

Frequent GNAQ and GNA14 Mutations in Hepatic Small Vessel Neoplasm

Nancy M. Joseph, MD, PhD

汇 报 人：谭凤梅

指导老师：范林妮

背景-肝脏 血管肿瘤分类

WHO 肝和肝内胆管肿瘤分类^a

上皮性肿瘤：肝细胞性

良性

肝细胞腺瘤	8170/0
局灶性结节状增生	

恶性相关和恶性前病变

大细胞改变（曾称为“异型增生”）	
小细胞改变（曾称为“异型增生”）	
异型增生结节	
低级别	
高级别	

恶性

肝细胞肝癌	8170/3
肝细胞肝癌，纤维板层亚型	8171/3
肝母细胞瘤，上皮亚型	8970/3
未分化癌	8020/3

上皮性肿瘤：胆管性

良性

胆管腺瘤（胆管周腺错构瘤和其它）	8160/0
微囊性腺瘤	8202/0
胆管腺纤维瘤	9013/0

恶性前病变

胆管上皮内肿瘤，3 级（BillN - 3）	8148/2 *
胆管内乳头状肿瘤伴低或中级别上皮内肿瘤	8503/0
胆管内乳头状肿瘤伴高级别上皮内肿瘤	8503/2 *
粘液性囊性肿瘤伴低或中级别上皮内肿瘤	8470/0
粘液性囊性肿瘤伴高级别上皮内肿瘤	8470/2

恶性

肝内胆管癌	8160/3
胆管内乳头状肿瘤伴相关的浸润性癌	8503/3 *
粘液性囊性肿瘤伴相关的浸润性癌	8470/3

混合性或来源不明的恶性肿瘤

钙化性巢状上皮间质肿瘤	8975/1 *
癌肉瘤	8980/3
混合型肝细胞和胆管癌	8180/3
肝母细胞瘤，上皮 - 间质混合型	8970/3
恶性横纹肌样瘤	8963/3

间质肿瘤

良性

血管平滑肌脂肪瘤（PEComa）	8860/0
海绵状血管瘤	9121/0
婴儿型血管瘤	9131/0
炎性假瘤	
淋巴管瘤	9170/0
淋巴管血管瘤	
间质错构瘤	
孤立性纤维性肿瘤	8815/0

恶性

血管肉瘤	9120/3
胚胎型肉瘤（未分化肉瘤）	8991/3
上皮样血管内皮瘤	9133/3
Kaposi 肉瘤	9140/3
平滑肌肉瘤	8890/3
横纹肌肉瘤	8900/3
滑膜肉瘤	9040/3

生殖细胞肿瘤

畸胎瘤	9080/1
卵黄囊瘤（内胚窦瘤）	9071/3

淋巴瘤

继发性肿瘤

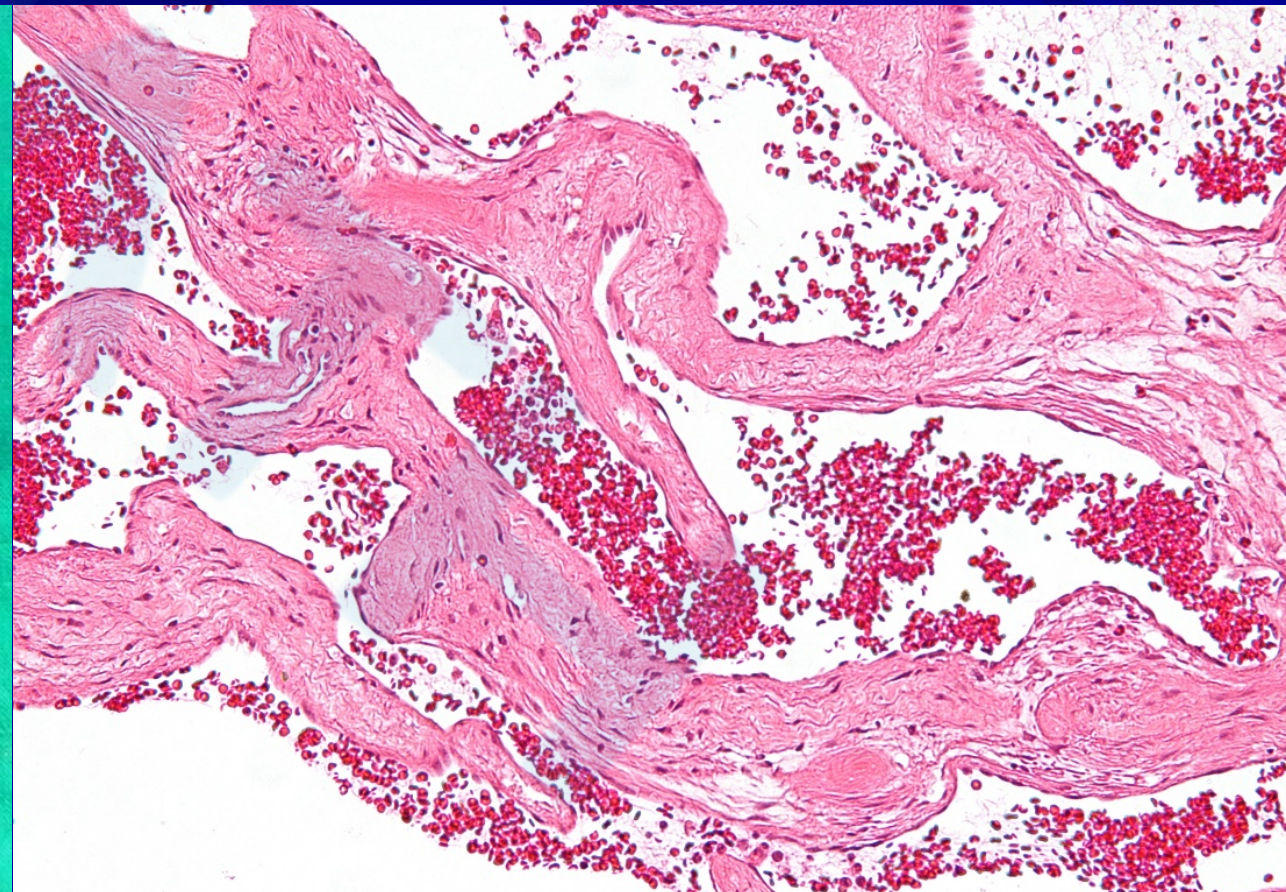
PEComa：血管周上皮样细胞肿瘤。

^a 形态学编码依据国际肿瘤分类编码（ICD - O）^{904A} 和医学系统命名法（SNOMED）。生物学行为编码为/0 指良性肿瘤，/1 指非特异性的，交界性或生物学行为未定，/2 指原位癌和Ⅲ级上皮内肿瘤，/3 指恶性肿瘤。

* 新编码由 IARC/WHO 的 ICD - O 委员会在 2010 年 3 月会议上批准应用。

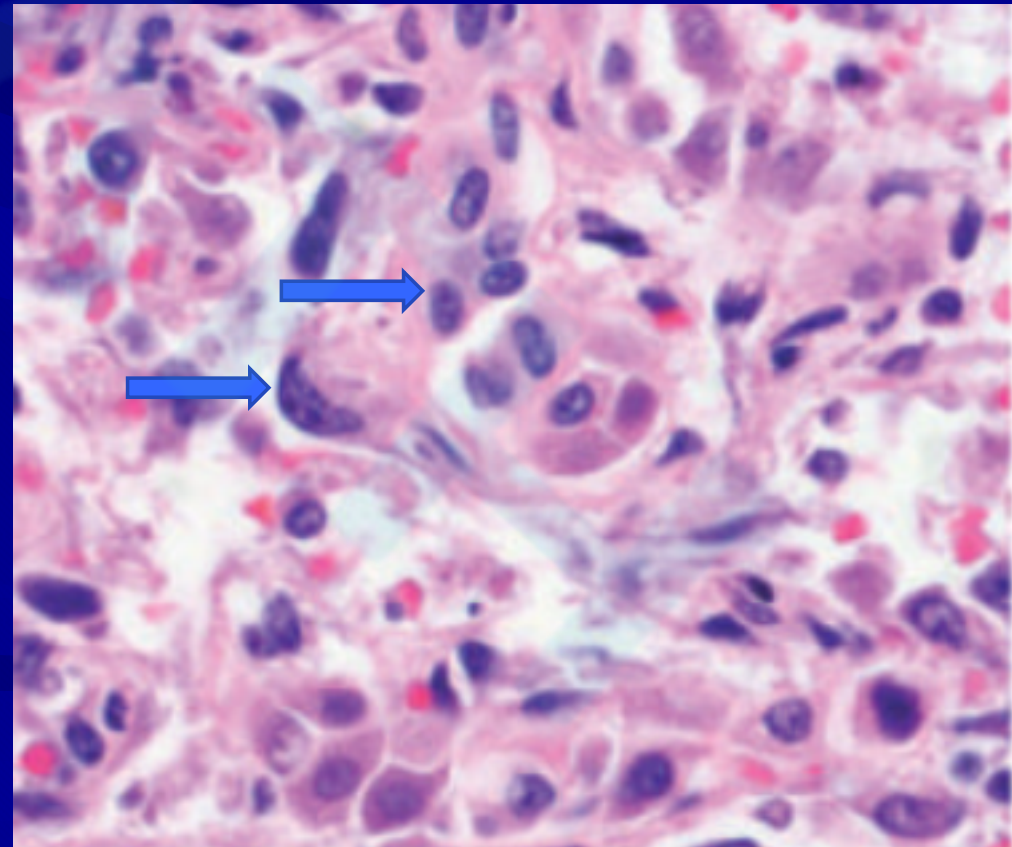
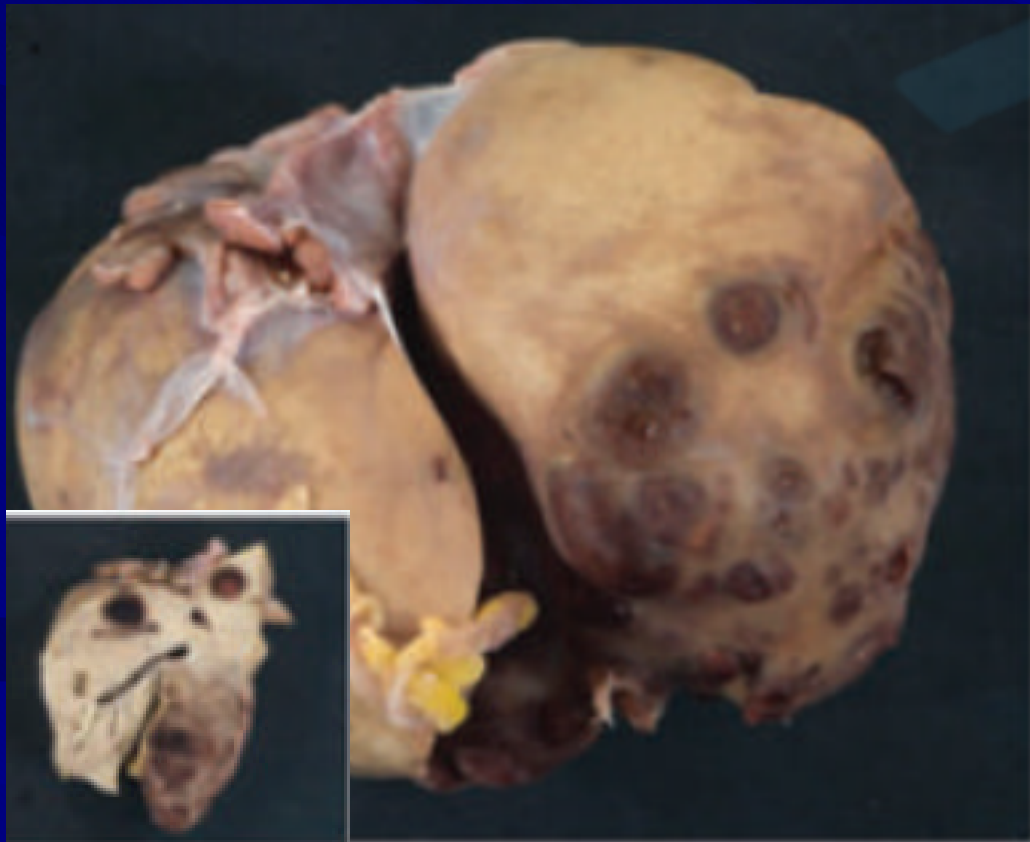
背景-肝脏海绵状血管瘤

- 海绵状血管瘤（CH）是界限清楚的良性肿瘤，通过组织学评估很容易诊断，因为它具有特征性的大血管，内衬平坦一致的内皮细胞，血管之间有较宽的纤维间隔



背景-肝脏血管肉瘤

- 一种侵袭性肿瘤，多灶充血性结节，可潜入肝窦，分离肝板，压迫和浸润肝实质，有浸润性边缘
- 纺锤形到圆形内皮细胞形成，大小不一，有异型



背景-肝脏小血管肿瘤

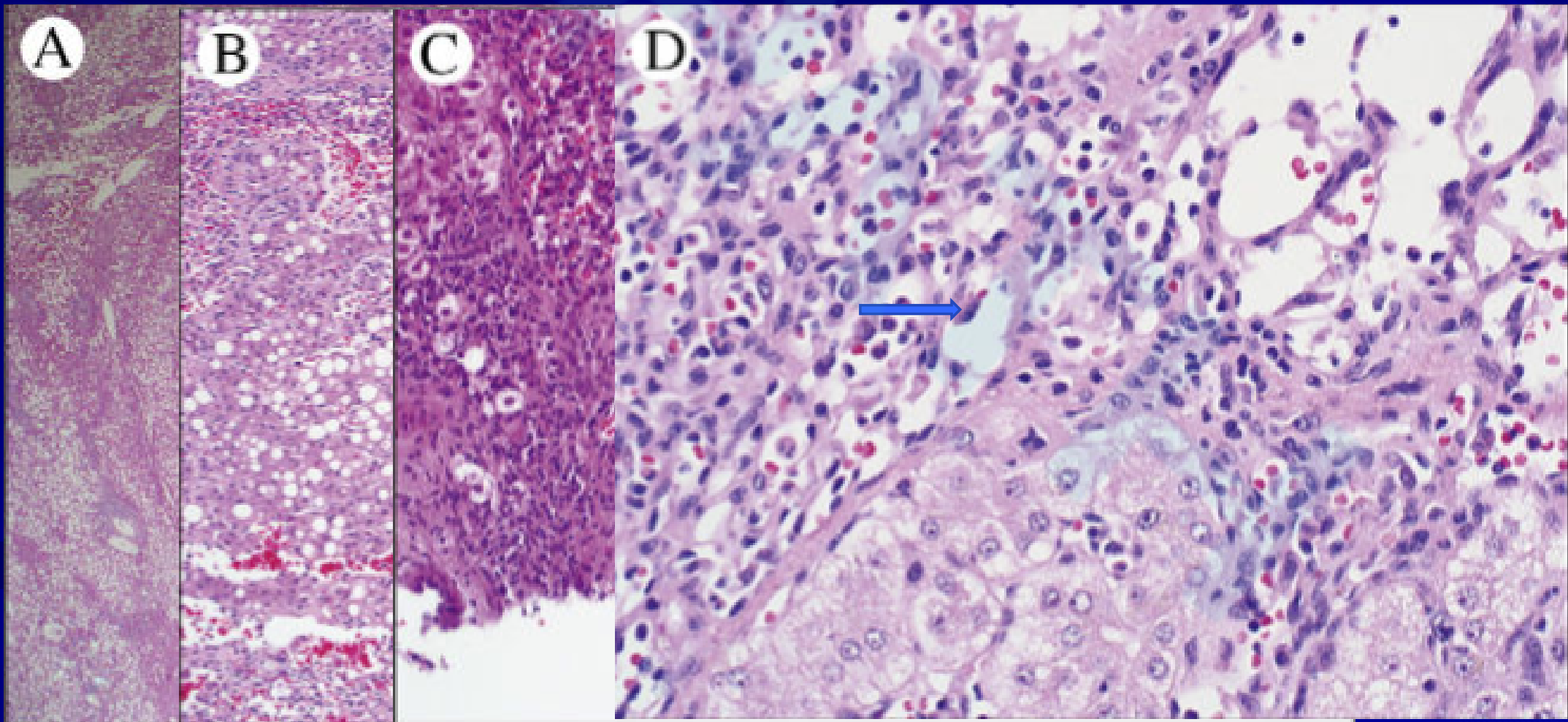
- Ryan M.Gill等于2016年首次报道
- 浸润性边缘的罕见血管肿瘤
- 多见于成人（平均年龄54岁），主要发生于左肝，也可同时累及右肝
- 大体特点



背景-肝脏小血管肿瘤

■ 镜下特点

- ✓ 由薄壁小血管组成，单层扁平上皮（**内皮肥胖**），浸润性边界（类似血管肉瘤），但**HSVN**细胞没有异型性



背景-肝脏小血管肿瘤

■ 免疫组化特点

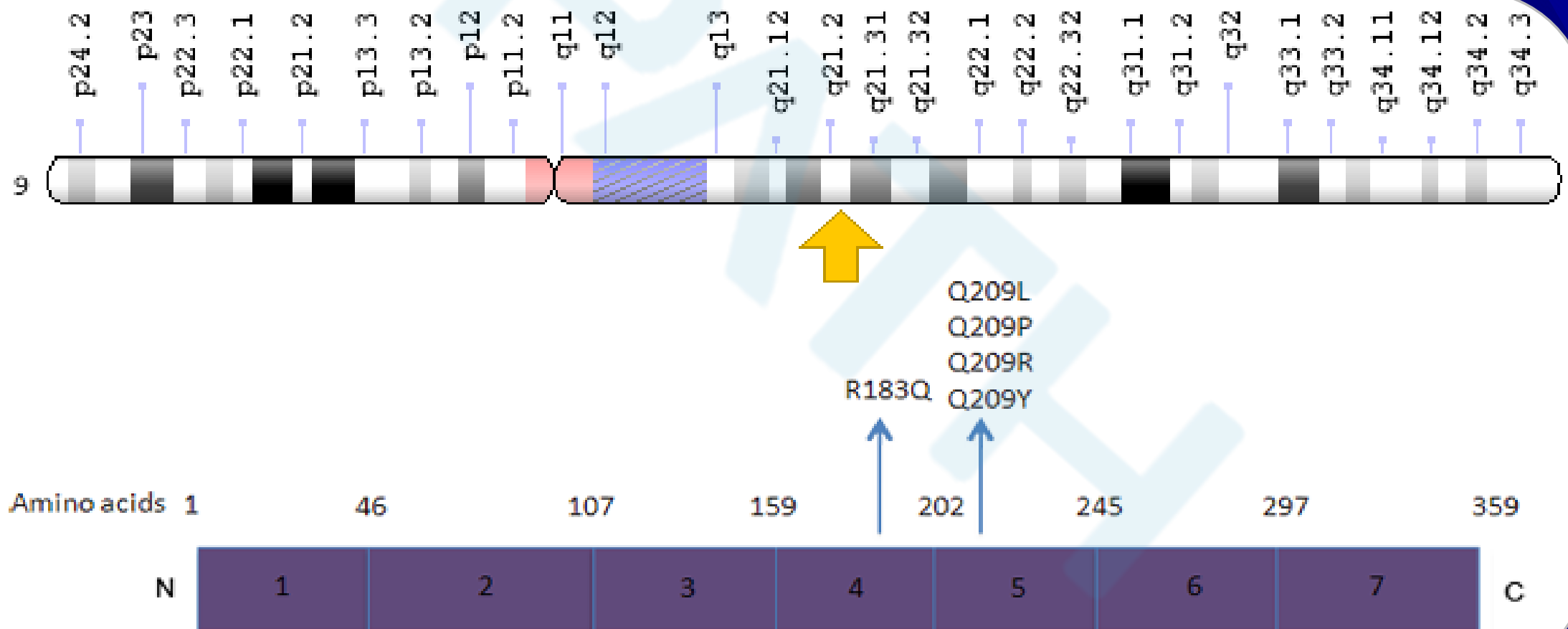
- ✓ **ki - 67**增殖指数低(平均值**3.7 %**), **p53**表达也弱
- ✓ **CD34**、**CD31**和**FLI - 1**标记阳, 染色比较均匀一致

■ 遗传学特征

- ✓ **2/3**的**HSVN**发生**GNAQ p.Q209H**突变
- ✓ (**p.Q209H** 是**GNAQ**基因的一个位点)

背景-GANQ

- GNAQ：鸟嘌呤核苷酸结合蛋白
- 位于人类 9q21，分子量为 42142Da，包含 7 个外显子



背景-GANQ、GNA11、GNA14

- GNA11、GNA14和GNA15是GNAQ的同源物，与GNAQ氨基酸序列相似性分别约90%、80%和57%

基因	突变位点	发生肿瘤
GNAQ	p.Q209H	2/3HSVN
	/	吻合状血管瘤
	/	非综合征型葡萄酒色斑
GNAQ 和 GNA11	4号外显子R183和5号外显子Q209	葡萄膜黑色素瘤 蓝痣
	Q209	先天性血管瘤
GNA14	p.Q205L	常发生于儿童血管肿瘤，如小叶毛细血管瘤、簇状血管瘤和卡波西血管内皮瘤

研究设想

- GNA14 p.Q205L会不会发生在肝脏小血管肿瘤
- 与GNAQ p.Q209H有无关系（同时出现还是单独出现）

材料和方法

- 病例来源：美国加州大学旧金山分校，8例HSV₁N，6例海绵状血管瘤（CH），4例同时具有HSV₁N和CH特征（VL）
- 免疫组化：Ki-67（至少200个细胞）
- 二代测序和突变分析：479个癌相关基因外显子和47个内含子

结果:

临床特征

1) 都发生于成人
性别和年龄差异
没有统计学意义

2) 大小:
HSVN 0.2~5.5cm
CH 0.8~2.8cm
VL 1.1~15cm

3) 预后较好

TABLE 1. Clinicopathologic Characteristics of 18 Indolent Vascular Lesions in the Liver

Case ID	Patient Age (y)	Patient Sex	Specimen Type	Size of Lesion (cm)	Ki-67 Index (%)	Clinical	Additional Treatment	Evidence of Metastases	Outcome	Maximum Follow-up (mo)
HSVN1*	58	F	Autopsy	1.5 (largest)	0	3 incidental liver tumors at autopsy for pulmonary embolism	NA	None	NA	NA
HSVN2	65	M	Wedge biopsy	2.2 (largest)	8	Bronchial carcinoid with imaging of liver showing 2 hypervascular lesions (segment 2, 2.2 cm and segment 6/7, 1.1 cm) suggestive of metastatic neuroendocrine tumor	Radiofrequency ablation, resection	None	ARD	1
HSVN3	47	M	Resection	1.1	5	RCC with incidental liver tumor	NA	None	NA	NA
HSVN4*	37	F	Resection	5.5	3	Pregnant with incidental liver tumor	None	None	ANED	6
HSVN5*	43	M	Resection	2.2	1	NAFLD, imaging initially suggests hemangioma, 4 y later tumor is ~50% larger and atypical for hemangioma on MRI	Resection	None	ANED	24 since resection, 72 since seen on imaging
HSVN6	54	M	Resection	4.2	7	Incidental liver tumor	TACE followed by resection several months later	None	ANED	24
HSVN7*	66	M	Explant	1.8	6	HCV with cirrhosis and imaging suggesting HCC	TACE followed by explant	None	NA	NA
HSVN8	65	M	Explant	0.2	2	65 M with end-stage liver disease secondary to alcoholic cirrhosis	None	None	ANED	12
VL9*	62	M	Resection	2.8	2	undergoes liver transplant	None	None	NA	NA
VL10*	49	F	Explant	1.3	1	Incidental liver tumor suggestive of hemangioma	None	None	ANED	66
VL11*	75	F	Resection	1.5	NA	PBC with hepatic encephalopathy and ascites and imaging of liver with 1.3 cm hypervascular lesion without washout	None	None	NA	NA
VL12*	53	M	Resection	0.8	NA	History of breast cancer and left kidney RCC with lymph node metastases	None	None	NA	NA
CH13	53	F	Resection	7.6	0	Status/post whipple for a 3 cm NET with portal vein embolization	None	None	NA	NA
CH14	56	M	Explant	1.1	0	Incidentally found pedunculated hemangioma on imaging for appendicitis	None	None	NA	NA
CH15*	37	F	Resection	15	0	HCV with cirrhosis	None	None	NA	NA
CH16*	63	F	Resection	3.5	0	Right upper quadrant pain	None	None	NA	NA
CH17	36	M	Resection	4.3	0	Multiple hemangiomas in liver incidentally found during work up of gastric mass (schwannoma)	None	None	NA	NA
CH18	41	M	Resection	1.5	0	History of hepatic hemangioma	None	None	NA	NA
						Morbid obesity who undergoes wedge resection	None	None	NA	NA

*Histologic images for starred cases are shown in Figures 2 and 3.

The HSVN data was published in our initial description of HSVN,¹ but follow-up times have been adjusted to date.

ANED indicates alive with no evidence of disease; ARD, alive with residual disease; F, female; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; M, male; MRI, magnetic resonance imaging; NA, not available or the category is not applicable; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; RCC, renal cell carcinoma; TACE, transarterial chemoembolization.

结果：基因特征

- GNAQ p.Q209H 突变: 2/8 (25%) HSVN 和 1/4 (25%) VL
- GNAQ p.G48L 突变: 2/8 (25%) HSVN 和 1/4 (25%) VL

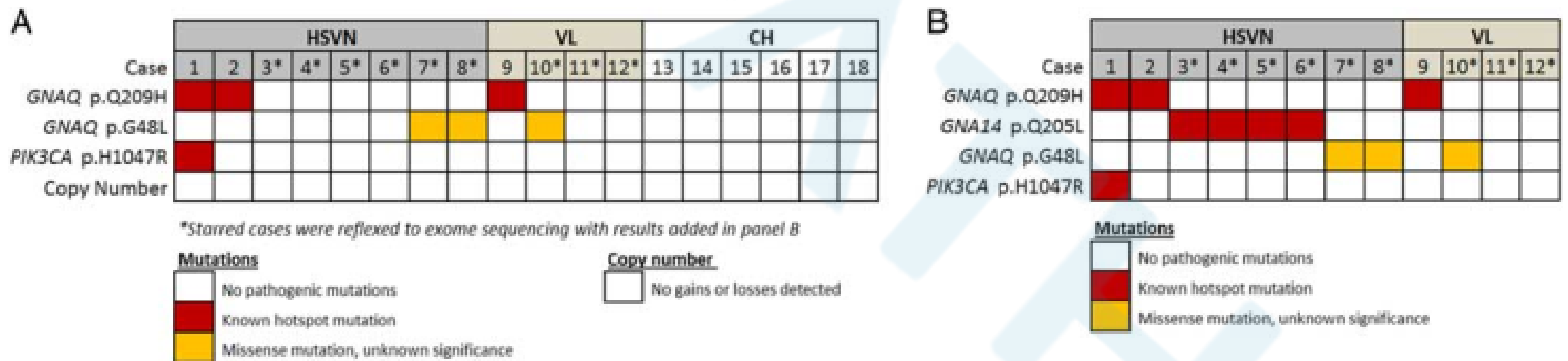


FIGURE 1. Genomic profiling results for 18 vascular tumors in the liver including 8 HSVN, 4 VL, and 6 CH. A, Tile plot summarizing the pathogenic and likely pathogenic alterations detected by capture-based NGS sequencing targeting 479 cancer-related genes. Cases starred with an asterisks were reflexed to exome sequencing, which revealed recurrent hotspot mutations in *GNA14*, a gene that was not included in the targeted panel. B, Tile plot summarizing the aggregated sequencing results obtained from both targeted panel and exome sequencing.

结果：遗传学改变与形态学的相关性

组织学上：肿瘤细胞多，小血管密集的地方

基因突变频率较高；

相反，肿瘤细胞较少，小血管稀疏的地方

基因突变频率较低。

基因突变的频率与肿瘤多少及小血管密度呈正相关。

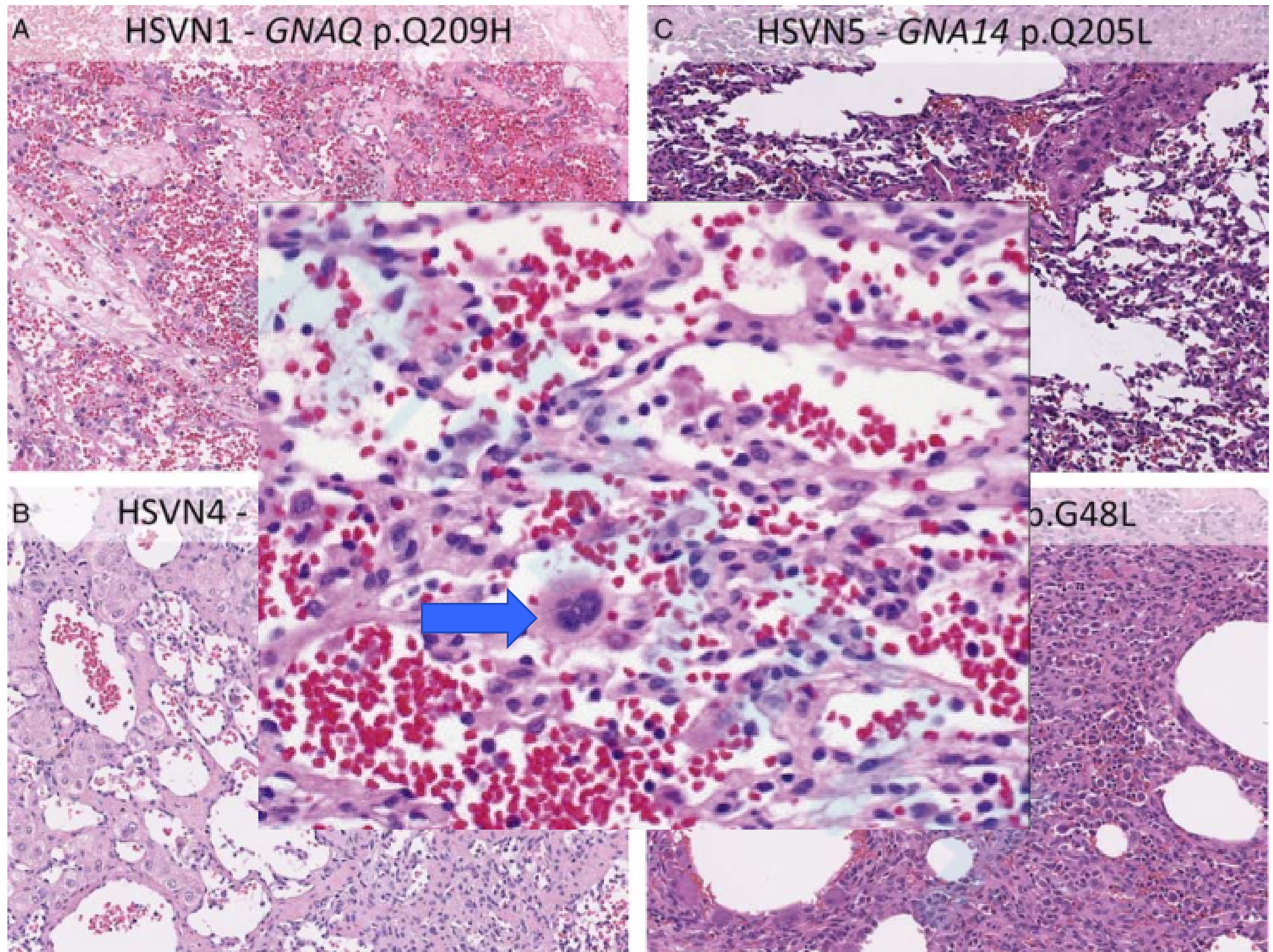


FIGURE 2. Hematoxylin and eosin–stained sections of HSVN with *GNAQ* p.Q209H hotspot mutation (A), *GNA14* p.Q205L hotspot mutation (B, C) and *GNAQ* p.G48L mutation (D). All HSVN are morphologically composed of small vascular spaces lined by flat to plump endothelial cells without significant cytologic atypia or mitoses. All HSVN demonstrated infiltrative borders which can be appreciated in (B), (C). Occasional HSVN had prominent extramedullary hematopoiesis (D).

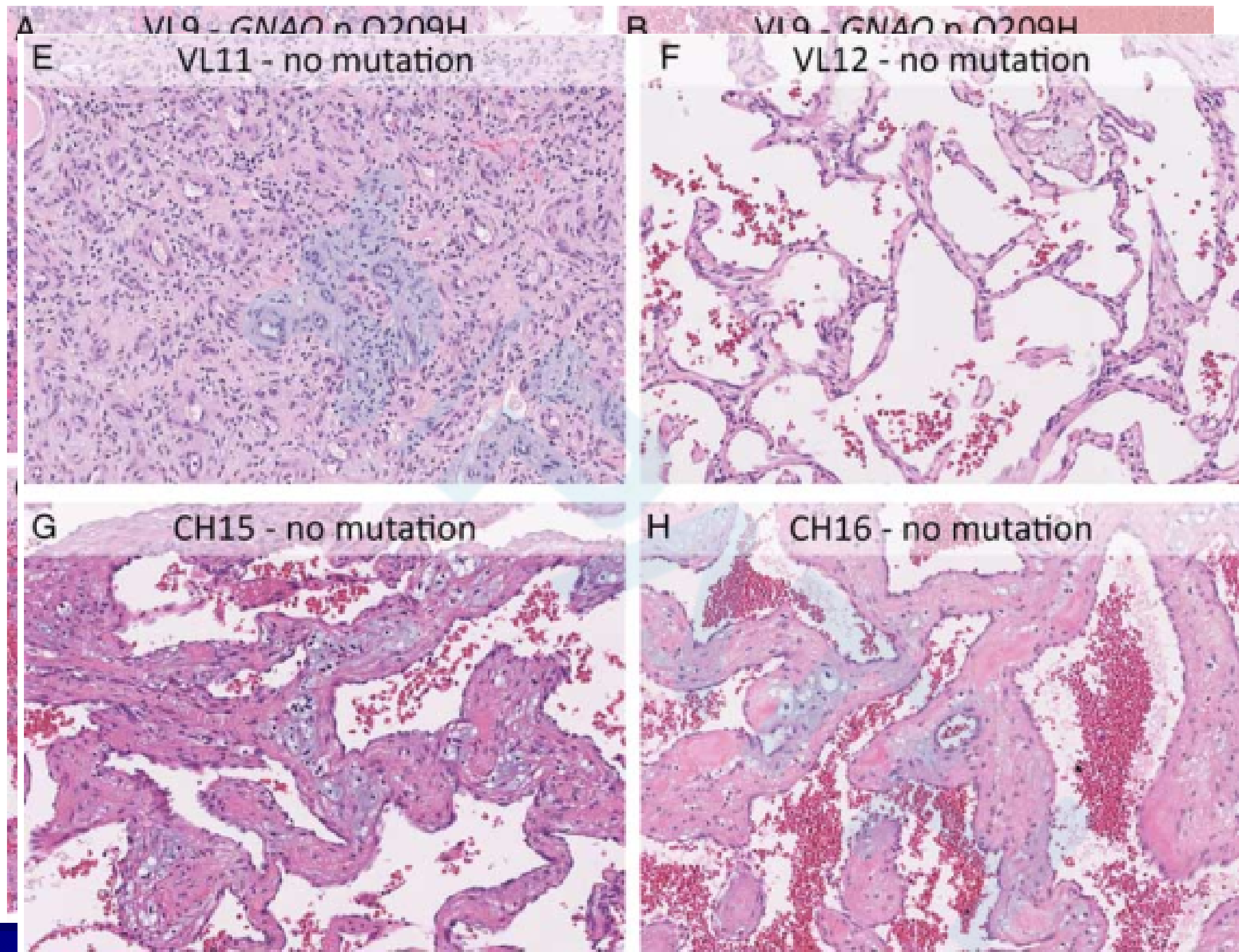


FIGURE 3. Hematoxylin and eosin-stained sections of VL and CH. VL9 with *GNAQ* p.Q209H mutation demonstrated areas indistinguishable from HSVN (A) but also had areas composed of larger vascular spaces with increased wall thickness (B). VL10 with a *GNAQ* p.G48L mutation had similar small vessel areas (C) as well as larger vascular spaces (D). E, VL11 was entirely composed of thick-walled small vessels. F, VL12 had thin walls but otherwise resembled CH. G and H, Two CH demonstrating classic thick-walled large vascular channels.

讨论一：肝脏血管肿瘤的基因突变

- 本文新发现2例HSVN和1例具有小血管区的VL发生了GNAQ p.G48L的错义突变
- GNAQ或GNA14的突变主要发生在小血管组成的区域
- 有研究报道GNAQ、GNA11、GNA14在各种血管畸形和良性肿瘤中出现，如：葡萄酒色痣、先天性血管瘤、吻合状血管瘤
- 先天性血管瘤和吻合状血管瘤的分子发病机制相似

讨论一：肝脏血管肿瘤的基因突变

- 血管肉瘤会发生**TP53**、**PTPRB**、**PLCG1**、**BRAF**等的基因突变，但还未发现**GNAQ**、**GNA11**、或**GNA14**的突变

讨论二：肝脏血管肿瘤的归类

- 研究发现所有的HSVN发生了GNAQ或GNA14的互斥突变，有2例VL也发生了GNAQ突变，虽然这2例VL也由小血管组成，但是由于它还具有大血管组成的区域，而且边界也很清楚，所以还是把它归入VL
- 本文VL9和10大部分区域由小血管组成，GNAQ或GNA14也发生了突变，VL9出现了浸润性边缘，VL10未出现，按照定义应该将VL9诊断为具有大血管区的HSVN

讨论三：肝脏血管瘤的起源

- 发生于肾脏和肝脏的吻合状血管瘤的形态特征相似，类似于本文的VL9和10，VL9和10 GNAQ的突变证实了HSVN和肝脏吻合状血管瘤的突变位点相似，只是HSVN有浸润性边缘

结论（HSVN诊断要点）：**GNAQ或GNA14突变、小血管、浸润性边缘、细胞无异型性、Ki-67增殖指数低、P53表达弱**

- 大多数良性血管瘤G蛋白基因突变机制相似，所以可以说HSVN和肝脏吻合状血管瘤都是由先天性血管瘤发展而来的

谢谢聆听！

THANK YOU VERY MUCH!

