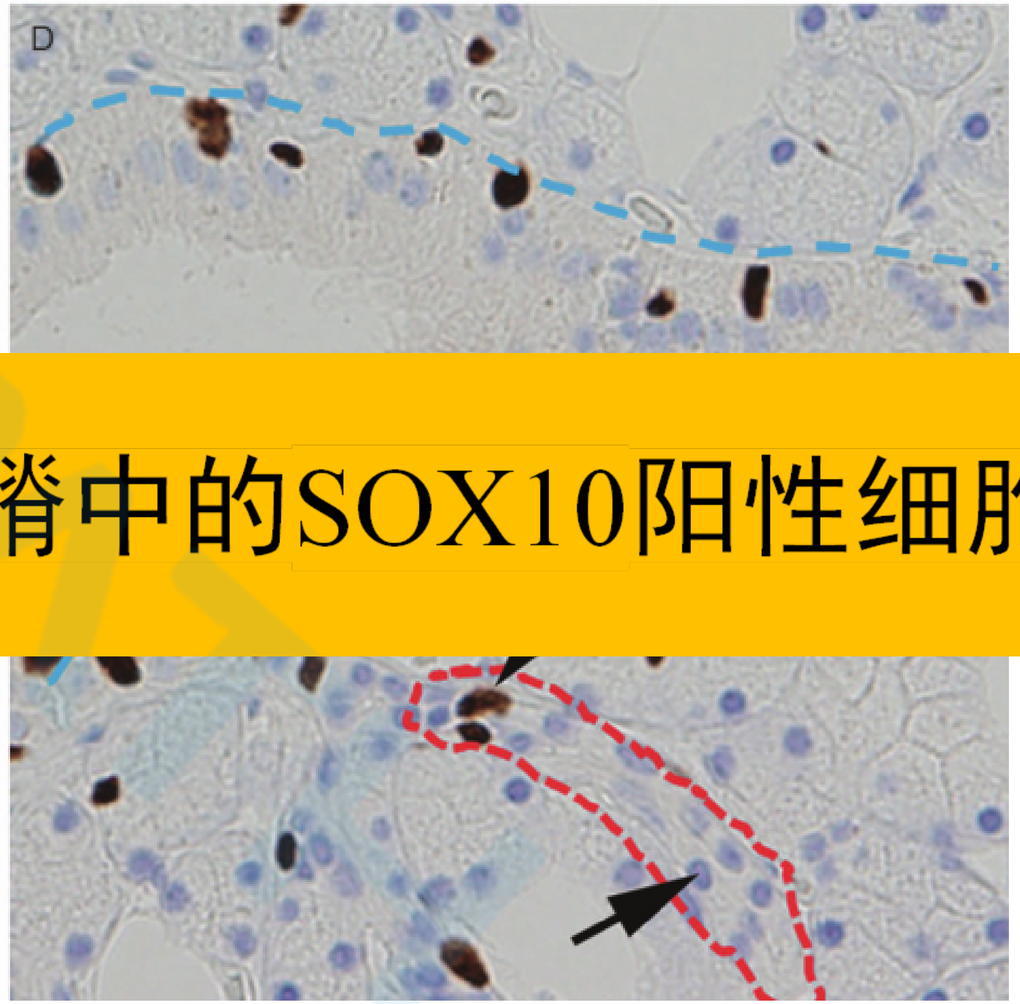
SOX10(绿色)
p63(红色)

Modern Pathology advance online publication, 5 April 2013; doi:10.1038/modpathol.2013.54

背景知识

Background knowledge





涎腺可能来源于神经嵴中的SOX10阳性细胞

SOX10

p63

Modern Pathology advance online publication, 5 April 2013; doi:10.1038/modpathol.2013.54

背景知识
Background knowledge

ELSEVIER

Human Pathology
Volume 56, October 2016, Pages 134-142

Original contribution

SOX10-positive salivary gland tumors: a growing list, including mammary analogue secretory carcinoma of the salivary gland, sialoblastoma, low-grade salivary duct carcinoma, basal cell adenoma/adenocarcinoma, and a subgroup of mucoepidermoid carcinoma ☆ ☆☆

Min-Shu Hsieh MD [a, b], Yi-Hsuan Lee MD [a], Yih-Leong Chang MD [a, b] ✉

背景知识
Background knowledge

In general, SOX10 expression can be observed in salivary gland tumors with either one of the 4 major types of cells:

①acinic cells （AciCC）

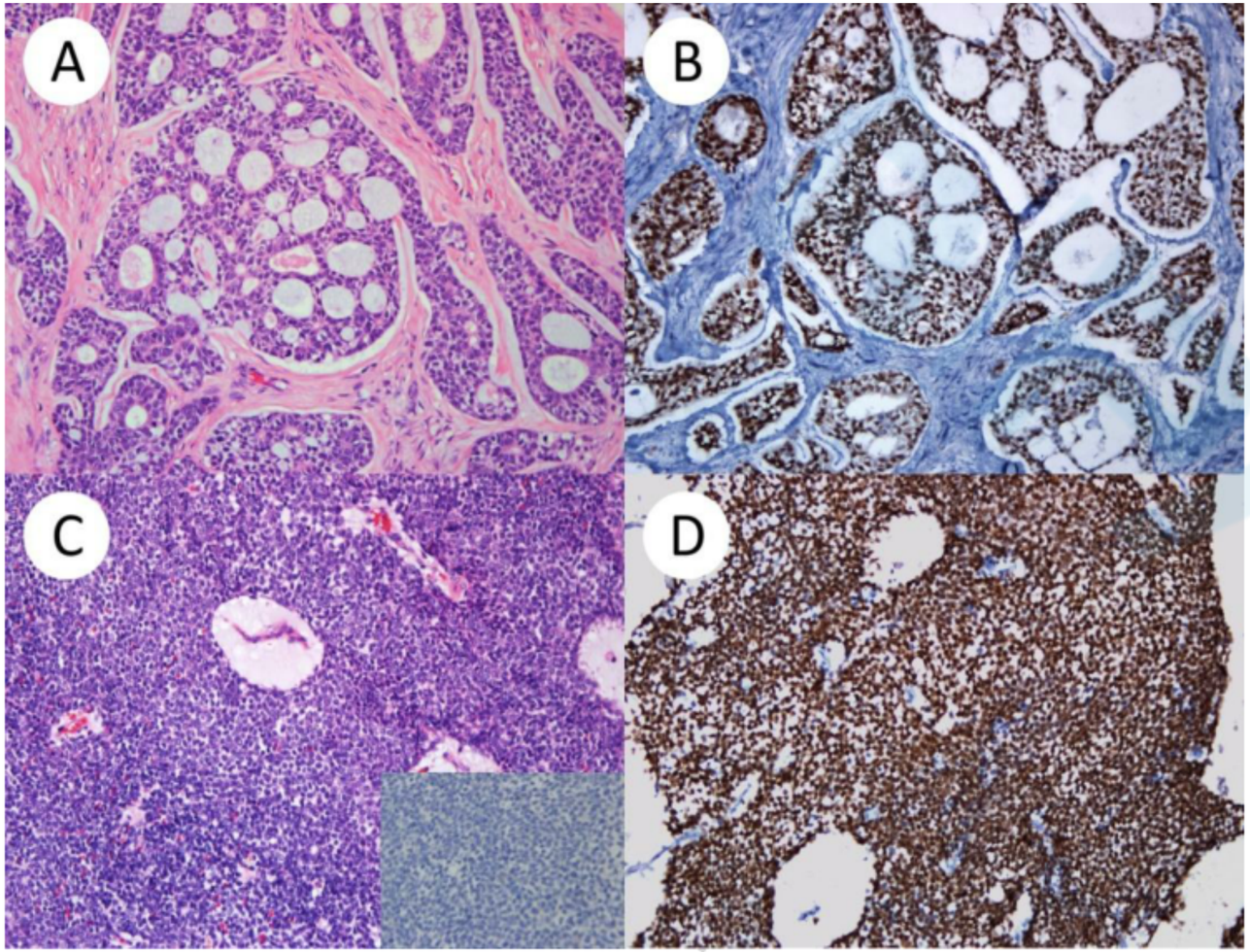
②cuboidal ductal cells with low grade cytologic（MASC， low-grade salivary duct carcinoma)

③basaloid cells (AdCC, basal cell adenoma/adenocarcinoma, sialoblastoma)

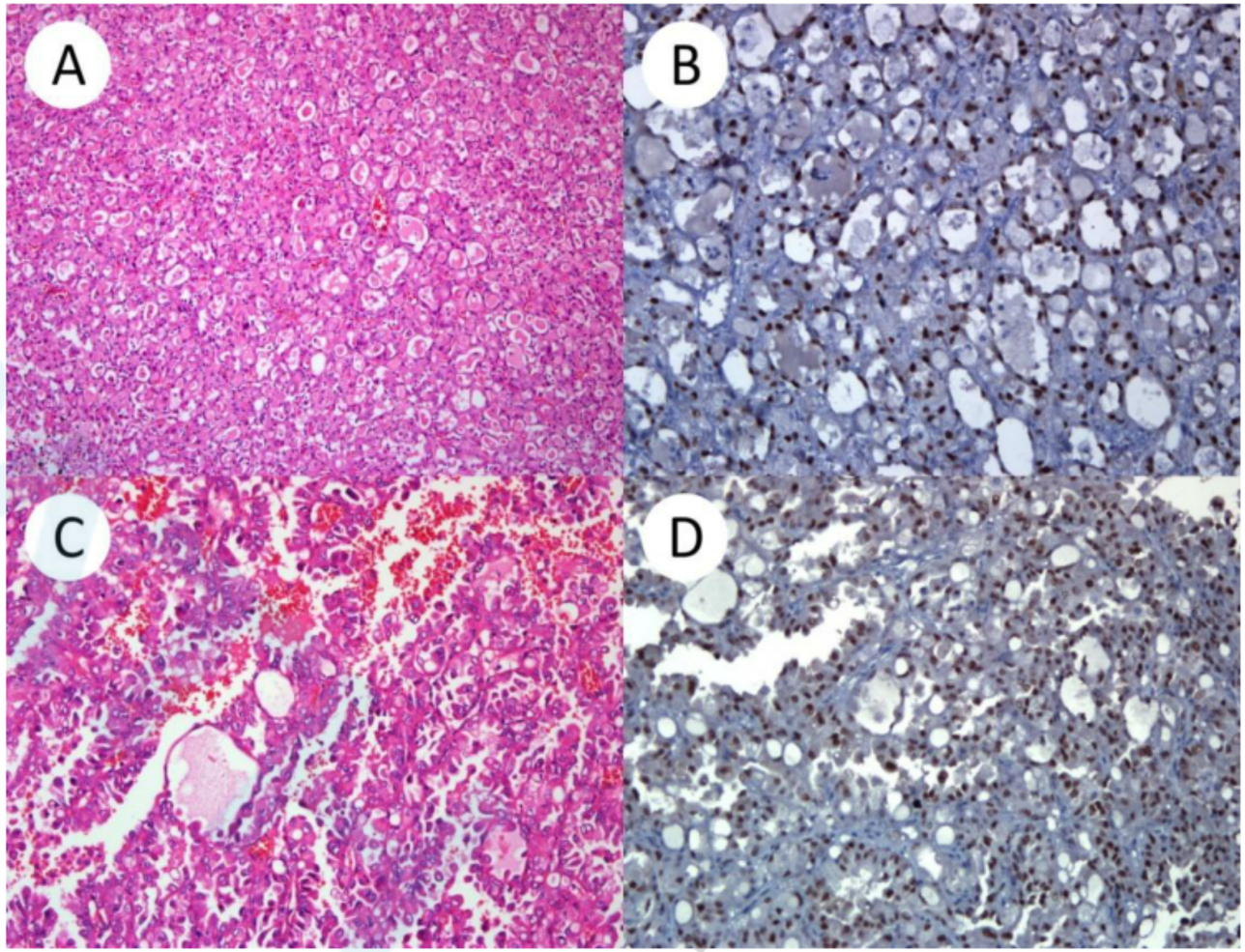
④myoepithelial cells (myoepithelial tumor)

背景知识

Background knowledge



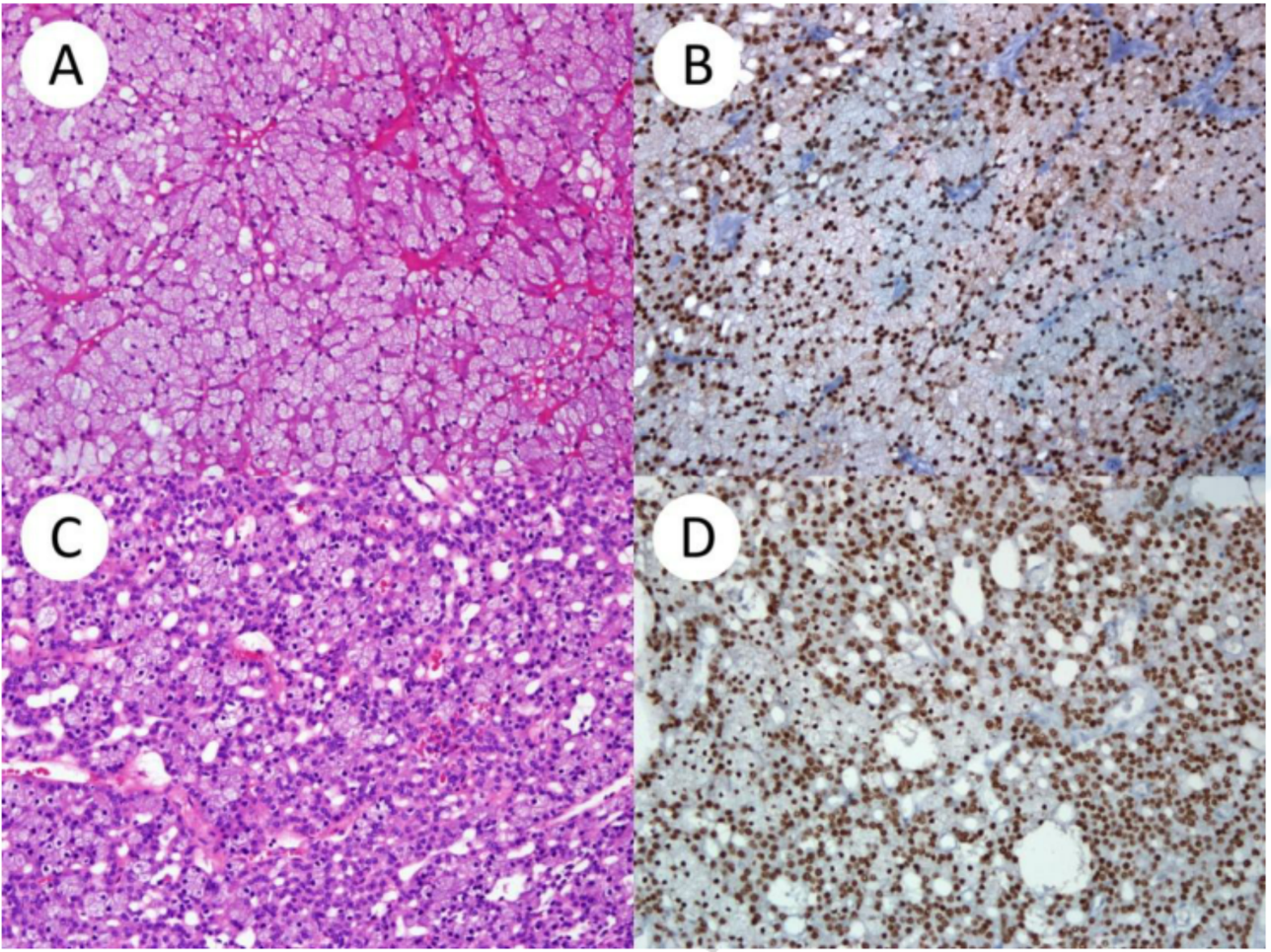
ADCC



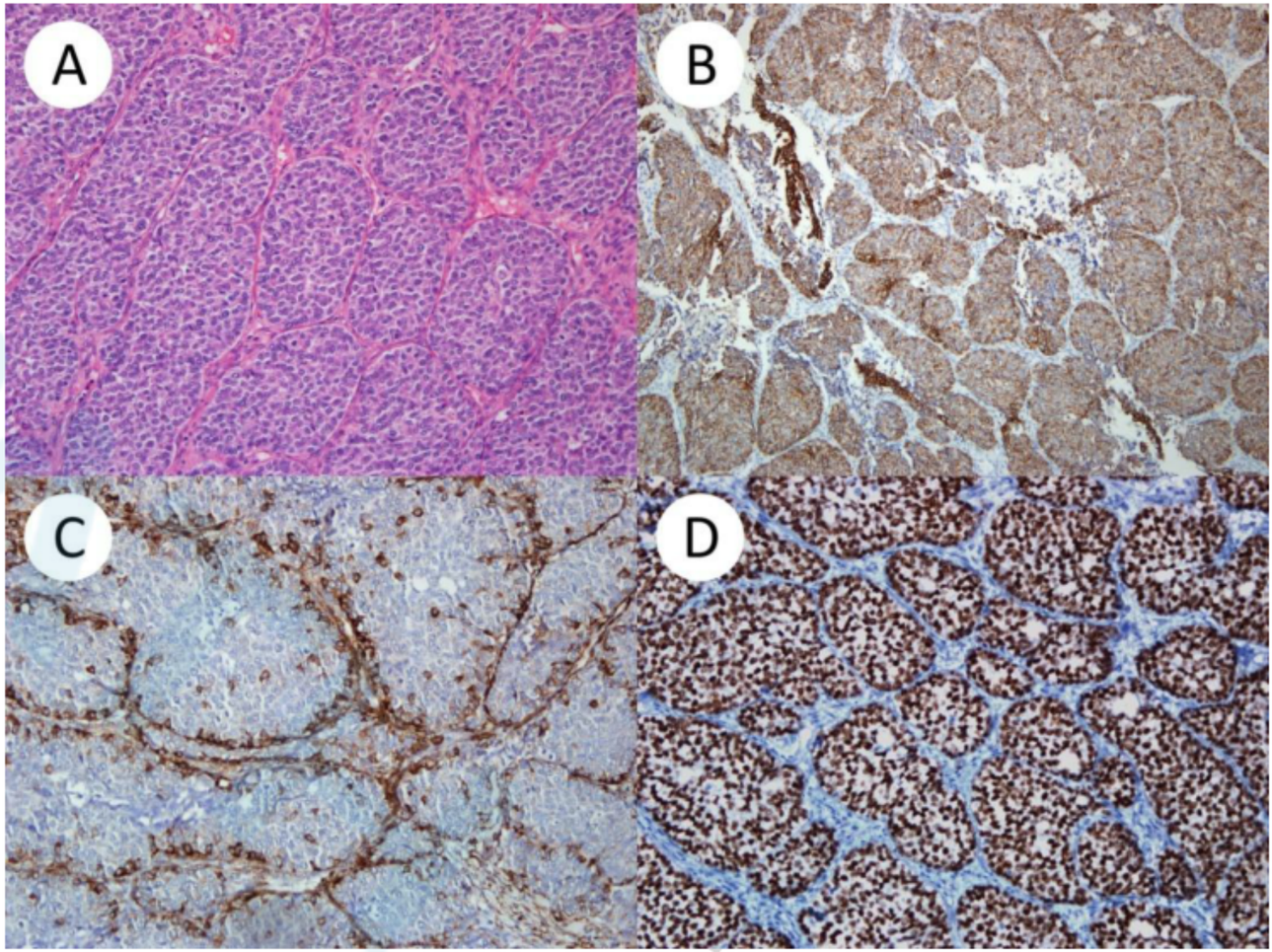
MASC

背景知识

Background knowledge

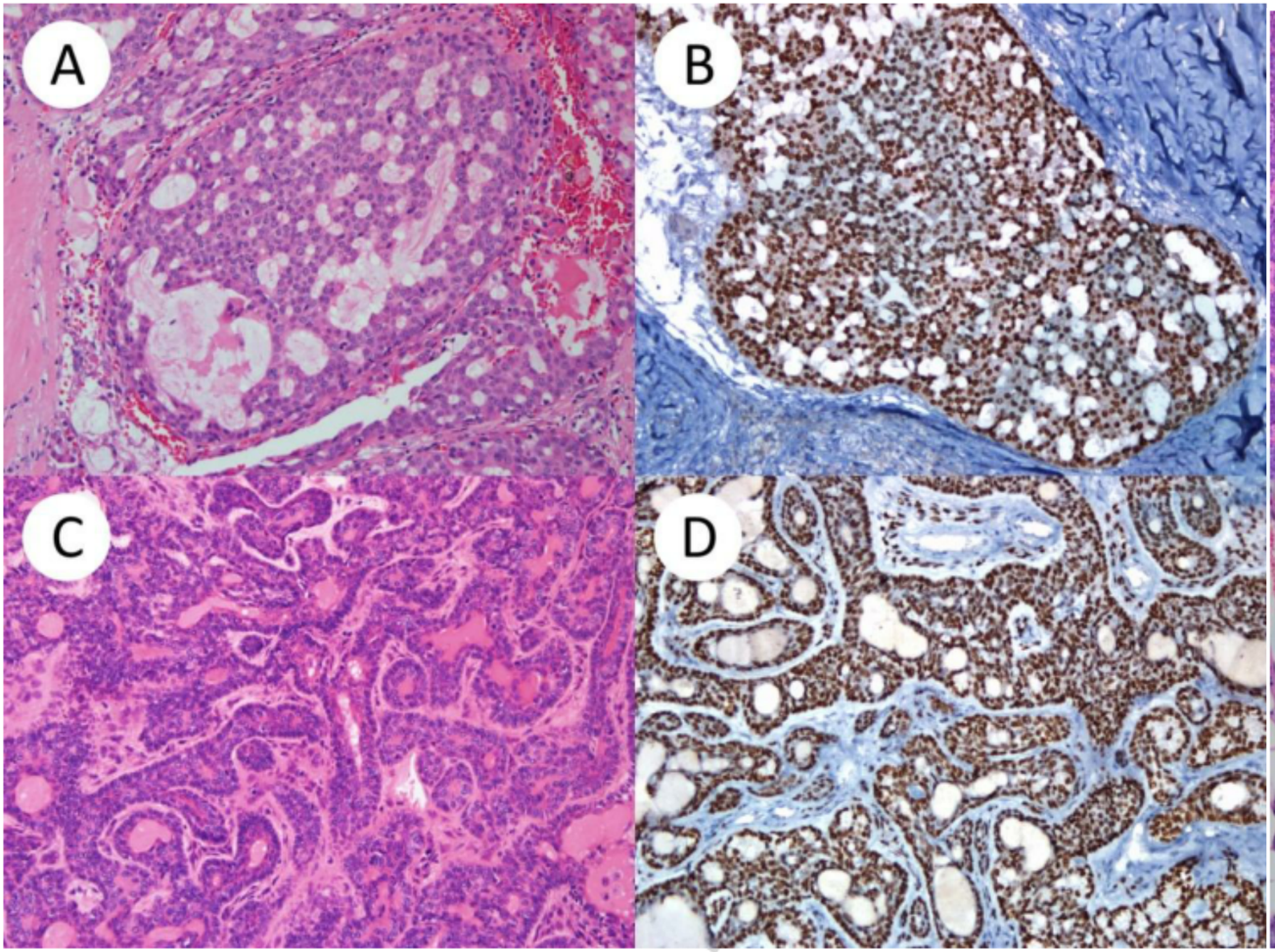


AciCC

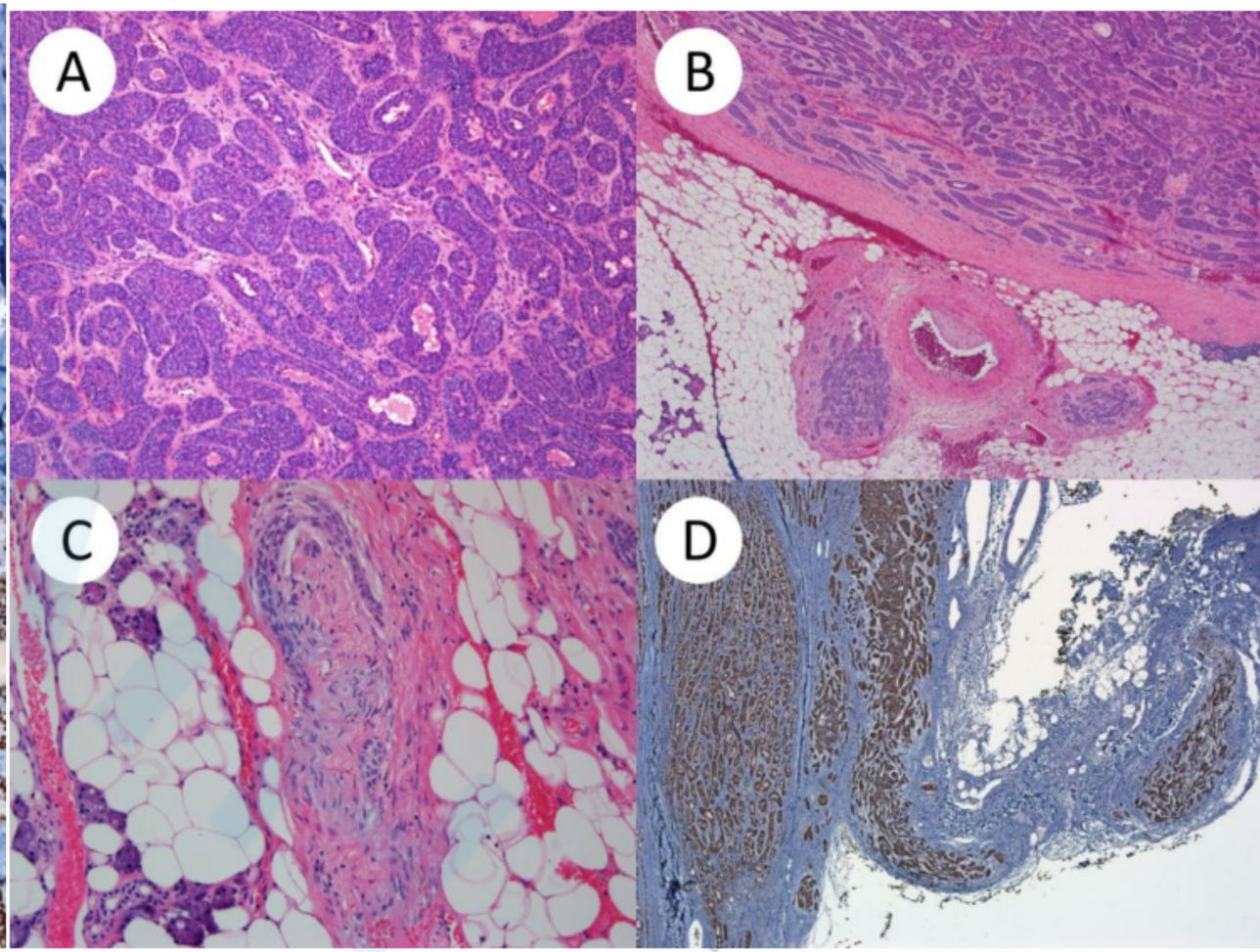


sialoblastoma

Low-grade salivary duct carcinoma



Basal cell adenoma



Basal cell adenocarcinoma

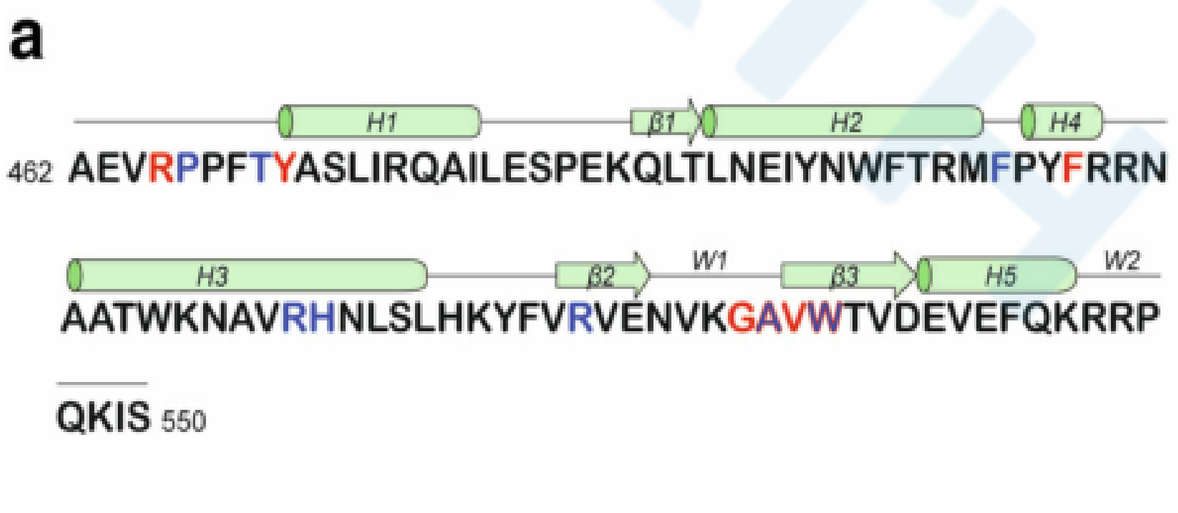
背景知识

Background knowledge

- FOX（The forkhead box）转录因子家族在发育、癌变、新陈代谢和免疫等多种生物学过程中发挥重要作用。FOX家族在人类中有50个成员，FOX蛋白进一步分为FOXA到FOXS亚家族，每个亚家族有1-6个成员

- FOXP亚组由四个基因(FOXP1-FOXP4)编码，对小鼠突变的分析表明，FOXP1在脊髓运动神经元、淋巴细胞和心肌细胞的发育中起关键作用

- FOXP1（transcription factor forkhead box protein P1）属于FOX转录因子家族的亚家族P。



背景知识
Background knowledge

Gene Expression Patterns xxx (2016) 1–9

Contents lists available at ScienceDirect

Gene Expression Patterns

journal homepage: http://www.elsevier.com/locate/gep

Expression of forkhead box transcription factor genes *Foxp1* and *Foxp2* during jaw development

Jeffry M. Cesario [a], Asma A. Almaidhan [b], Juhee Jeong [a, *]

[a] Department of Basic Science and Craniofacial Biology, New York University College of Dentistry, 345 East 24th Street, New York, NY 10010 United States
[b] Department of Orthodontics, New York University College of Dentistry, 345 East 24th Street, New York, NY 10010 United States

FOXP1可以在神经嵴来源的细胞和中胚层来源的细胞中都有表达，而大多数基因只在这两个谱系中的一个中表达

FOXP1基因突变时可能会出现FOXP1综合征，表现为语言缺陷、智力低下和（或）自闭症谱系障碍，还可以表现出面部和颈部肌肉的全身性功能缺陷(咀嚼、吞咽、咳嗽、大笑困难)和特征性面部特征(三角脸、突出的额头、短而宽的鼻子、低垂的耳朵、向下倾斜的眼睛、高弓的腭部、宽大的牙齿)。

Gene Expr Patterns. 2016;20:111–119.

背景知识

Background knowledge

Odontogenic carcinomas	
Ameloblastic carcinoma	9270/3
Primary intraosseous carcinoma, NOS	9270/3
Sclerosing odontogenic carcinoma	9270/3
Clear cell odontogenic carcinoma	9341/3*
Ghost cell odontogenic carcinoma	9302/3*
Odontogenic carcinosarcoma	8980/3
Odontogenic sarcomas	9330/3
Benign epithelial odontogenic tumours	
Ameloblastoma	9310/0
Ameloblastoma, unicystic type	9310/0
Ameloblastoma, extraosseous/peripheral type	9310/0
Metastasizing ameloblastoma	9310/3
Squamous odontogenic tumour	9312/0
Calcifying epithelial odontogenic tumour	9340/0
Adenomatoid odontogenic tumour	9300/0
Benign mixed epithelial and mesenchymal odontogenic tumours	
Ameloblastic fibroma	9330/0
Primordial odontogenic tumour	
Odontoma	9280/0
Odontoma, compound type	9281/0
Odontoma, complex type	9282/0
Dentinogenic ghost cell tumour	9302/0
Benign mesenchymal odontogenic tumours	
Odontogenic fibroma	9321/0
Odontogenic myxoma/myxofibroma	9320/0
Cementoblastoma	9273/0
Cemento-ossifying fibroma	9274/0
Odontogenic cysts of inflammatory origin	
Radicular cyst	
Inflammatory collateral cysts	
Odontogenic and non-odontogenic developmental cysts	
Dentigerous cyst	
Odontogenic keratocyst	
Lateral periodontal cyst and botryoid odontogenic cyst	
Gingival cyst	
Glandular odontogenic cyst	
Calcifying odontogenic cyst	9301/0
Orthokeratinized odontogenic cyst	
Nasopalatine duct cyst	

目的

Research purpose

几种牙源性肿瘤可显示与基底样涎腺肿瘤的形态相似性，因此在小型活检和不典型部位的肿瘤中，这种区分可能具有挑战性。

通过使用基因组学方法，找到可用于牙源性肿瘤诊断分类的具有敏感性和特异性的标记物

Part

02 材料与方法

MATERIALS AND METHODS

病例选择

Case Selection

经IRB批准，从加州大学旧金山皮肤病理学和口腔病理服务部、温哥华综合医院和斯坦福大学医院收集了108例牙源性肿瘤。

这些病例包括：

35例成釉细胞瘤，
5例成釉细胞纤维瘤（ABF）
2例成釉细胞癌（ABC）
4例牙源性钙化囊肿（COC）
3例牙源性腺样瘤（AOT）
2例腺牙源性囊肿（GOC）
1例透明细胞癌（CCC）
56例牙源性角化囊肿

从斯坦福大学医院的外科病理档案中检索了173例涎腺肿瘤。

这些病例包括：

9例基底细胞腺瘤
63例腺样囊性癌
7例多形性(低级别)腺癌
9例肌上皮瘤
43例多形性腺瘤
7例腺泡细胞癌
3例涎腺导管癌
9例嗜酸细胞瘤
22例黏液表皮样癌
1例低级别腺癌（NOS）

病例选择

Case Selection

28例成釉细胞瘤，
3例成釉细胞纤维瘤（ABF）
2例成釉细胞癌（ABC）
4例牙源性钙化囊肿（COC）
3例牙源性腺样瘤（AOT）
2例腺牙源性囊肿（GOC）
1例透明细胞癌（CCC）

43例牙源性肿瘤

6例基底细胞腺瘤
4例多形性(低级别)腺癌
3例肌上皮瘤
4例腺鳞癌
20例腺样囊性癌

37例涎腺肿瘤

接受 LCM，RNA-seq
并生成基因表达谱

进行层次聚类分析及
差异基因表达分析

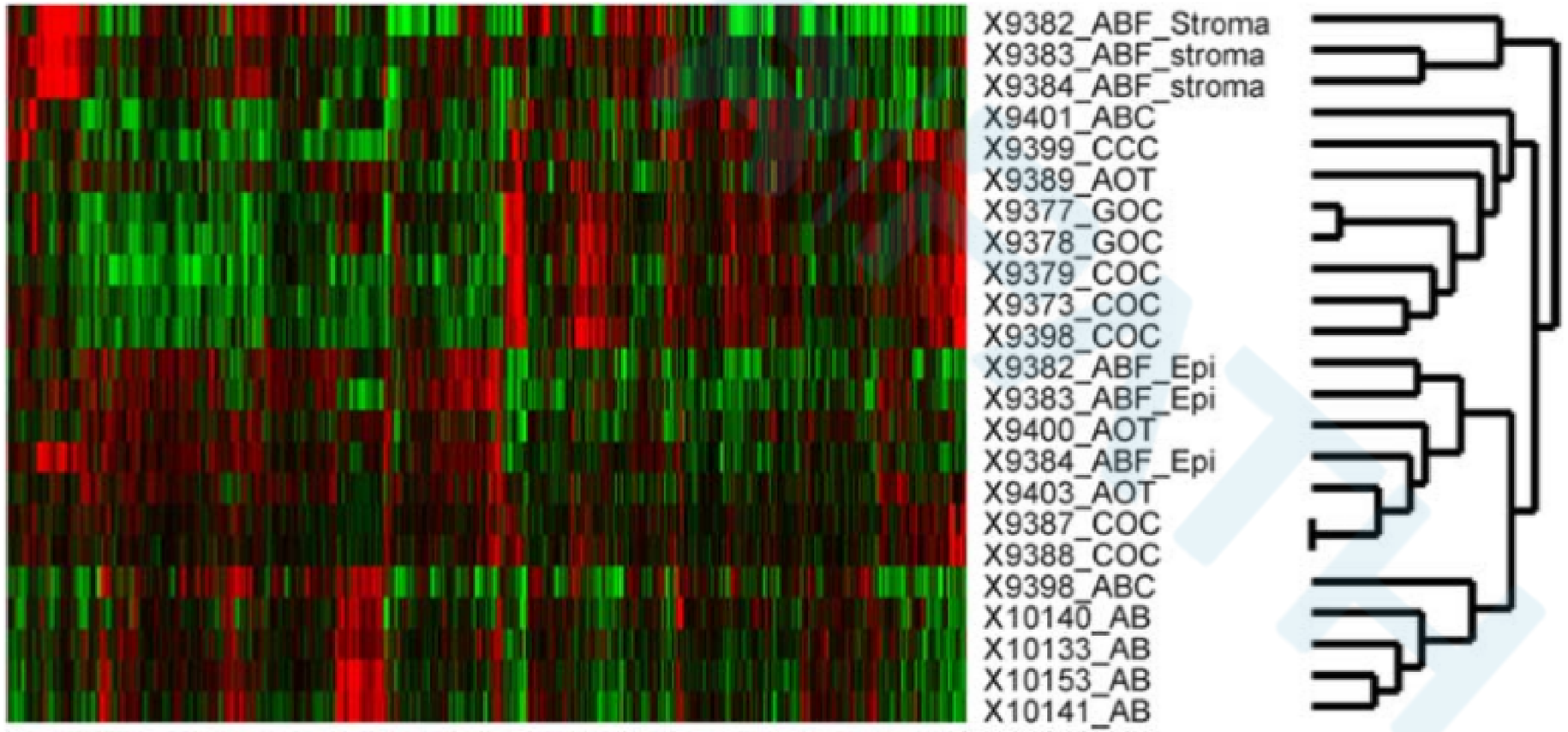
Part

03 结果

RESULTS

基因表达谱分析

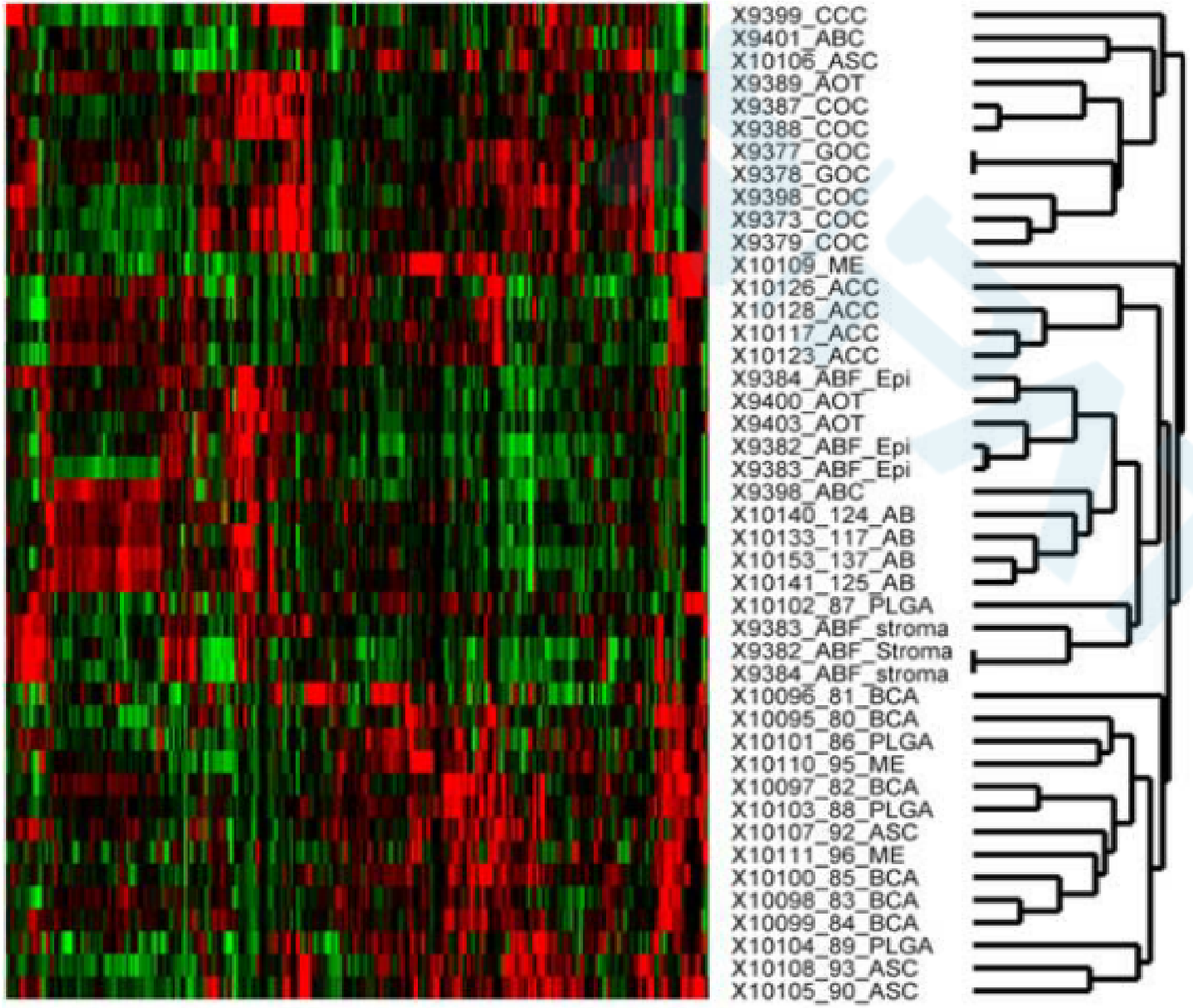
Gene Expression Profile Analysis



成釉细胞瘤（AB）
成釉细胞纤维瘤（ABF）
成釉细胞癌（ABC）
牙源性钙化囊肿（COC）
牙源性腺样瘤（AOT）
腺牙源性囊肿（GOC）
透明细胞癌（CCC）

基因表达谱分析

Gene Expression Profile Analysis



成釉细胞瘤（AB）
成釉细胞纤维瘤（ABF）
成釉细胞癌（ABC）
牙源性钙化囊肿（COC）
牙源性腺样瘤（AOT）
腺牙源性囊肿（GOC）
透明细胞癌（CCC）
肌上皮瘤（ME）
多形性低级别腺瘤（PLGA）
基底细胞腺瘤（BCA）
腺鳞癌（ASC）

基因表达谱分析

Gene Expression Profile Analysis

为了确定对鉴别成釉细胞瘤有用的生物标志物，用DESeq 2进行了差异基因表达分析。

在大量基因中，我们鉴定出6个表达阳性的候选基因：

PITX2(校正后P=9.57E−29)
FLRT2(校正后P=1.04E−20)
MSX2(校正后P=1.30E−09)
PTHLH(校正后P=1.16E−12)
EPHA7(校正后P=1.60E−09)
FOXP1(校正后P=6.93E−08)。

SOX10在成釉细胞瘤中呈阴性表达(校正后P=7.53E−24)，而在基底细胞腺瘤、多形性腺癌、腺样囊性癌和肌上皮瘤中呈中性或阳性表达。

结 果
Results

TABLE 1. FOXP1/SOX10 Immunophenotypes in 108 Odontogenic Tumors

	n (%)			
	FOXP1$^+$/ SOX10$^-$	**FOXP1$^+$/ SOX10$^+$**	**FOXP1$^-$/ SOX10$^-$**	**FOXP1$^-$/ SOX10$^+$**
Ameloblastoma	34/35 (97)	0/35 (0)	1/35 (3)	0/35 (0)
ABC	2/2 (100)	0/2 (0)	0/2 (0)	0/2 (0)
ABF	5/5 (100)	0/5 (0)	0/5 (0)	0/5 (0)
COC	4/4 (100)	0/4 (0)	0/4 (0)	0/4 (0)
AOT	1/3 (33)	0/3 (0)	2/3 (67)	0/3 (0)
GOC	2/2 (100)	0/2 (0)	0/2 (0)	0/2 (0)
Clear cell odontogenic carcinoma	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)
Odontogenic keratocyst	53/56 (95)	0/56 (0)	3/56 (5)	0/56 (0)

结 果
Results

TABLE 2. FOXP1/SOX10 Immunophenotypes in 173 Salivary Gland Tumors

	n (%)			
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Basal cell adenoma (9 cases)	0/9 (0)	8/9 (89)	1/9 (11)	0 (0)
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Low-grade adenocarcinoma, not otherwise specified* (1 case)	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)

*This case was subsequently reclassified as ameloblastoma after consensus review.

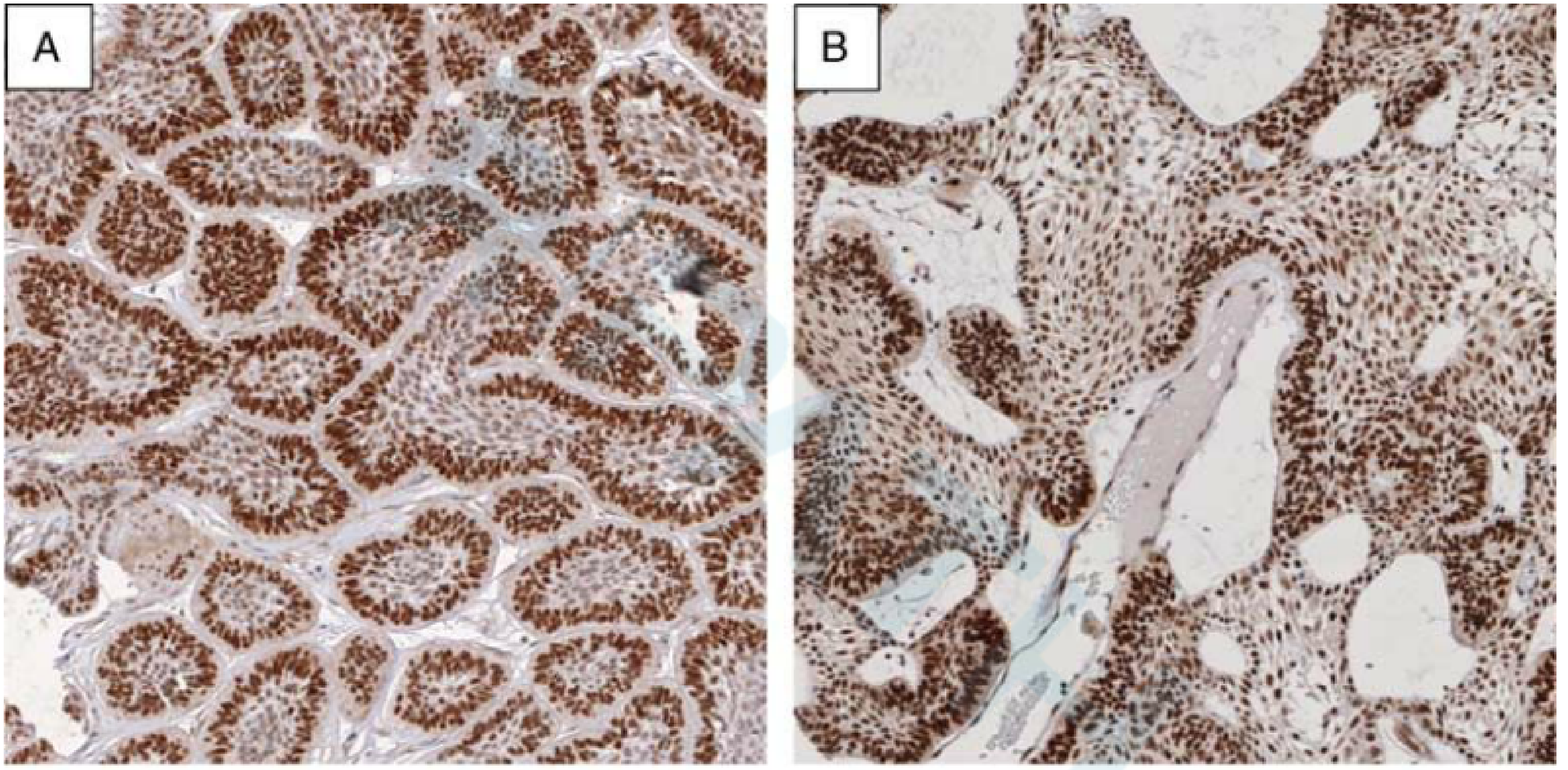
- ✓ SOX10在涎腺肿瘤中表达率很高，在腺泡状细胞癌中始终观察到SOX10的表达
- ✓ 所有成釉细胞瘤均对SOX10阴性（0/35）
- ✓ FOXP1和SOX10的共表达见于很多涎腺肿瘤
- ✓ 另有一例未明确说明的低级别腺癌病例显示了强烈的FOXP1表达和完全阴性的SOX10表达。经过共识审查后，该病例随后被重新分类为成釉细胞瘤。

结 果
Results

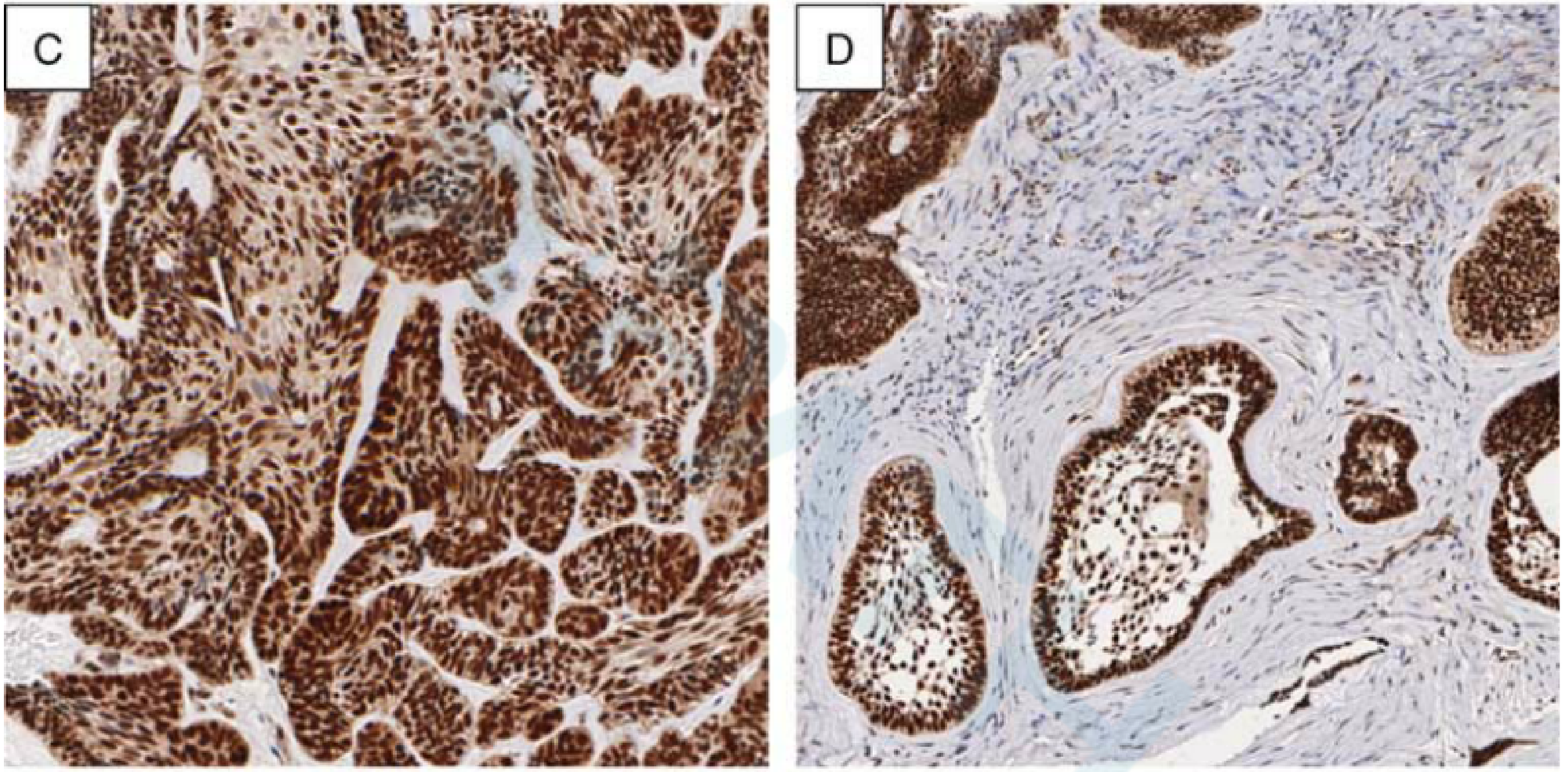
免疫组化染色的判读标准：

SOX10染色结果
阴性(肿瘤细胞核着色<10%)
阳性(肿瘤细胞核着色≥10%)

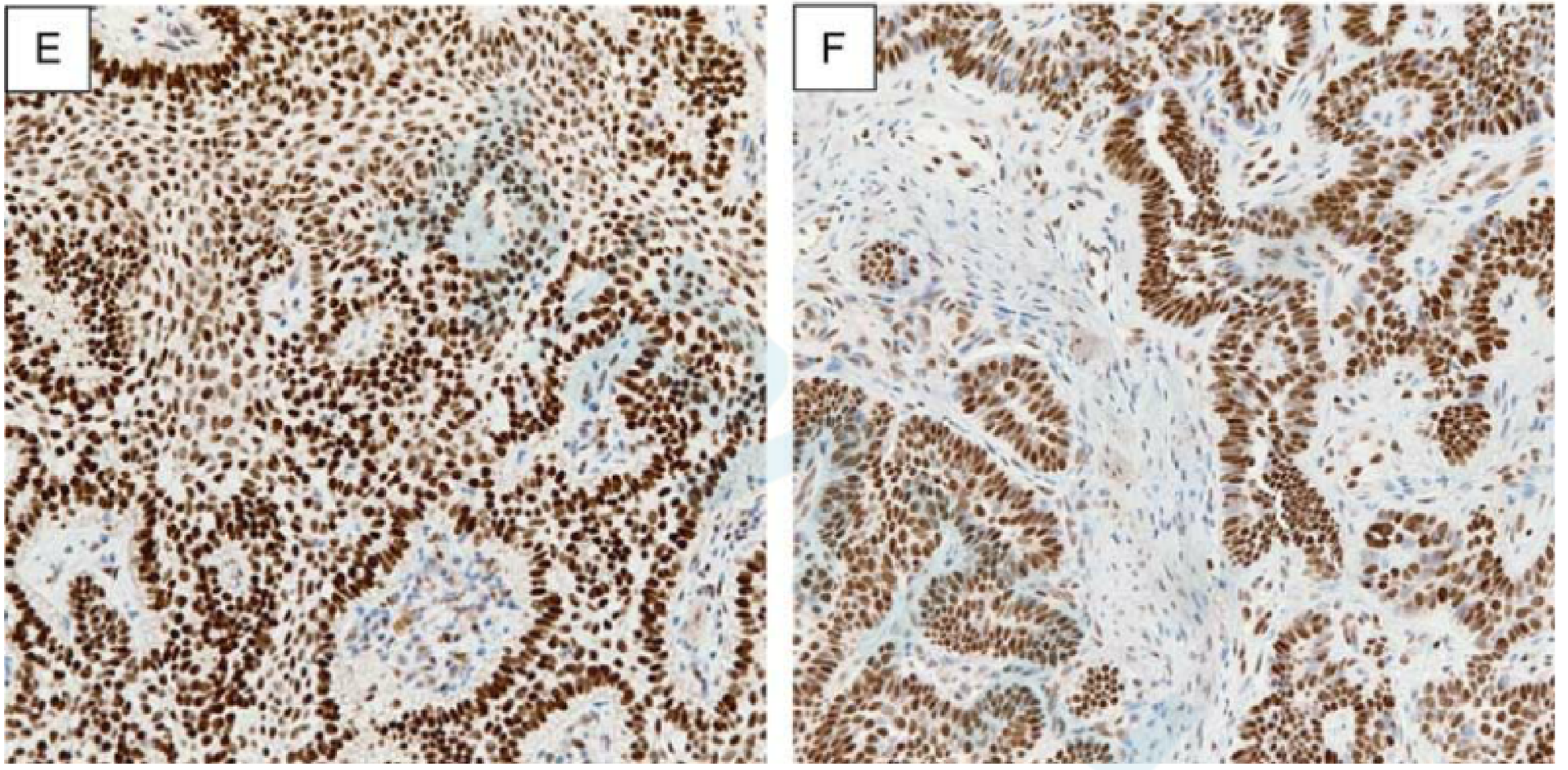
FOXP1染色结果：
阴性(肿瘤细胞核着色<50%)
阳性(肿瘤细胞核着色≥50%)



maxillary ameloblastomas



mandibular ameloblastomas



sinonasal ameloblastomas

Part

04 结论

DISCUSSION

讨 论
Dissuction

一、目前缺乏鉴别牙源性肿瘤与基底样涎腺肿瘤的标记物

- ✓ 现有的报道中很少描述对牙源性肿瘤比较敏感和特异的IHC标记物
- ✓ 成釉细胞瘤是最常见的牙源性肿瘤，已被证明在48%至63%的发生在下颌骨肿瘤中存在BRAF V600E突变。 然而，IHC阳性的BRAF V600E表达仅在成釉细胞瘤的一小部分中观察到，从而限制了其作为诊断标记的使用
- ✓ 已显示一部分牙源性肿瘤具有CTNNB1突变，可以出现免疫组化 β -catenin的核着色以及LEF1（淋巴增强因子1）的表达

讨 论
Dissuction

A comparative analysis of LEF-1 in odontogenic and salivary tumors☆

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最近的一项比较分析显示，LEF-1的表达和β-catenin核表达在基底样涎腺肿瘤和各种牙源性肿瘤中的共同表达，且在牙源性肿瘤中的表达频率较低，因此不能作为鉴别诊断标记物。

Human Pathology (2015) 46, 255–259

讨 论
Dissuction

二、鉴别牙源性肿瘤与基底样涎腺肿瘤具有重要的临床意义

- ✓ 成釉细胞瘤和基底样涎腺肿瘤之间的鉴别具有挑战性，尤其是在口内、鼻窦和不典型部位以及在小活检标本中
- ✓ 临床对于不同的诊断具有不同的处理方式
- ✓ 牙源性肿瘤的具有敏感性和特异性标志物可以解决这一诊断难题

讨 论
Dissuction

三、FOXP1+/SOX10-可用于鉴别牙源性肿瘤与基底样涎腺肿瘤

TABLE 1. FOXP1/SOX10 Immunophenotypes in 108 Odontogenic Tumors

	n (%)			
	FOXP1$^+$/SOX10$^-$	FOXP1$^+$/SOX10$^+$	FOXP1$^-$/SOX10$^-$	FOXP1$^-$/SOX10$^+$
Ameloblastoma	34/35 (97)	0/35 (0)	1/35 (3)	0/35 (0)
ABC	2/2 (100)	0/2 (0)	0/2 (0)	0/2 (0)
ABF	5/5 (100)	0/5 (0)	0/5 (0)	0/5 (0)
COC	4/4 (100)	0/4 (0)	0/4 (0)	0/4 (0)
AOT	1/3 (33)	0/3 (0)	2/3 (67)	0/3 (0)
GOC	2/2 (100)	0/2 (0)	0/2 (0)	0/2 (0)
Clear cell odontogenic carcinoma	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)
Odontogenic keratocyst	53/56 (95)	0/56 (0)	3/56 (5)	0/56 (0)

- ✓ FOXP1在35例成釉细胞瘤中只有1例表达水平低（明确表达；<50%的肿瘤细胞被染色）。该肿瘤可能由于脱钙而失去了部分抗原性
- ✓ 所有牙源性肿瘤病例均不表达SOX10，这表明SOX10可能是在困难和异常部位排除涎腺肿瘤的有效阴性标记
- ✓ 3例牙源性腺样瘤（AOT）中的2例具有FOXP1- / SOX10-表达模式。
- ✓ FOXP1和SOX10在其他肿瘤中的表达谱目前未知

讨 论
Dissuction

- ✓ SOX10在涎腺肿瘤中染色结果与以往报道一致。
- ✓ 本文首次报道了FOXP1在涎腺肿瘤中的表达谱，许多涎腺肿瘤具有FOXP1和SOX10的共表达。
- ✓ 2例多形性腺瘤显示FOXP1 + / SOX10-，FOXP1仅在间质区域染色，而在腺体区域没有染色。

TABLE 2. FOXP1/SOX10 Immunophenotypes in 173 Salivary Gland Tumors

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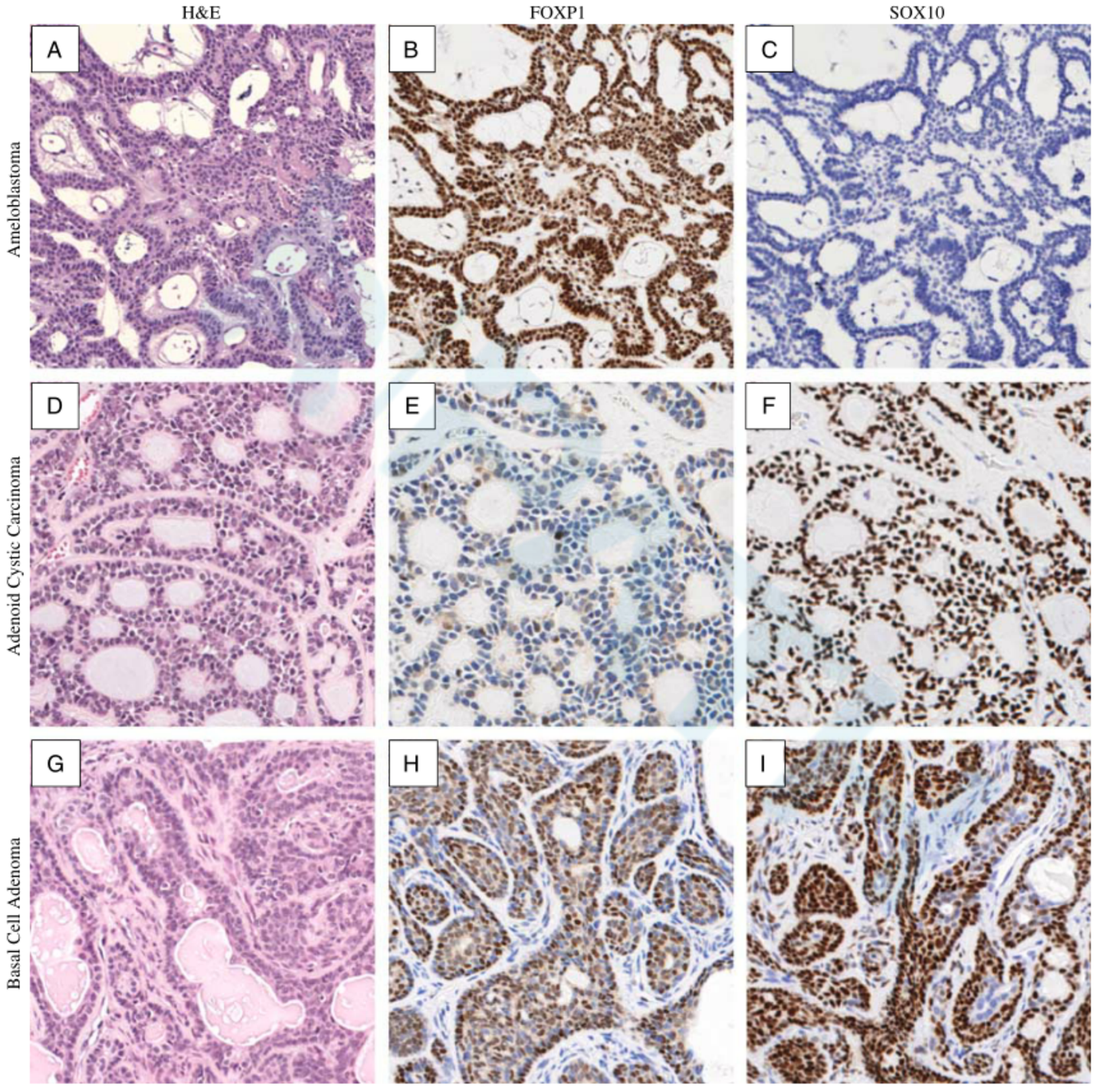
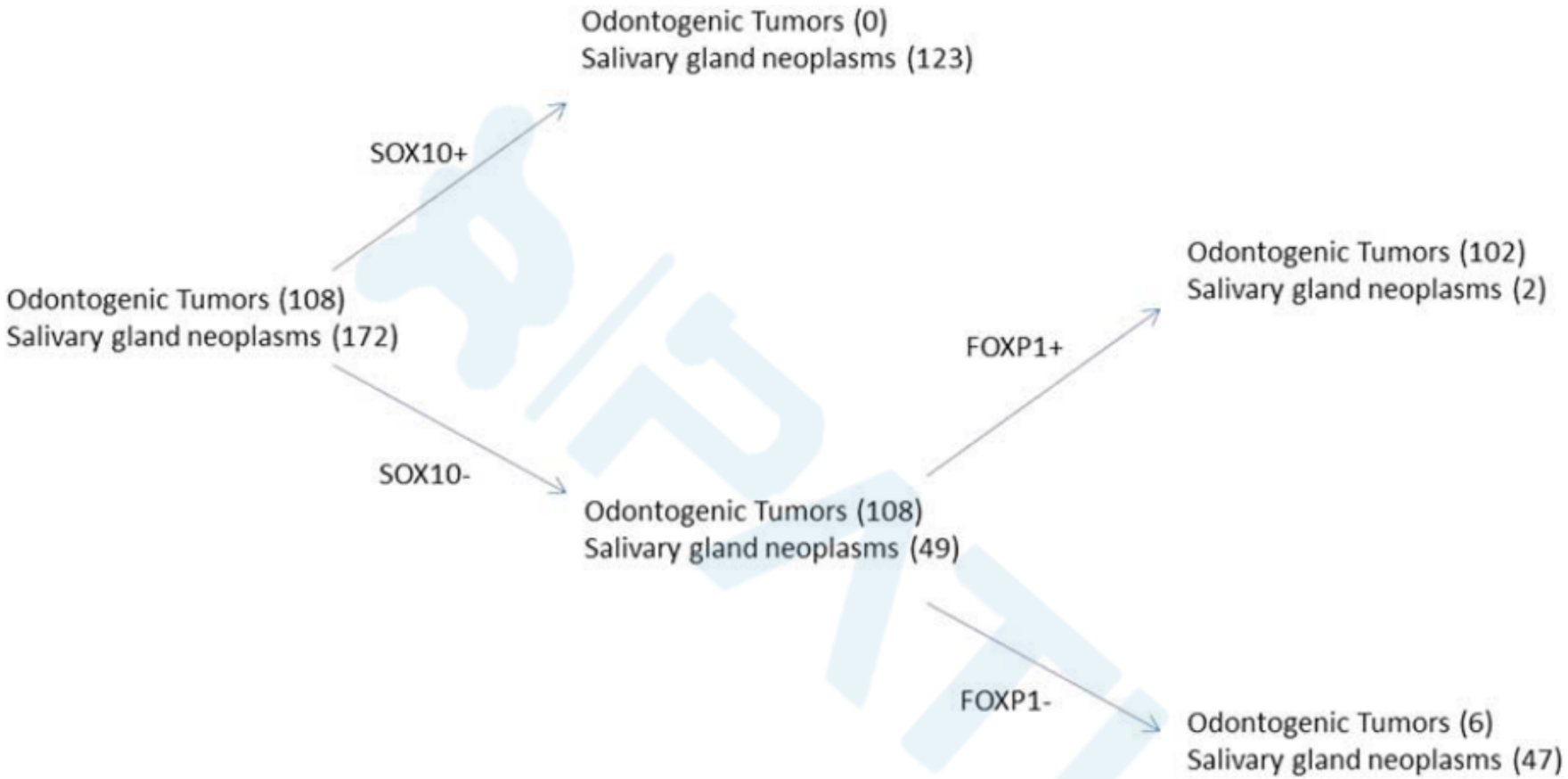

H&E
FOXP1
SOX10
Ameloblastoma
Adenoid Cystic Carcinoma
Basal Cell Adenoma
A
B
C
D
E
F
G
H
I

讨 论
Dissuction



FOXP1 +/ SOX10免疫表型对牙源性肿瘤的敏感性为94%，特异性为96%；
FOXP1 +/SOX10-免疫表型对成釉细胞瘤的敏感性为97%，特异性为100%。

讨 论
Dissuction

综上，

- ✓ FOXP1 +/SOX10-免疫表型可以可靠地区分成釉细胞瘤与基底细胞腺瘤，腺样囊性癌，多形性腺癌和肌上皮瘤等，另外可以对头颈部以外的牙源性肿瘤和涎腺肿瘤的鉴别提供诊断辅助

- ✓ 虽然少数多形性腺瘤可能会出现意外的FOXP1 + / SOX10-模式，尤其是在间质软骨黏液成分中，但通过将FOXP1的表达位置限制在细胞导管上皮中，是可以鉴别的。

- ✓ 进一步研究FOXP1和SOX10在其他基底细胞样肿瘤（鳞状细胞癌的基底样亚型，鼻窦未分化癌等）中的表达，可能会有对头颈部肿瘤进行临床上有意义的的诊断分类提供线索

THANK YOU