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Genetic Underpinnings of Renal Cell Carcinoma With Leiomyomatous Stroma

Megan Parilla, MD, Mir Alikhan, MD, Mustafa Al-Kawaaz, MD, Sushant Patil, PhD, Sabah Kadri, PhD, Lauren L. Ritterhouse, MD, PhD, Jeremy Segal, MD, PhD, Carrie Fitzpatrick, PhD, and Tatjana Antic, MD

汇报人： 钱雪霞
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Part one

研 究 背 景

Background

Renal Cell Carcinoma With Leiomyomatous Stroma (RCC-LS)

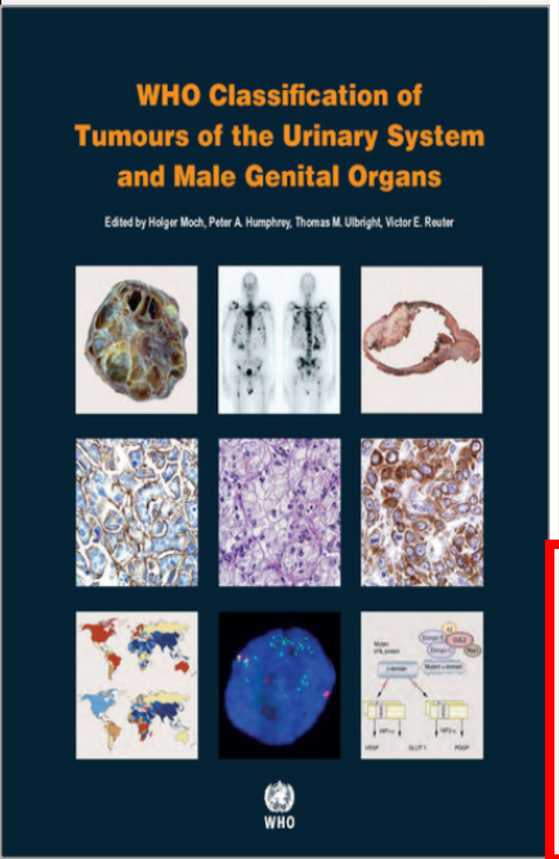


Table 1.02 Features of emerging/provisional renal cell carcinomas

	Clinical	Morphological	Molecular	Outcome
Oncocytic renal cell carcinoma occurring after neuroblastoma	• Increased incidence of renal cell carcinoma among neuroblastoma survivors • Heterogeneous group, with some MiT family translocation renal cell carcinomas • One distinct oncocytic group with or without exposure to chemotherapy	• Solid, cystic, and papillary • Oncocytic cells with vacuoles and calcification • No distinctive immunohistochemistry	• No molecular marker	• Limited follow-up
Thyroid-like follicular renal cell carcinoma	• Broad age range • Slight female predominance	• Tan-brown gross appearance • Resembles thyroid parenchyma, with follicles and colloid • No distinctive immunohistochemistry, but thyroid transcription factor 1 and thyroglobulin are negative	• Limited studies and no distinctive molecular marker	• Most are indolent • There are rare examples of lymph node and lung metastasis
ALK rearrangement–associated renal cell carcinoma	• Rare (< 10 cases reported) • 3 distinct cases with ALK-vinculin fusion in children with sickle cell trait	For paediatric cases: • Medullary location • Large polygonal/spindle cells • Eosinophilic cytoplasm with intracytoplasmic lumina	• *ALK-VCL* gene fusion	• Limited follow-up
Renal cell carcinoma with (angio)leiomyomatous stroma	• Adults • Male predominance • Historically categorized as a clear cell or clear cell papillary renal cell carcinoma • Has also been called renal angiomyoadenomatous tumour • Occurs sporadically or is associated with tuberous sclerosis	• Branching tubules / papillary tufts • Clear cells • Prominent vascular and smooth muscle stroma • Positive for CK7, 34βE12, and CD10; negative for racemase	• No 3p deletion • No trisomy 7 or 17 • *TCEB1* gene mutation recently described	• Indolent, but limited follow-up

Renal Cell Carcinoma With Leiomyomatous Stroma（RCC-LS）

- 组织学特点：丰富的平滑肌基质内可见胞浆透亮的细胞呈分支的小管状或乳头状排列。
- 临床特征：多见于成年男性，肿瘤表现为惰性生长，绝大多数为偶然发现，可能与结节性硬化综合征（TSC）相关。曾被归类为透明细胞肾细胞癌（ccRCC）以及透明细胞乳头状肾细胞癌（ccpRCC）。曾被称为肾血管肌瘤样肿瘤(RAT)。
- 免疫组化：CK7、34βE12、 CD10阳性，P504S阴性
- 分子特征： 没有3 p缺失、TCEB1基因突变（最近报道）
- 预后： 良好，但随访数据有限

肾血管肌瘤样肿瘤renal angiomyoadenomatous tumour（RAT）

- 首次报道：Michal等于2000年以病例报告的形式首次描述了肾血管肌瘤样肿瘤(RAT)。

ELSEVIER

Annals of Diagnostic Pathology

Volume 4, Issue 5, October 2000, Pages 311-315

Case Reports

Benign renal angiomyoadenomatous tumor: A previously unreported renal tumor

Michal Michal MD, Ondrej Hes MD, Frantisek Havlicek MD

- 定义：是一种低级别的肾细胞癌，有透明至嗜碱性的细胞组成，呈乳头状或管状结构，有突出的肌瘤样间质。

Background

Renal angiomyoadenomatous tumor: morphologic, immunohistochemical, and molecular genetic study of a distinct entity

Authors | Authors and affiliations

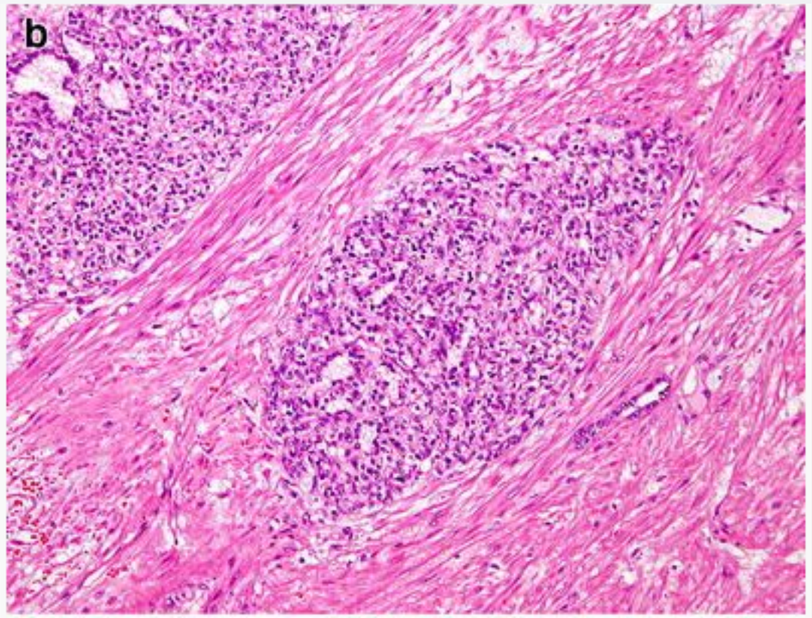
M. Michal, O. Hes, J. Nemcova, R. Sima, N. Kuroda, S. Bulimbasic, M. Franco, N. Sakaida, D. Danis, D. V. Kazakov, C. Ohe, M. Hora

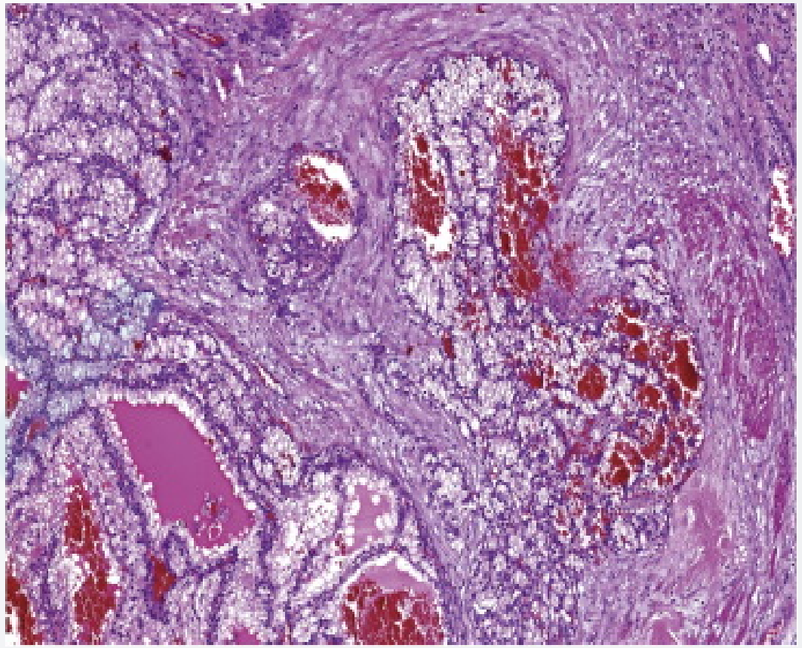
Clinical features

	Sex/age	Side	Size	Follow-up
Case 1	M/58	Right	2.3 × 2.3 × 1.8 cm	9 months AW
Case 2	M/49	Left	Diameter 4.6 cm	1 year AW
Case 3	M/93	Right	8.5 × 8 × 3 cm	8 months AW, then LOF
Case 4	F/73	Left	Diameter 2.5 cm	29 months DWT[a]
Case 5	M/50	Right	Diameter 2.5 cm	LOF

F female, *M* male, *AW* alive and well, *LOF* loss on follow-up, *DWT* died without tumor

[a]Patient died of metastatic disease of colonic adenocarcinoma



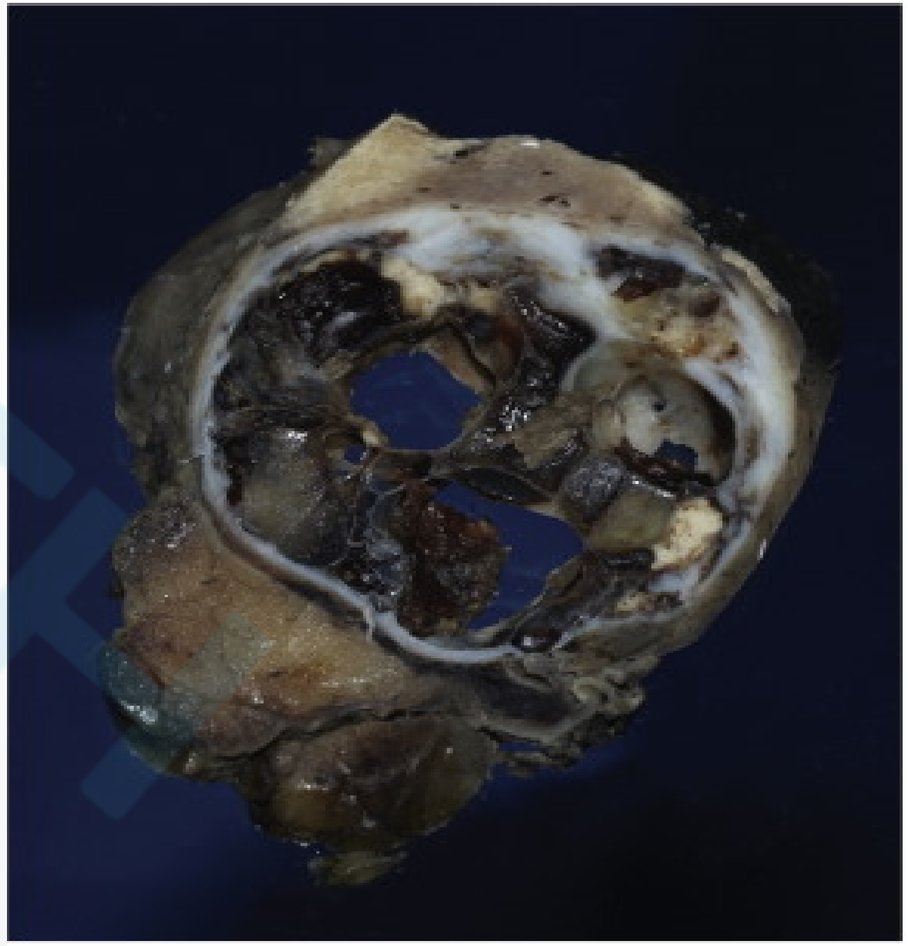


肾血管肌瘤样肿瘤renal angiomyoadenomatous tumour（RAT）

- 大体特征：实性境界清楚的肿物，切面呈褐色至棕色，常由较厚的灰白包膜所包绕，可见囊性变及分隔。

- 临床特征：多见于成年男性，肿瘤表现为惰性生长，绝大多数为偶然发现，可能与结节性硬化综合征（TSC）相关。

- 免疫组化：CK7、CK20、AE1/AE3、CAM5.2、Vim阳性。同时有文献报道，TSC-associated RAT-like RCC具有特征性的SDHB的表达缺失。

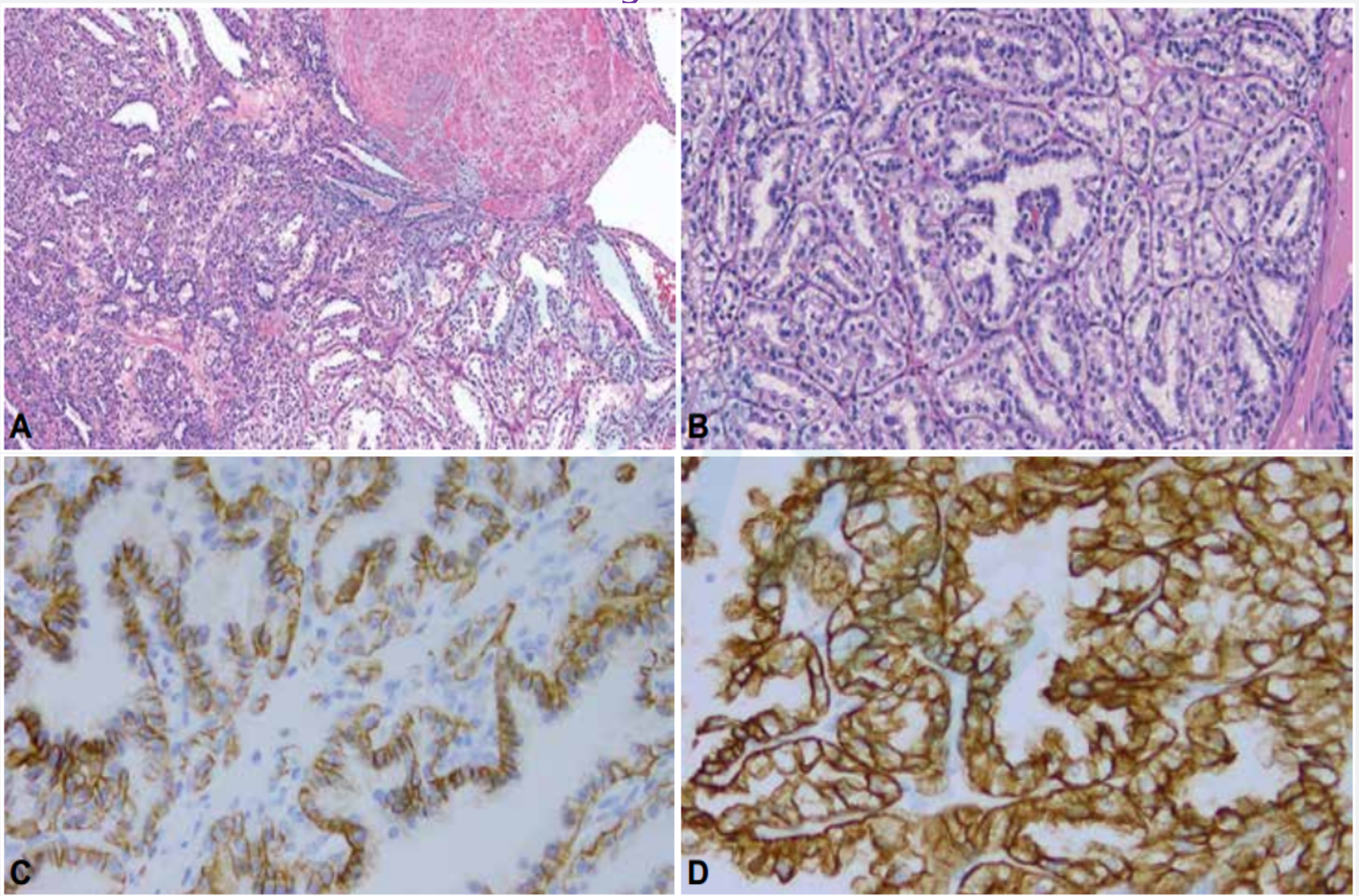


O. Hes et al. / Annals of Diagnostic Pathology 21 (2016)

透明细胞乳头状肾细胞癌（Clear cell papillary renal cell carcinoma ，ccpRCC）

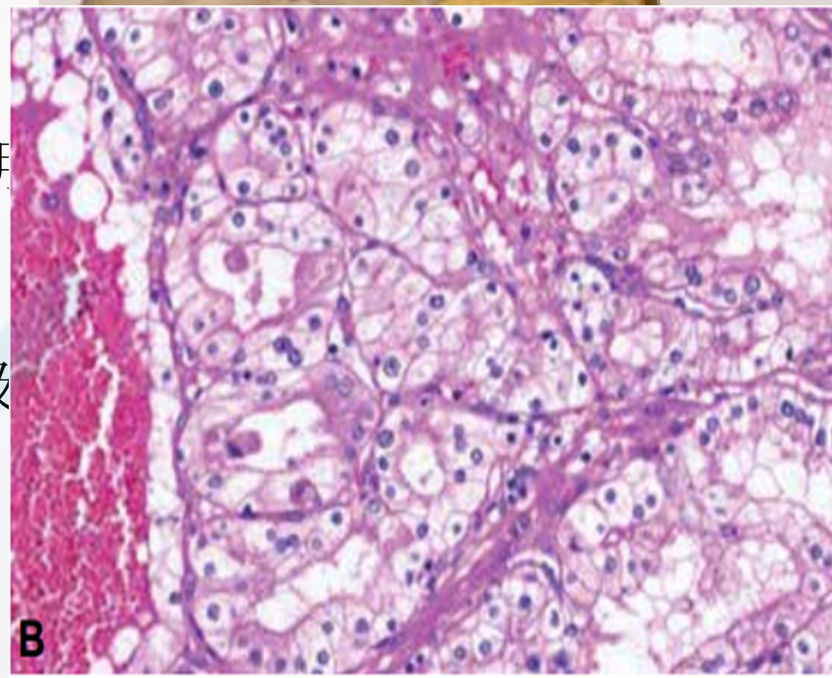
- 定义：是一种由淡染透明的上皮细胞排列成管状、乳头状结构构成的惰性肾脏上皮性肿瘤。
- ICD-O code： 8323/1
- 大体特征：肿瘤通常较小多单发，多位于肾皮质，实性界清无包膜。
- 流行病学：占肾脏肿瘤的1-4%，发病年龄为18-88岁，无性别倾向。
- 免疫组化：CK7弥漫阳性，CA9呈杯口状膜着色，PAX2，PAX8，34βE12阳性，CD10阴性或灶阳
- 分子检测：没有VHL基因的突变

Background



透明细胞肾细胞癌（Clear cell renal cell carcinoma ，ccRCC）

- 定义：是由胞浆透明或嗜酸的细胞构成的一组恶性肾上皮性肿瘤。
- ICD-O code： 8310/3
- 大体特征：肿瘤通常实性无包膜或有假包膜的肿块，切面呈金黄色，常见出血、坏死及囊性变。
- 免疫组化：Vim、EMA、CA9阳性，RCC、CD10通常阳性，CK7常阴性（25%可灶阳）
- 分子检测：约60%的病例具有VHL基因突变或VHL启动子甲基化及染色体3p的杂合性缺失



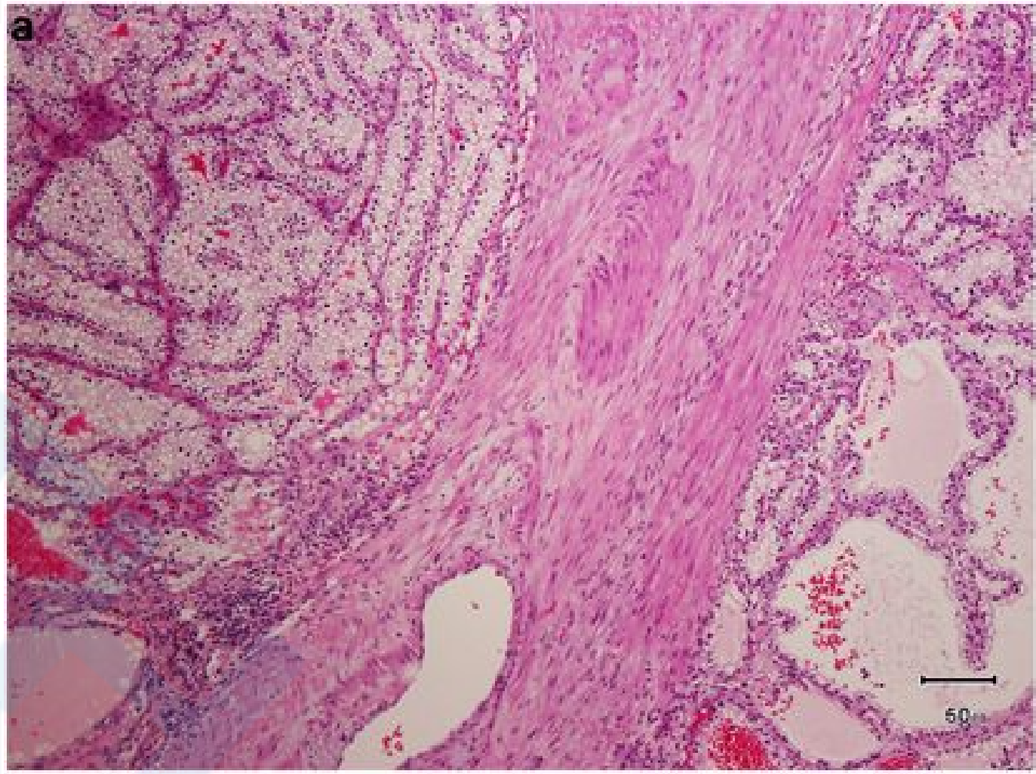
TCEB1突变的肾细胞癌（TCEB1-mutated renal cell carcinoma ）

Original Article | Published: 13 February 2015

TCEB1-mutated renal cell carcinoma: a distinct genomic and morphological subtype

A Ari Hakimi ✉, Satish K Tickoo, Anders Jacobsen, Judy Sarungbam, John P Sfakianos, Yusuke Sato, Teppei Morikawa, Haruki Kume, Masashi Fukayama, Yukio Homma, Ying-Bei Chen, Alexander I Sankin, Roy Mano, Jonathan A Coleman, Paul Russo, Seishi Ogawa, Chris Sander, James J Hsieh & Victor E Reuter

Modern Pathology **28**, 845–853 (2015) | Download Citation ⬇



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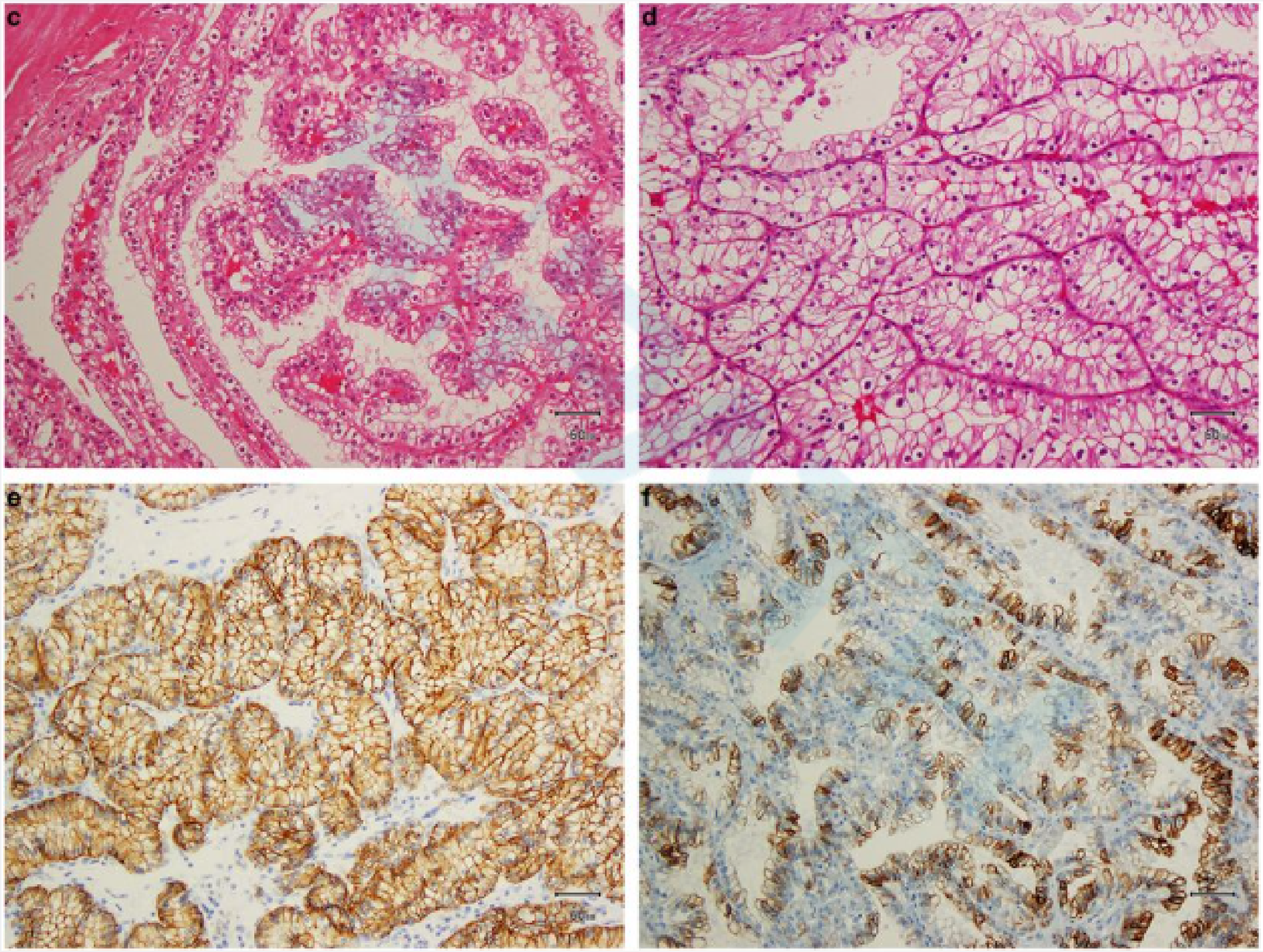

- **目的：**

RCC-LS、ccRCC、ccpRCC以及TCEB1-mutated RCC的形态学表现多有重叠，且根据免疫组化染色也难以对其进行适当的分类，因此需要借助其分子分析来对其进行更准确、适当的分类以及了解其更多的遗传基础。

Part two

材料和方法

MATERIALS AND METHODS

MATERIALS AND METHODS

- **病例选择**

2005.01-2017.12 University of Chicago Medical Center

4种免疫组化染色协助分类（CA9、CK7、CD10、SDHB）

对所有15例病例进行二代测序

综合以上结果对所有病例进行最终诊断

Part three

结 果

RESULTS

RESULTS

TABLE 1. Clinical Features and Pathologic Staging of Selected RCC-LS

Case	Sex	Age (y)	Tumor Size (cm)/Stage	Follow-up
1	Male	38	1.8/pT1a	Free of RCC×11 y/alive and disease free
2	Male	54	3.5/pT1a	Free of RCC×7 y/alive and disease free
3	Male	54	1.7/pT1a	No follow-up available
4	Female	77	2.0/pT1a	Free of RCC×8 y/died of lung carcinoma
5	Female	75	2.6/pT1a	Free of RCC× at least 5 y/lost to follow-up
6	Male	68	6.5 and 4.4/pT1b(m)	Free of RCC×at least 6 y/lost to follow-up
7	Male	49	2.7/pT1a	Free of RCC×11 y/alive and disease free
8	Male	71	2.7/pT1a	Free of RCC×4 y/alive and disease free
9	Female	49	2.7/pT1a	Free of RCC×11 y/alive and disease free
10	Male	33	2.7/pT1a	No follow-up available
11	Female	39	2.7/pT1a	No follow-up available
12	Male	49	2.7/pT1a	Free of RCC×at least 4 y/lost to follow-up
13	Male	29	3.0 and 1.9/pT1a(m)	Possible metastasis to pancreas vs. possible pancreatic neoplasm
14	Female	56	3.0/pT1a	Free of RCC×2 y/alive and disease free
15	Female	62	0.8 and 1.4/pT1a(m)	No follow-up available

性别比例：F：M=6：9
年龄：29-77y（53.3y）
肿瘤大小：平均2.7cm
分期：均为T1，且无已知的淋巴结转移
随访：可随访的病例中无人因此类疾病去世

The ages ranged from 29 to 77 years old at the time of diagnosis with a mean age of 53.3 years old. All had relatively small tumors (mean: 2.7 cm) with nearly all tumors staged as T1 and there was no known nodal metastasis. Of the 15 cases, one case (case 13) was from a patient with a diagnosis of TSC that had a recent possible metastasis to the pancreas, although a primary synchronous pancreatic neoplasm is also possible. The remaining patients with follow-up were all either alive and free of RCC or free of RCC at the time of their unrelated death.

TABLE 2. Immunohistochemical Features and Molecular Alterations of Selected RCC-LS

Case	Clinical TSC	CAIX	CK7	CD10 (Membranous)	SDHB Retained	IHC-based Diagnosis	Chromosome Alterations	Gene Mutations*	Final Integrated Diagnosis
1	N	Full pos	Strong diffuse	Moderate focal	Y	?	Monosomy 8	TCEB1 p.Ser23Leu	TCEB1-mutated RCC
2	N	Full pos	Strong diffuse	Moderate focal	Y	?	Monosomy 8	TCEB1 p.Ala106Asp	TCEB1-mutated RCC
3	N	Full pos	Strong diffuse	Moderate focal	Y	?	Monosomy 8	TCEB1 p.Tyr79Cys	TCEB1-mutated RCC
4	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Gain 18; Gain 7, Partial 19p loss	TET2 p.Tyr867His TET2 p.Pro1723Ser	CCP RCC
5	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Gain 18; Loss 9	None	CCP RCC
6	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Gain 18; partial 19p loss	TSC2 p.Arg1795Cys TET2 p.Asn767Asp	CCP RCC
7	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Data too noisy to call CNV	None	CCP RCC
8	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Neutral/Normal	None	CCP RCC
9	N	Cup pos	Moderate diffuse	Neg	Y	CCP RCC	Loss 1q & 8p, Focal 3p loss	None	CCP RCC
10	N	Cup pos	Strong diffuse	Strong focal	Y	?	Neutral/Normal	TSC1 c.2626-3C > T	Unclassified
11	N	Full pos	Weak very focal	Strong diffuse	Y	C C RCC	Partial 3p loss	VHL c.341-2_347del; MTOR p.Thr1834_ Thr1837del SETD2 p.Thr2037Ala	CC RCC
12	N	Full pos	Strong focal	Strong focal	Y	?	Loss 3	VHL p.Ser68*; TET2 p.Glu846Asnfs*27	CC RCC
13	Y	Full pos	Strong focal	Moderate focal	N	TSC-associated RAT-like RCC	Neutral/normal	TSC1 p.Leu669Phefs*19	TSC-associated RAT-like RCC
14	N	Cup pos	Strong focal	Moderate focal	Y	?	Neutral/normal	TSC2 p.Leu219Arg TSC2 p.Arg1200Trp	Unclassified
15	N	Full pos	Moderate focal	Strong focal	Y	?	Neutral/normal	TSC2 p.Trp304Arg SETD2 p. Gln7_Pro8del	Unclassified

RESULTS

TABLE 2. Immunohistochemical Features and Molecular Alterations of Selected RCC-LS

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9	N	Cup pos	Moderate diffuse	Neg	Y	CCP RCC	Loss 1q & 8p, Focal 3p loss	None	CCP RCC
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12	N	Full pos	Strong focal	Strong focal	Y	?	Loss 3	VHL p.Ser68*; TET2 p.Glu846Asnfs*27	CC RCC
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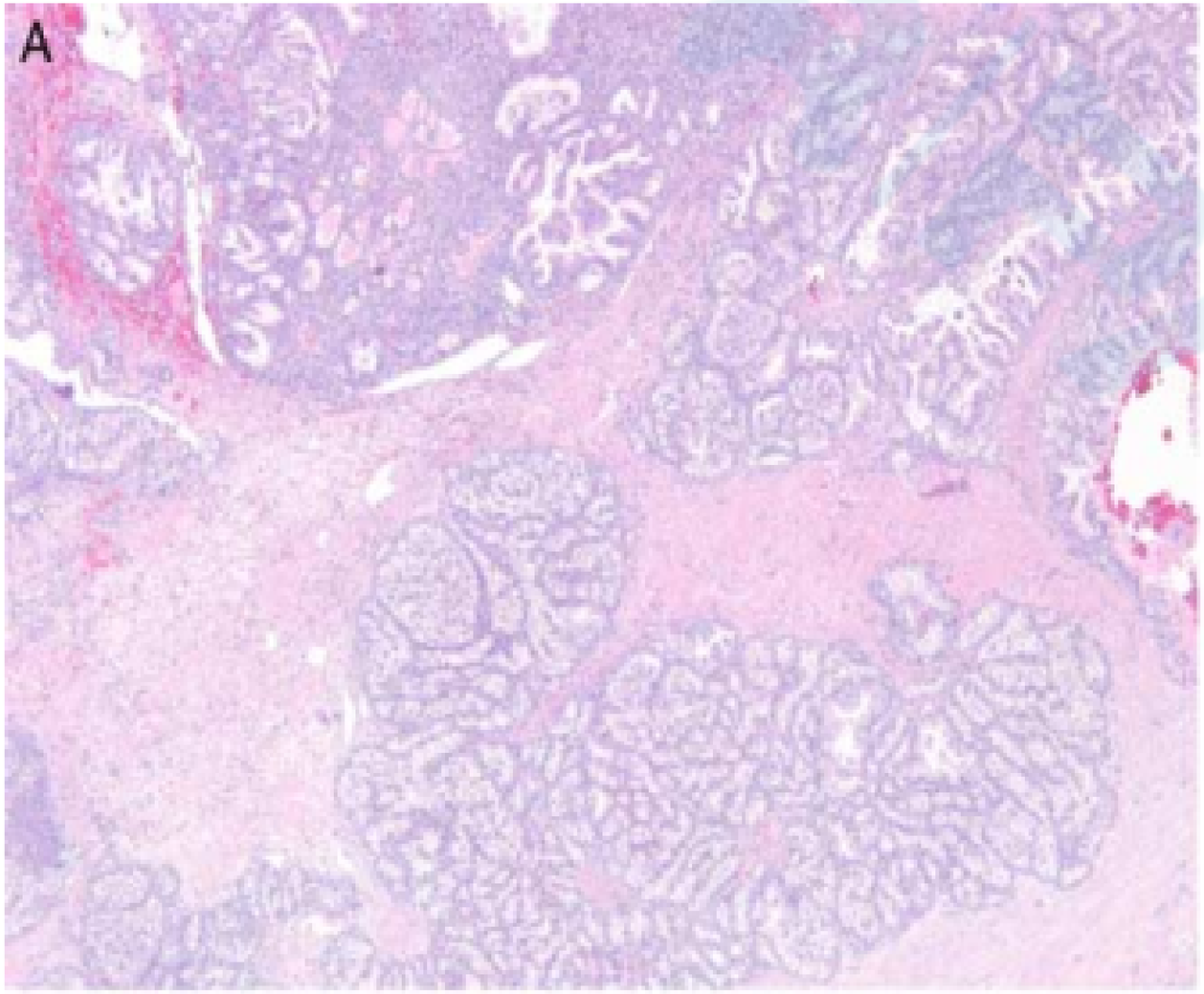
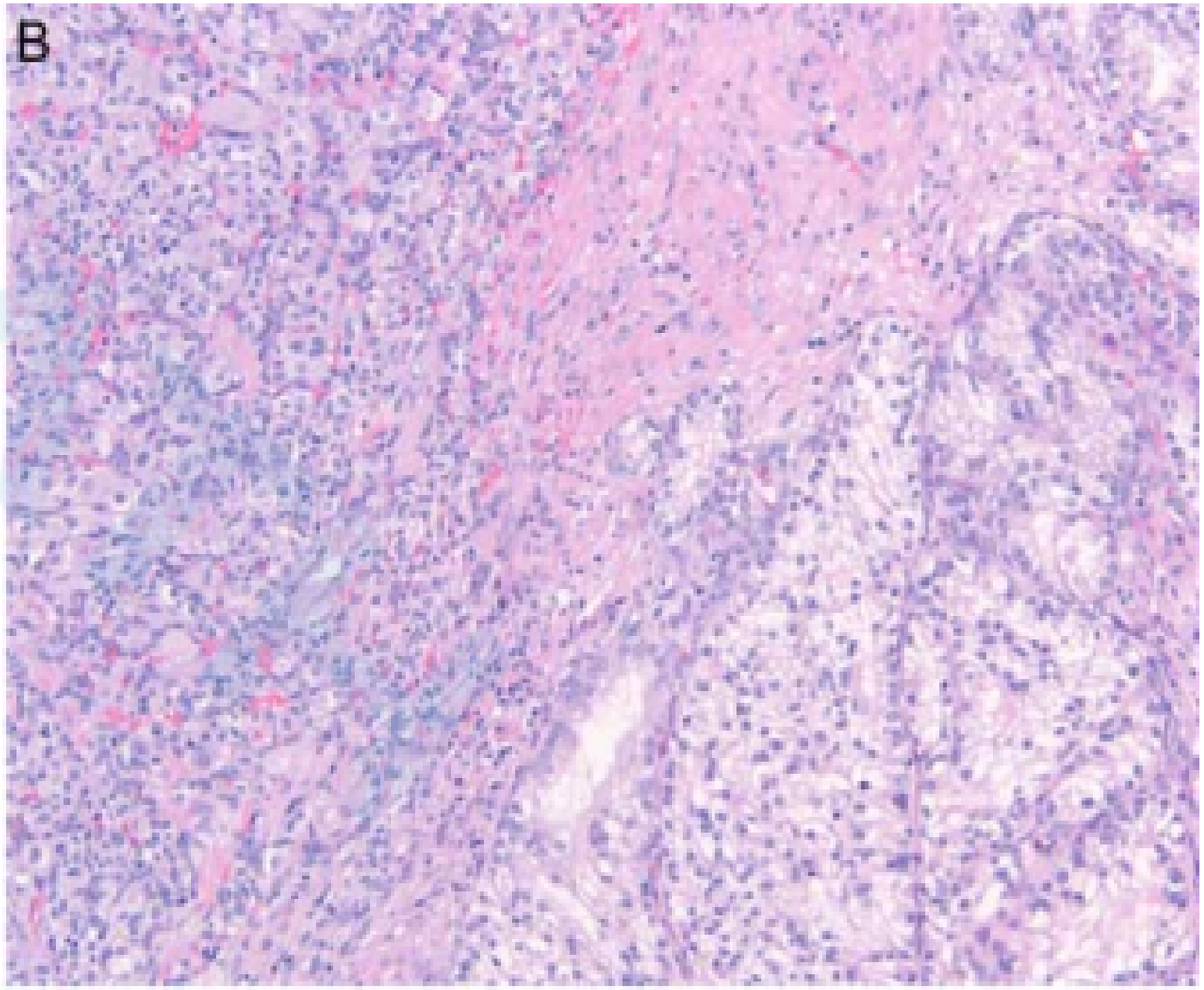
RESULTS

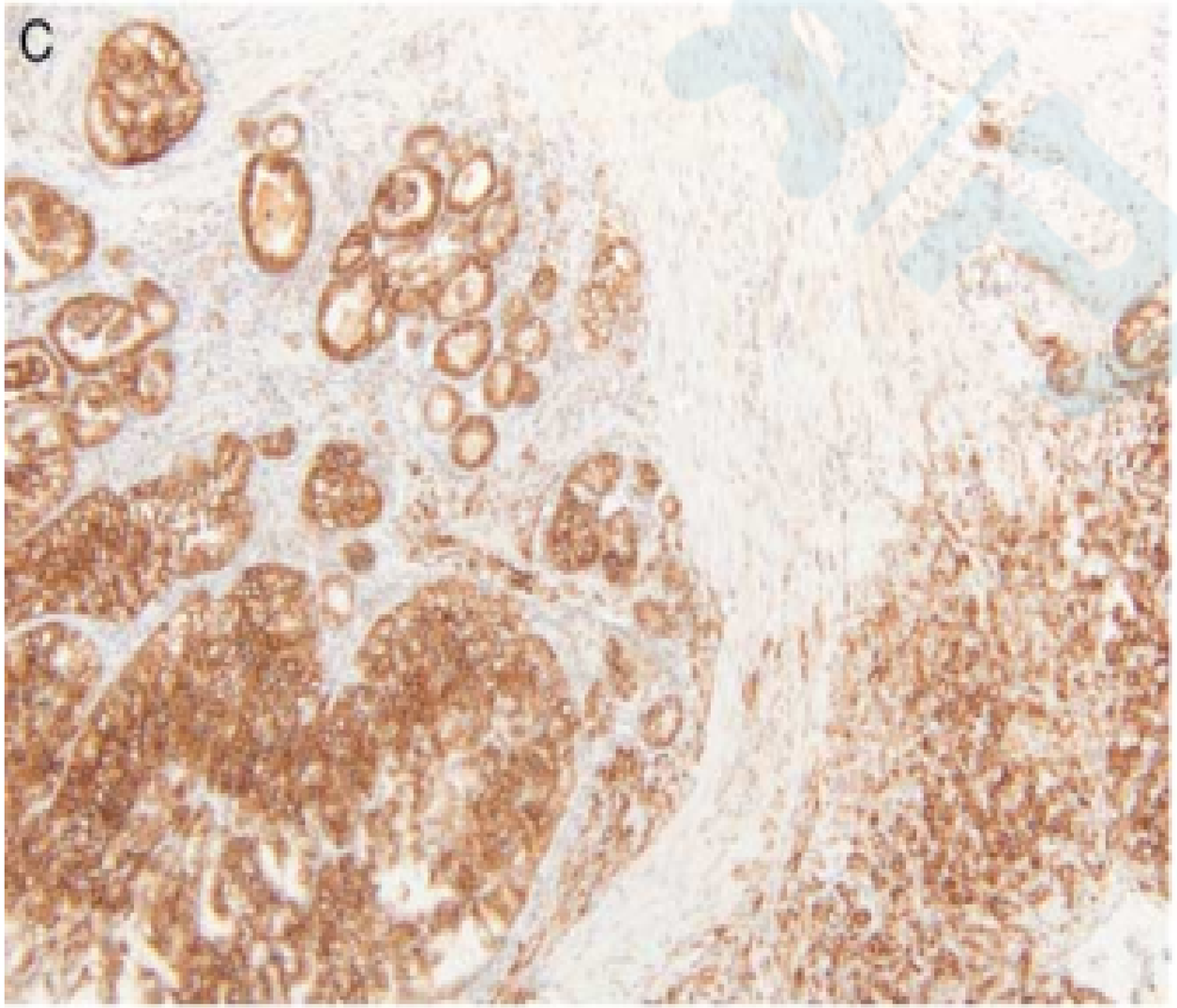


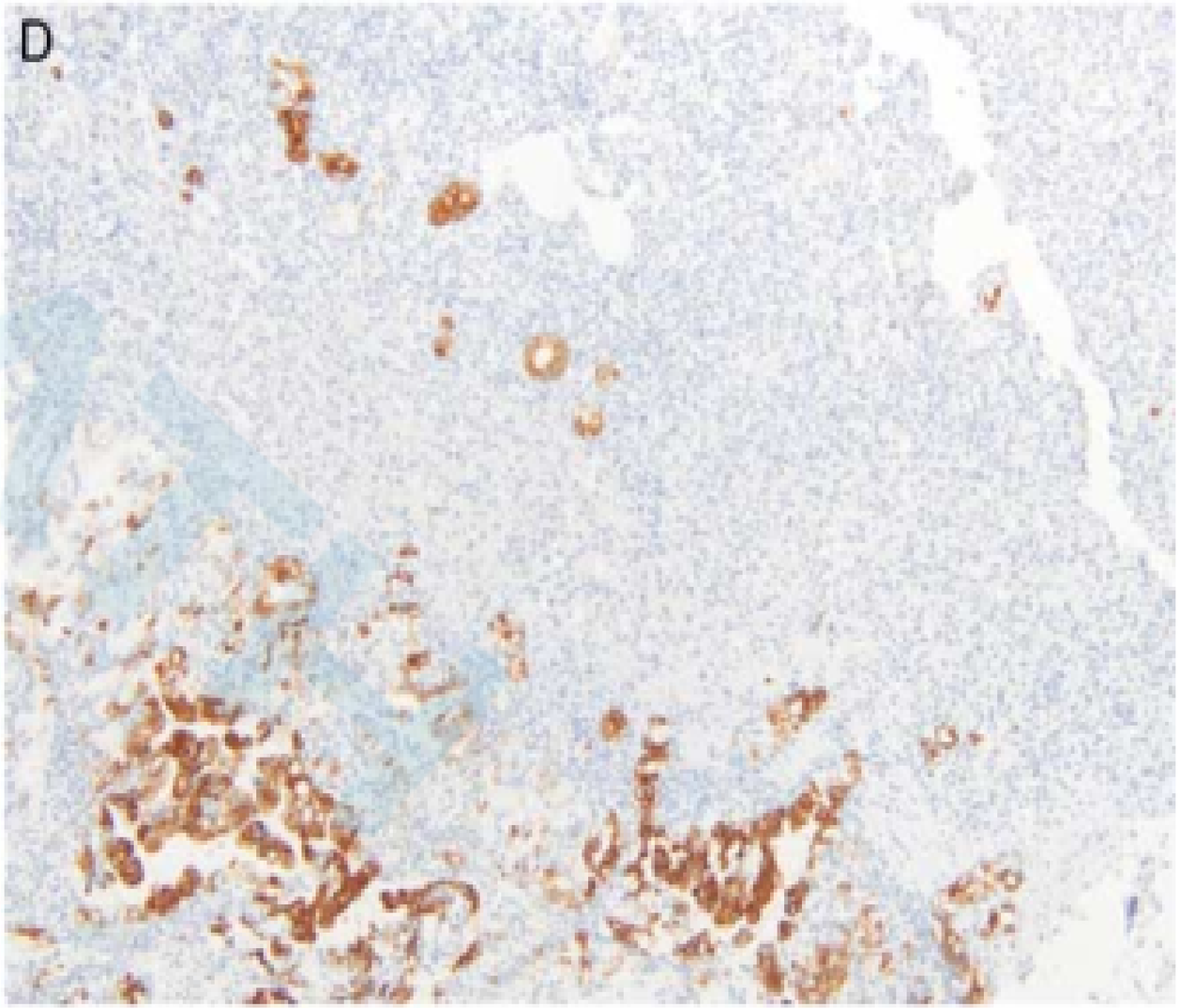


R E S U L T S

CA9

CK7

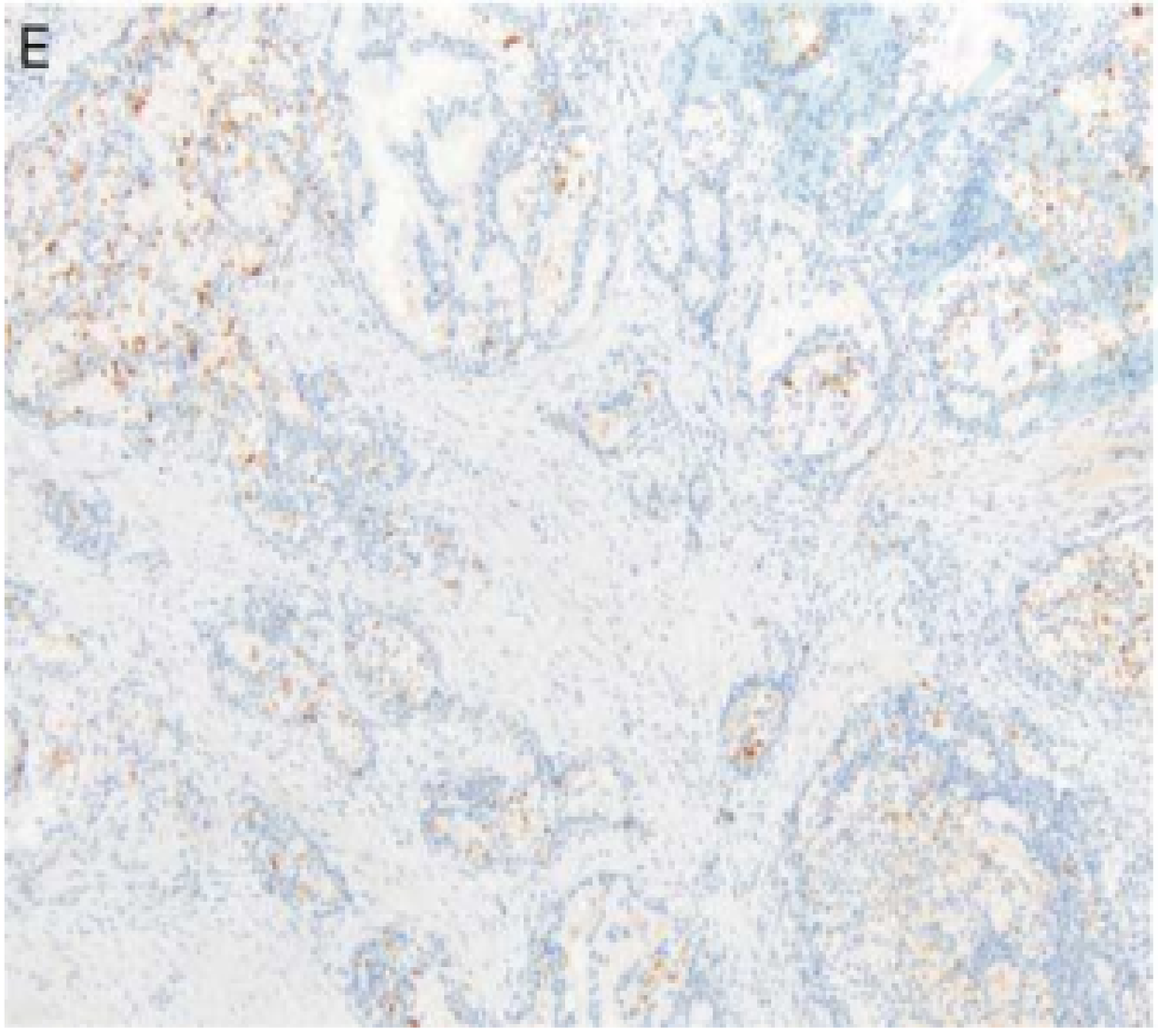


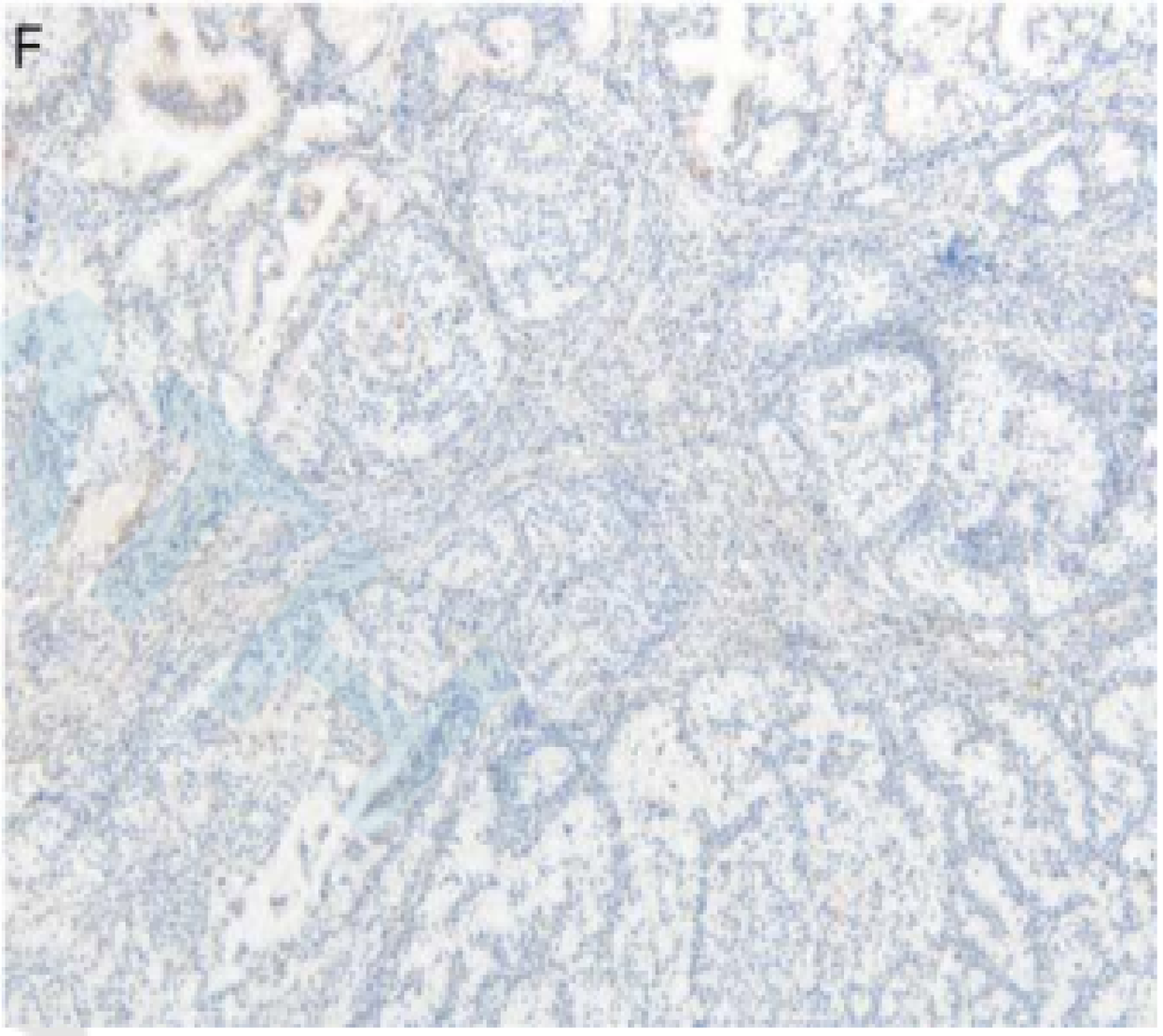


RESULTS

CD10

SDHB





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7	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Data too noisy to call CNV	None	CCP RCC
8	N	Cup pos	Strong diffuse	Neg	Y	CCP RCC	Neutral/Normal	None	CCP RCC
9	N	Cup pos	Moderate diffuse	Neg	Y	CCP RCC	Loss 1q & 8p, Focal 3p loss	None	CCP RCC
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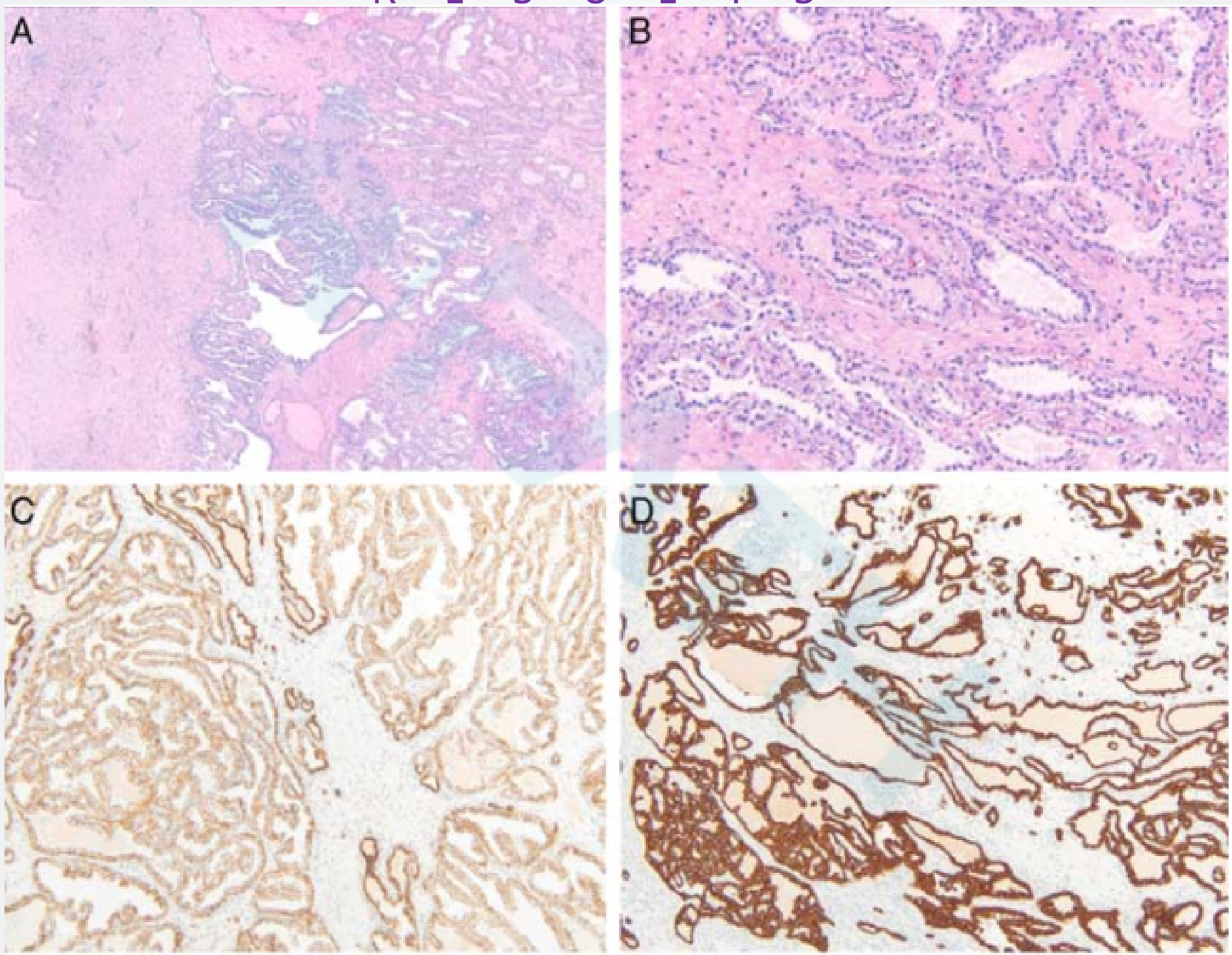
R E S U L T S

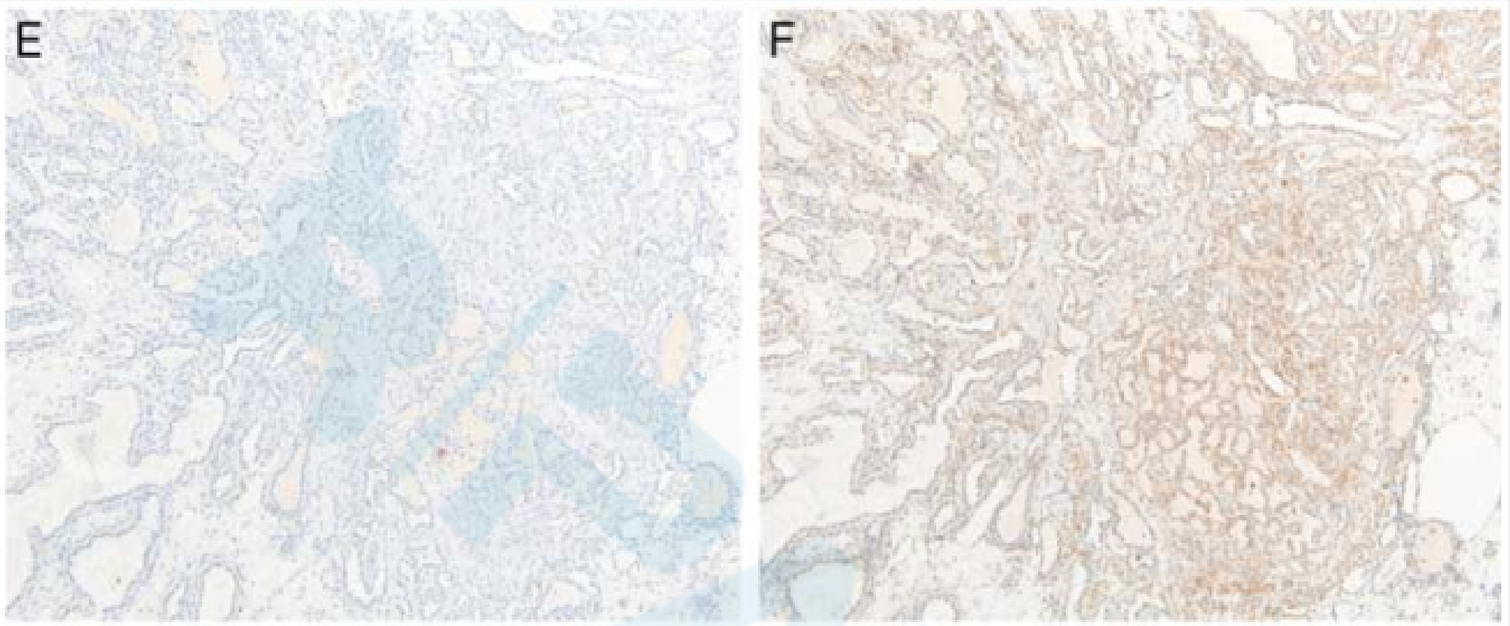


CA9

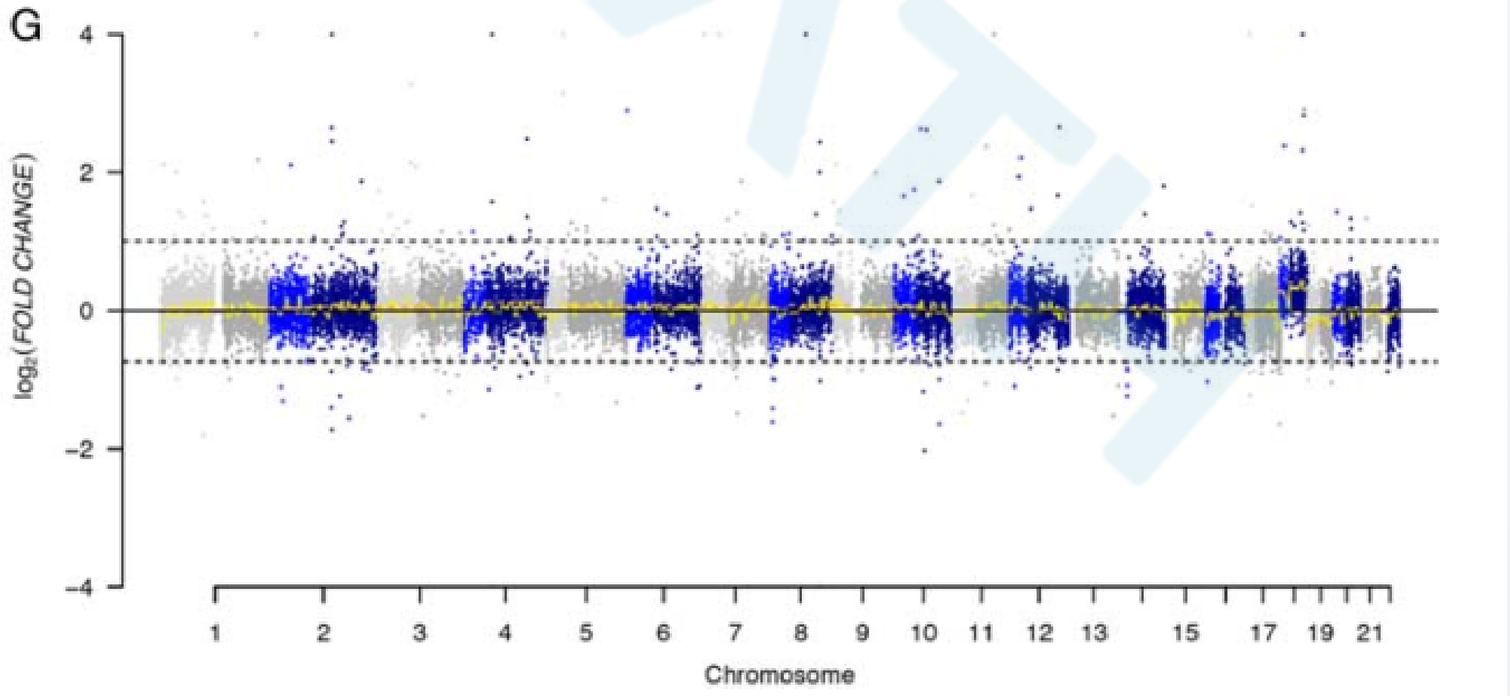
CK7

R E S U L T S

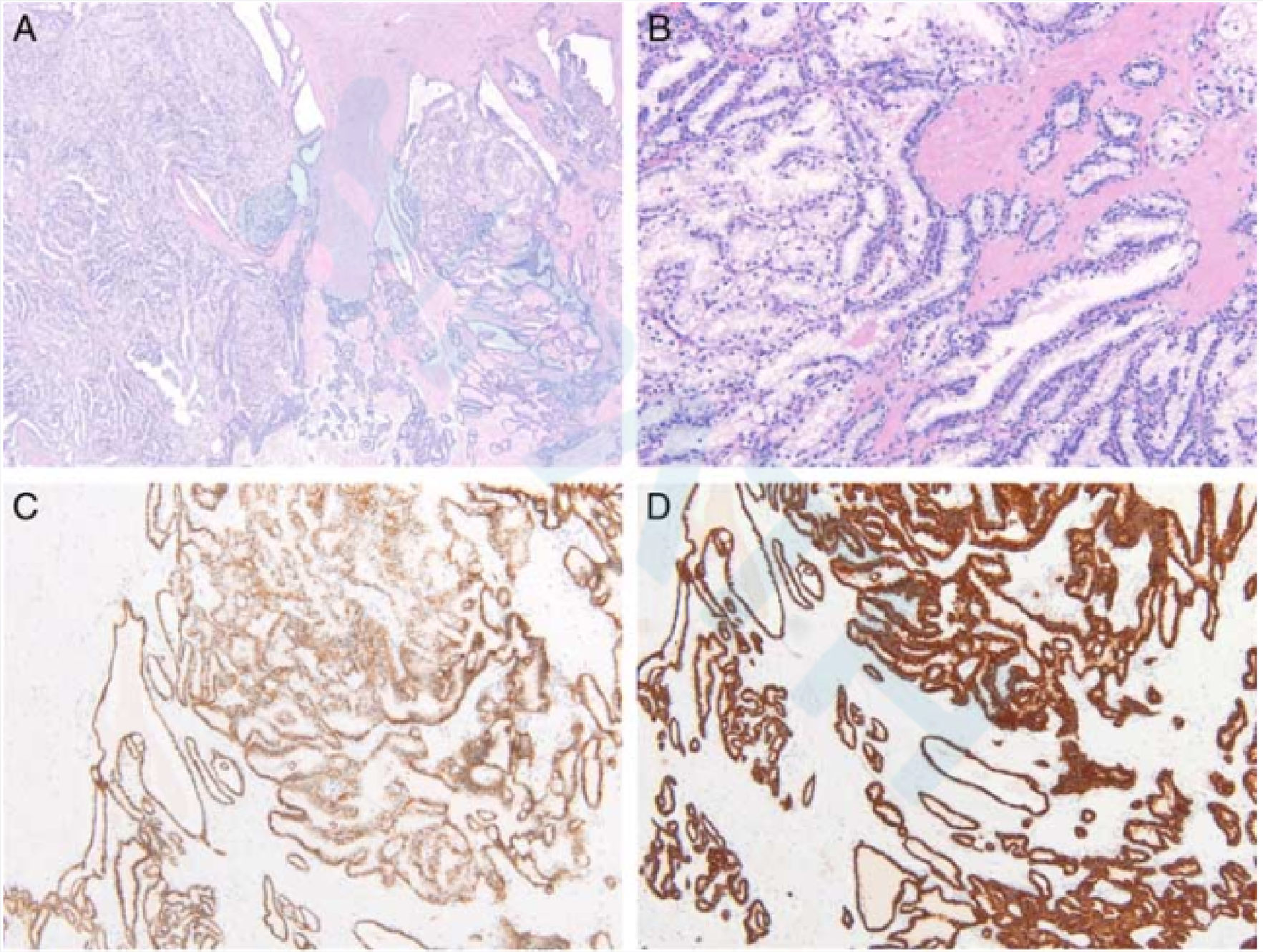
CD10



SDHB



R E S U L T S

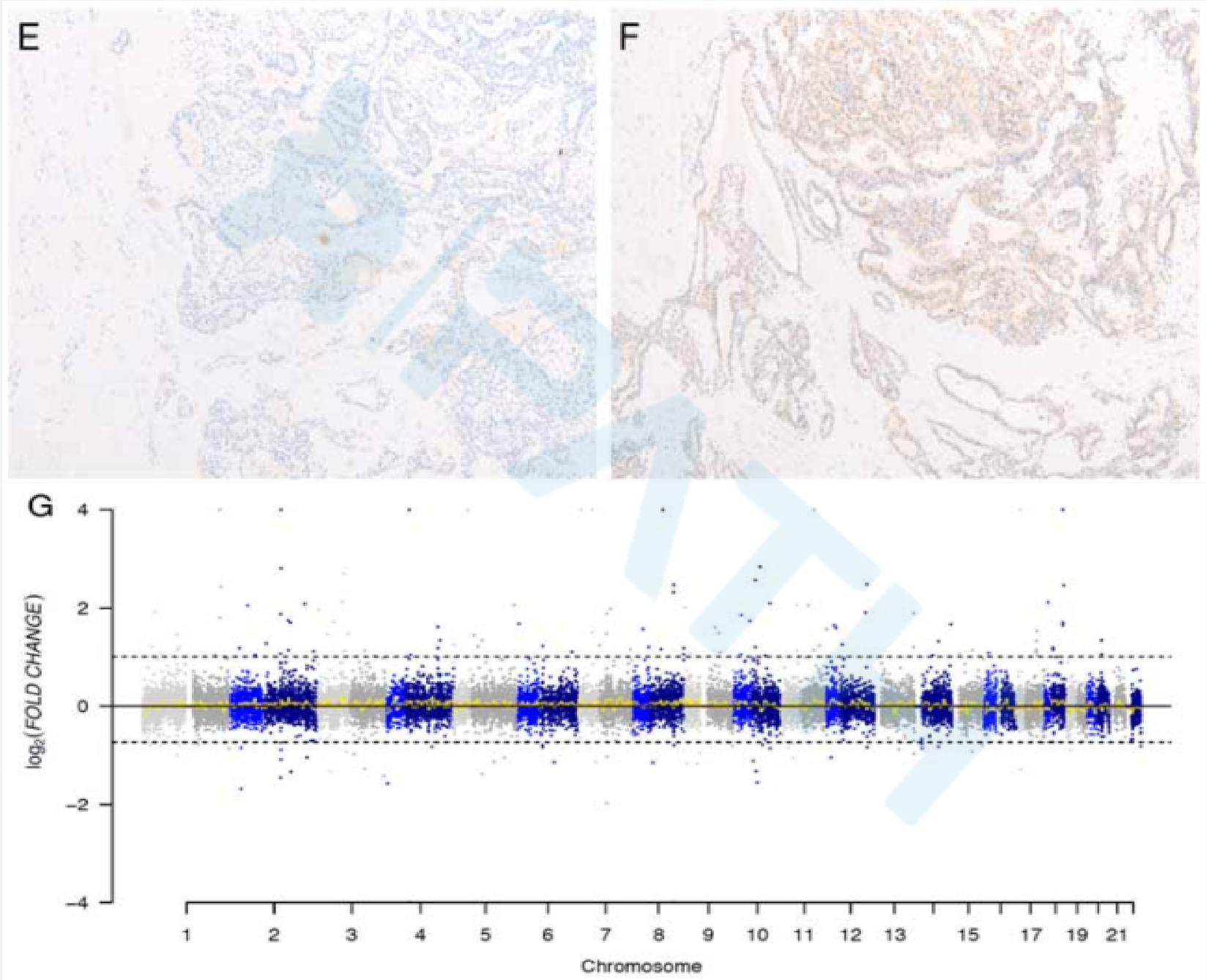


CA9

CK7

CD10

SDHB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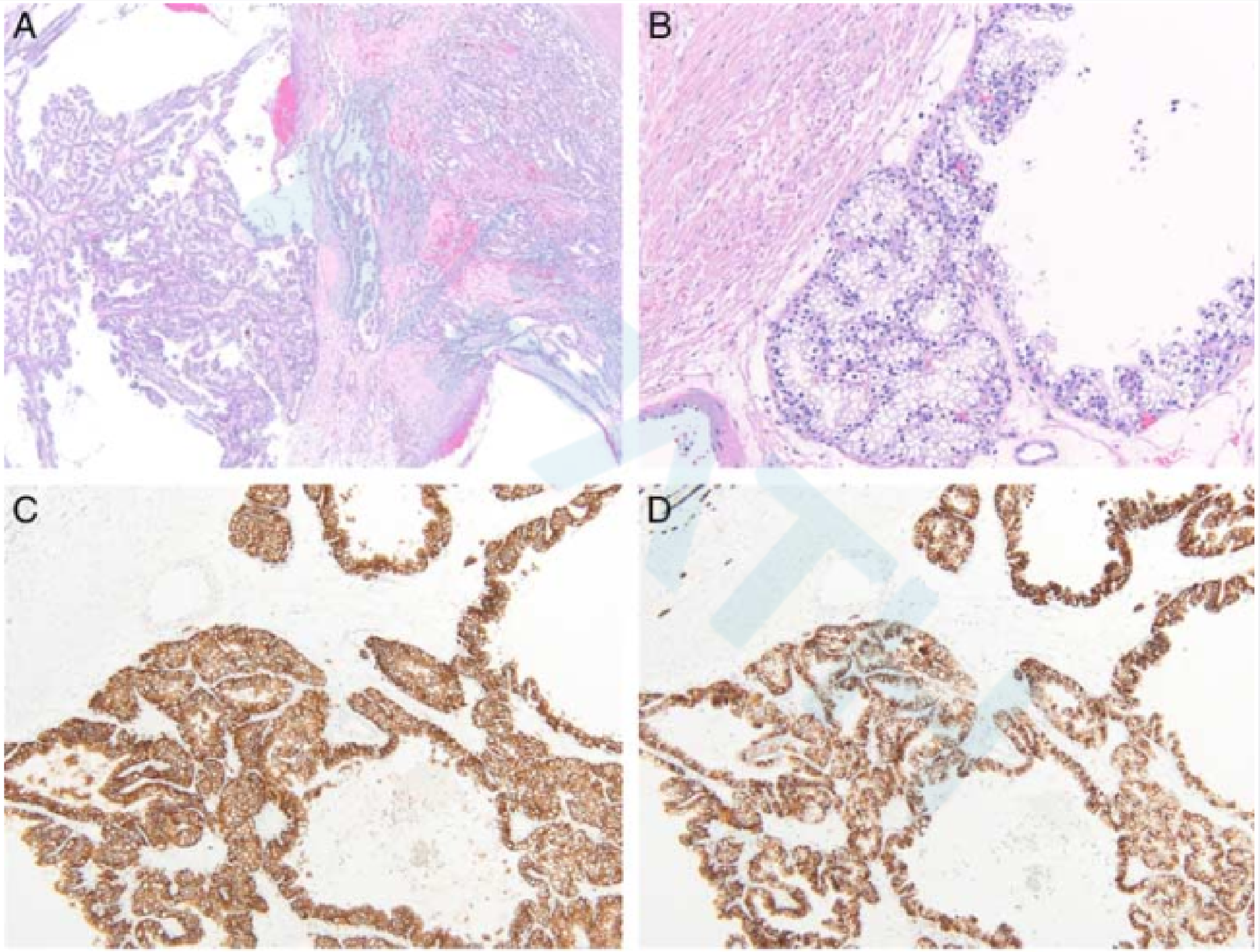
Chromosome

TABLE 2. Immunohistochemical Features and Molecular Alterations of Selected RCC-LS

Case	Clinical TSC	CAIX	CK7	CD10 (Membranous)	SDHB Retained	IHC-based Diagnosis	Chromosome Alterations	Gene Mutations*	Final Integrated Diagnosis
1	N	Full pos	Strong diffuse	Moderate focal	Y	?	Monosomy 8	TCEB1 p.Ser23Leu	TCEB1-mutated RCC
2	N	Full pos	Strong diffuse	Moderate focal	Y	?	Monosomy 8	TCEB1 p.Ala106Asp	TCEB1-mutated RCC
3	N	Full pos	Strong diffuse	Moderate focal	Y	?	Monosomy 8	TCEB1 p.Tyr79Cys	TCEB1-mutated RCC
10	N	Cup pos	Strong diffuse	Strong focal	Y	?	Neutral/Normal	TSC1 c.2626-3C>T	Unclassified
13	Y	Full pos	Strong focal	Moderate focal	N	TSC-associated RAT-like RCC	Neutral/normal	TSC1 p.Leu669Phefs*19	TSC-associated RAT-like RCC
14	N	Cup pos	Strong focal	Moderate focal	Y	?	Neutral/normal	TSC2 p.Leu219Arg TSC2 p.Arg1200Trp	Unclassified
15	N	Full pos	Moderate focal	Strong focal	Y	?	Neutral/normal	TSC2 p.Trp304Arg SETD2 p.Gln7_Pro8del	Unclassified

R E S U L T S

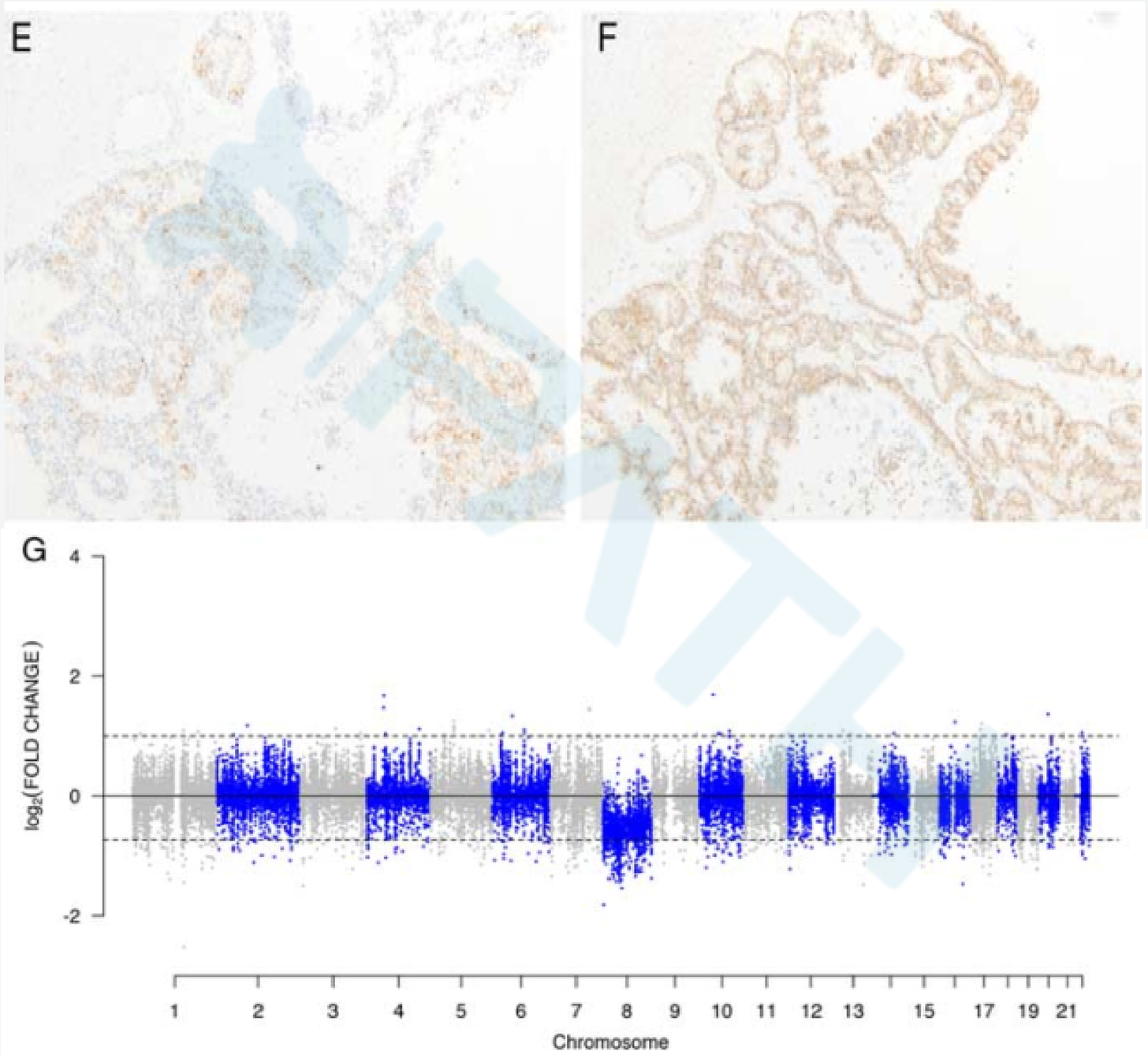


CA9

CK7

CD10

SDHB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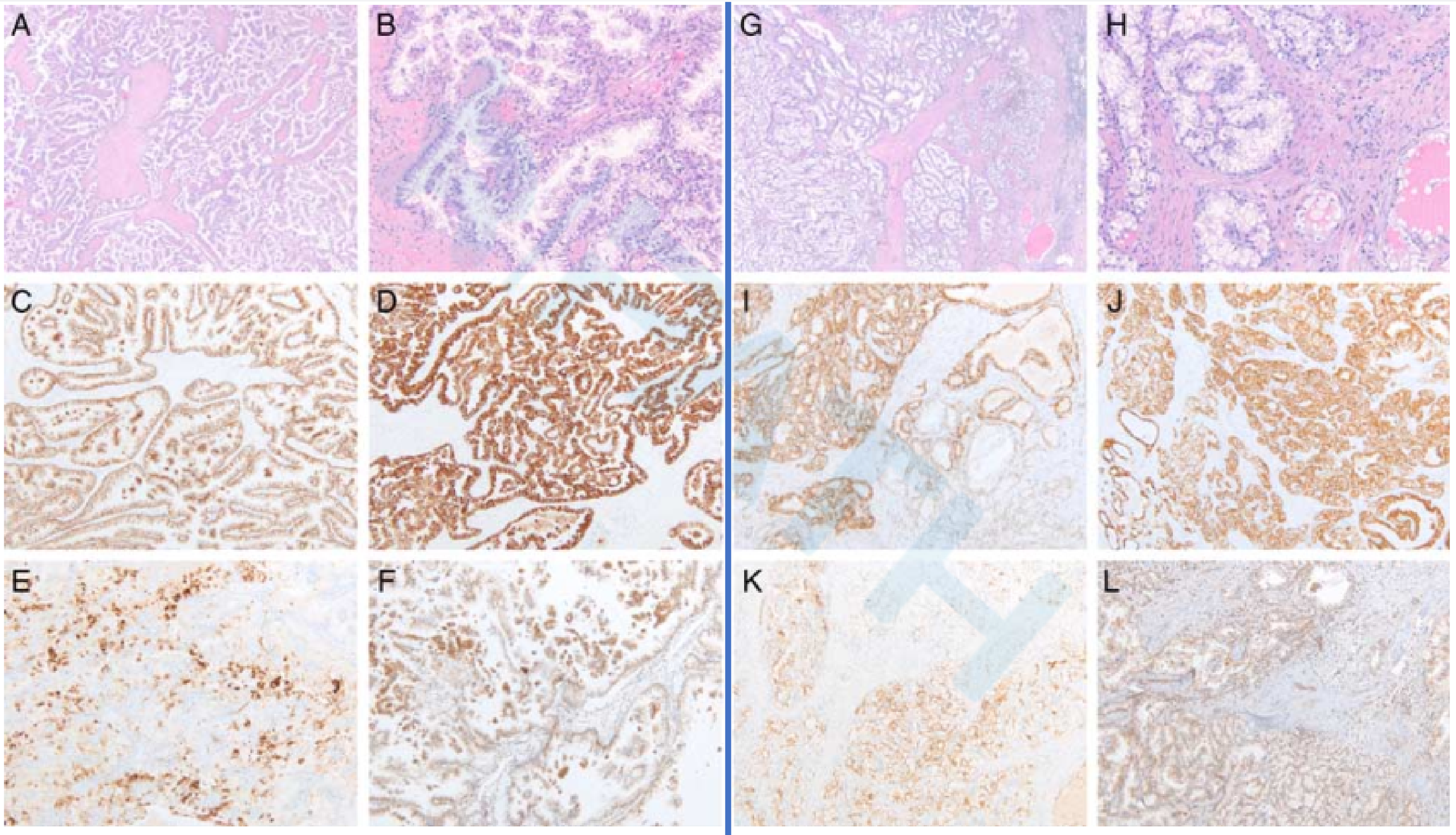
14	N	Cup pos	Strong focal	Moderate focal	Y	?	Neutral/normal	TSC2 p.Leu219Arg TSC2 p.Arg1200Trp	Unclassified
15	N	Full pos	Moderate focal	Strong focal	Y	?	Neutral/normal	TSC2 p.Trp304Arg SETD2 p.Gln7_Pro8del	Unclassified

R E S U L T S



Part four

讨　论

DISCUSSION

讨论1：TCEB1-mutated RCC 的诊断要点

- ✓ 通过形态和IHC鉴别其他类型具有丰富平滑肌基质的RCC与TCEB1突变的RCC相对困难，需要进行分子检测作为诊断依据。
- ✓ 本文3例病例的TCEB1基因突变为致病性突变。由于缺乏可配对的正常样本，无法确定为遗传或获得性突变。
- ✓ 简单的靶向PCR不足以检测临床相关所有的TCEB1突变，推荐使用TCEB1基因的全基因组测序。
- ✓ 在有限的数据中，CA9膜完整强阳性、CK7弥漫强阳性以及CD10弱阳性的表达模式表明可能存在TCEB1基因的突变，在此基础上进行分子检测可作为诊断手段。

讨论2：ccRCC及ccpRCC与RCC-LS的鉴别诊断及分子改变

- ✓ 具有丰富平滑肌基质ccpRCC可能与18号染色体的增加相关，但仍需更多的研究评估具有丰富平滑肌基质的ccpRCC与经典的ccpRCC之间的区别是否在于某个染色体缺失或增加。
- ✓ VHL基因突变以及染色体3p缺失可有助于诊断形态学或免疫组化不典型的ccRCC。

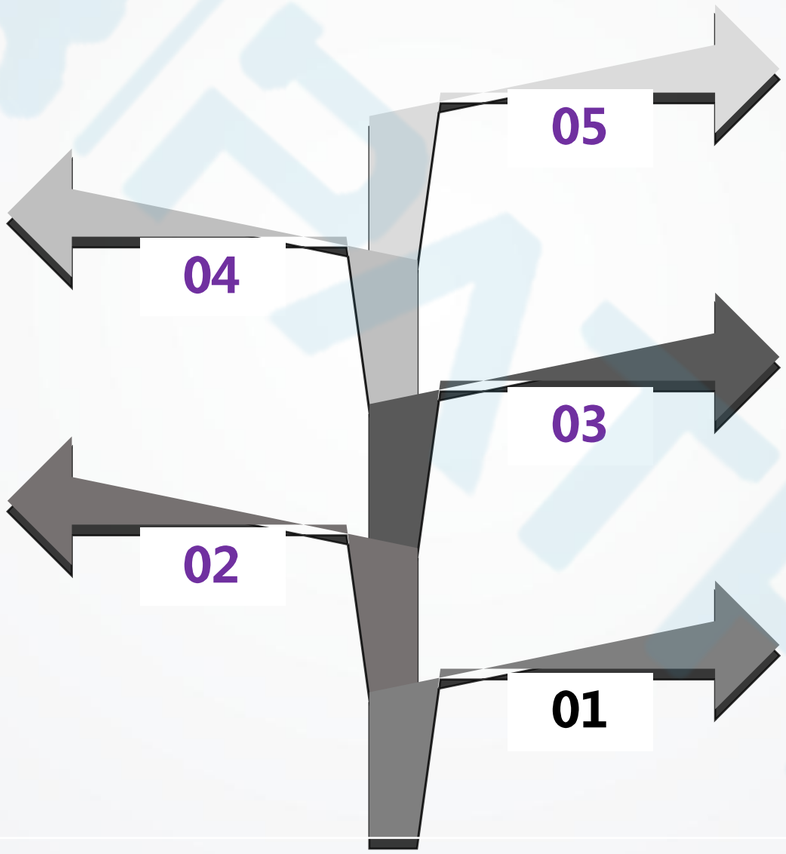
讨论3：临床背景及SDHB 的免疫组化染色缺失有助于诊断TSC-associated RAT-like RCC

- ✓ 临床诊断为TSC的患者发生RAT-like RCC在组织学上无法与其他RCC-LS区分，临床背景及SDHB 的免疫组化染色缺失可有助于最终诊断。
- ✓ 本文病例中，许多未分类的肿瘤SDHB 染色呈弱阳性，没有经验的情况下可能被判定为阴性，即SDHB缺失。根据文献推荐，在此类肿瘤中，任何量的SDHB免疫反应性均被判定为阳性。

讨论4：TSC基因突变的意义尚需进一步明确

- ✓ TSC患者发展为肾细胞癌不只表现为TSC-associated RAT-like RCC，还包括嫌色细胞样RCC和TSC相关ESC RCC 。
- ✓ 本文3例未分类的病例中均有TSC1和/或TSC2的突变，均为错义突变，目前尚不能确定其临床意义。
- ✓ 此外，尚有一例诊断为ccpRCC的病例（case 6）具有TSC2突变，目前突变意义也不明确，对于此类突变需进行进一步研究，确定其是否存在类似于ESC RCC的，散发性TSC基因突变相关的RCC。

DISCUSSION



unclassified RCC with extensive leiomyomatous stroma

TCEB1-mutated RCC

TSC-associated RAT-like RCC

ccRCC
variants with extensive leiomyomatous stroma

ccpRCC variants with extensive leiomyomatous stroma

Thank you

2019.09.04