

# Pheochromocytomas- Paragangliomas: The often forgotten NETs

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# Outline

- How do Paragangliomas/Pheos fit in the spectrum of NETs
- How do they present?
- How do we diagnose them vs. other NETs
- How do we manage them vs. other NETs
- What are the implications to other family members?

# Clinical Presentation

Specific symptoms

Non-specific symptoms

Compressive effects -  
Neck/chest/abdomen/pelvis

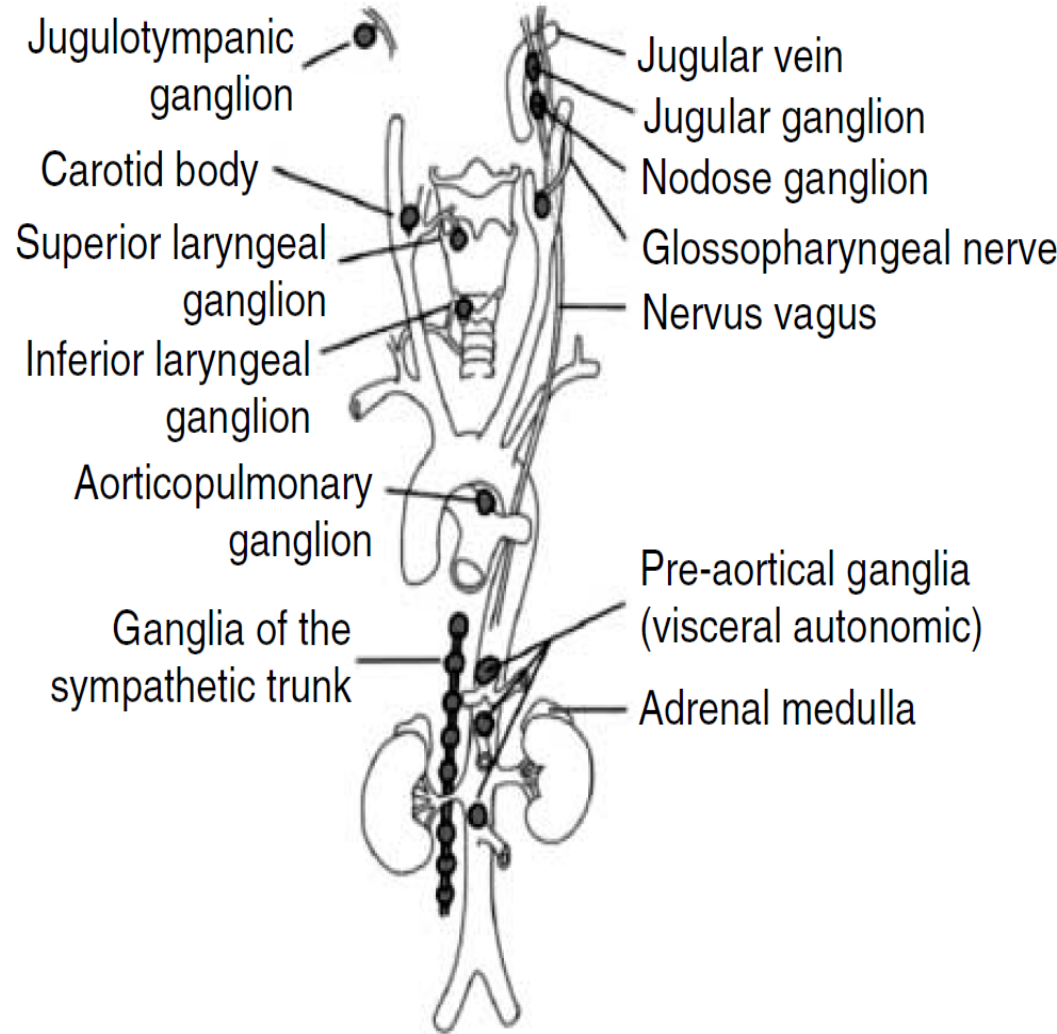
Incidental/unexpected finding

# Terminology in Neoplasms arising from Paraganglia

**Extra-adrenal: Paraganglioma**



**Intra-adrenal: Pheochromocytoma**

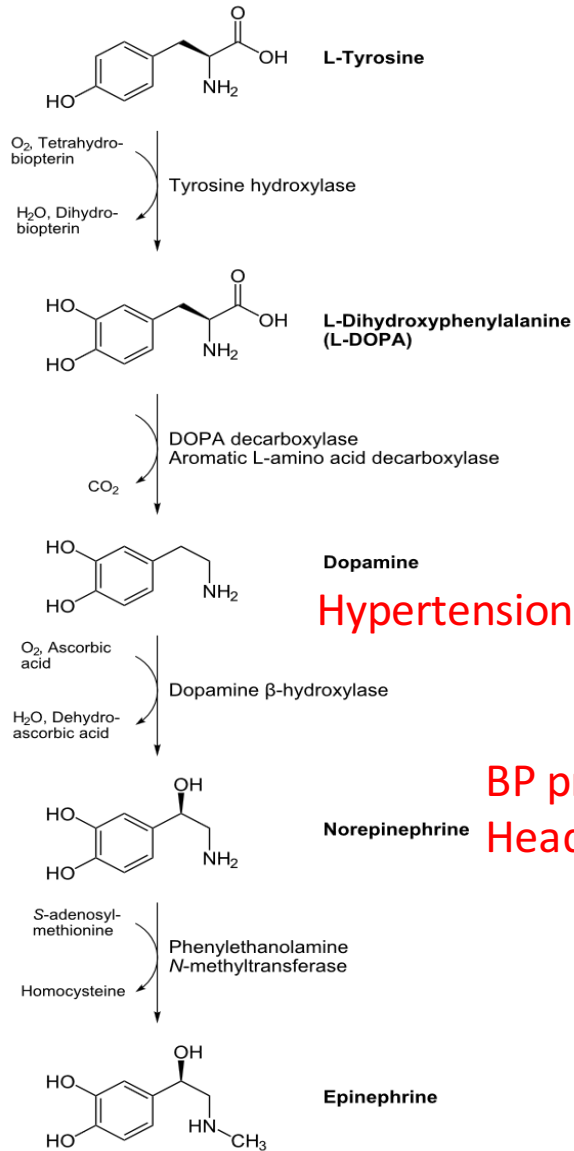


# Clinical Presentation

Age plays an important role in predicting the likelihood of inherited PPGLs syndromes.

The younger (< 50 yrs) an individual is at the time of presentation the more likely it is that their disease is hereditary.

The presence of paragangliomas and/or bilateral pheochromocytomas should alert to the possibility of familial disease.



**Hypertension**

**BP problems  
Headaches**

**Headaches/palpitations/Pallor**

**SDHB  
SDHD  
VHL**

**Sporadic  
noradrenergic**

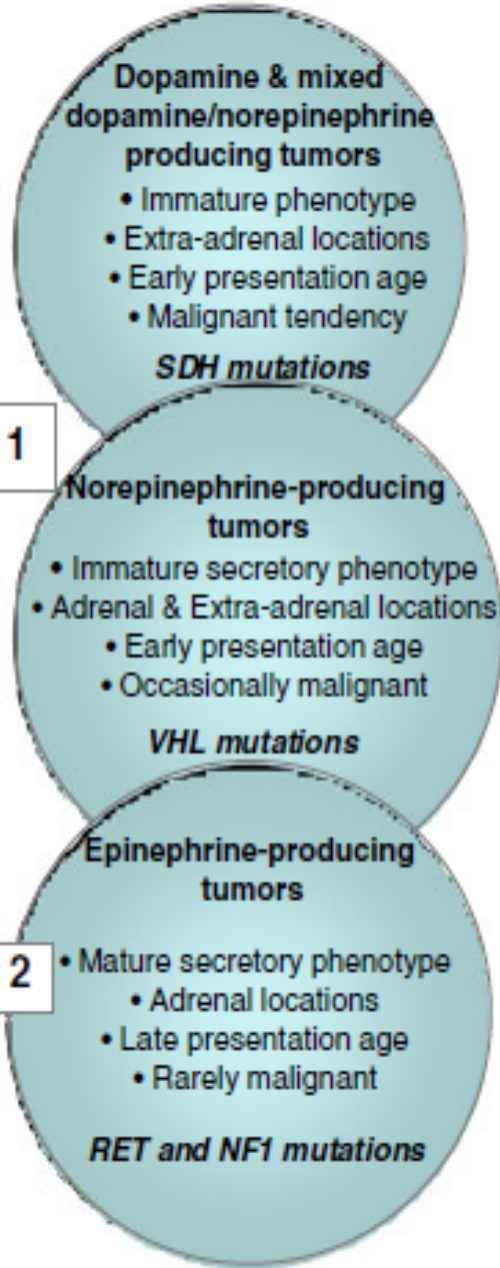
**RET  
NF1**

**Sporadic  
adrenergic**



**Cluster 1**

**Cluster 2**

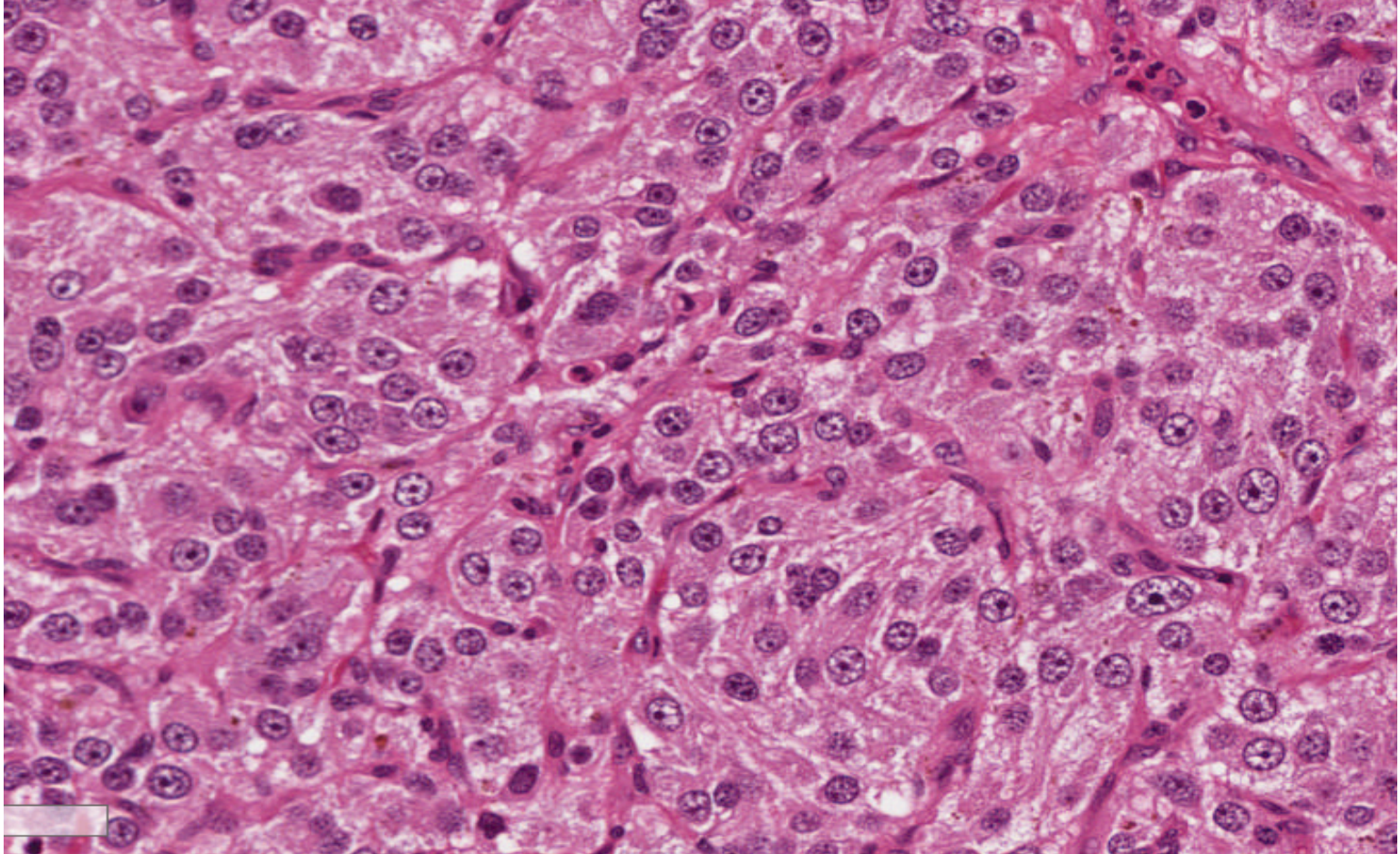


# Spectrum of Presentations

Table 1.18. Genotype-phenotype relations of familial syndromes associated with pheochromocytomas/paragangliomas

Syndrome	Cluster	Mutated gene	Biochemical phenotype	Clinical phenotype	Frequency of malignancy
von Hippel Lindau	One [434] Pseudohypoxia-driven tumours characterized by the activation of hypoxia inducible factors	<i>VHL</i>	Predominantly noradrenergic [435, 436]	Usually pheochromocytomas that may be unilateral or bilateral [432, 436]; sympathetic and parasympathetic paragangliomas may occur [411]. Other manifestations: central nervous system hemangioblastomas, renal cell carcinoma, pancreatic NET, endolymphatic sac tumours, benign cysts (kidneys, pancreas, epididymis, ovaries) [437].	<5% [411, 432, 437, 438]
Familial pheochromocytoma paraganglioma type 1		<i>SDHD</i>	Noradrenergic and dopaminergic [439]	Usually head and neck paragangliomas and less frequently pheochromocytomas or parasympathetic paragangliomas [440, 441]. Other manifestations: renal cell carcinomas [441], gastrointestinal stromal tumours [434], possibly pituitary tumours [91].	<5% [411, 441]
Familial pheochromocytoma paraganglioma type 2		<i>SDHAF2</i>	Generally non-functional tumours	Head and neck paragangliomas [426]	Very low [427, 442]
Familial pheochromocytoma paraganglioma type 3		<i>SDHC</i>	Frequently non-functional but may be noradrenergic[443] or dopaminergic	Most frequently head and neck paragangliomas[443] and exceptionally sympathetic paragangliomas [444]. Other manifestations: possibly pituitary tumours [445], gastrointestinal stromal tumours [434].	Very low [443]
Familial pheochromocytoma paraganglioma type 4		<i>SDHB</i>	Noradrenergic and dopaminergic [439]	Usually sympathetic paragangliomas and less frequently pheochromocytomas [433, 446]. Other manifestations: renal cell carcinoma [441], papillary thyroid cancer [440], gastrointestinal stromal tumours [434].	20%-35% [411, 433, 441, 446, 447]
Multiple endocrine neoplasia type 2a	Two [434] Kinase signalling group	<i>RET</i>	Predominantly adrenergic [435, 439, 448]	Usually bilateral pheochromocytomas [448-450]. Other manifestations: primary hyperparathyroidism, medullary thyroid carcinoma.	≤1% [433, 438, 448, 450, 451]
Multiple endocrine neoplasia type 2b				Usually bilateral pheochromocytomas [433, 450, 451]. Other manifestations: medullary thyroid carcinoma, marfanoid habitus, mucosal neuromas, ganglioneuromatosis of the gastrointestinal tract, skeletal abnormalities.	
Neurofibromatosis type 1		<i>NF-1</i>	Predominantly adrenergic [439]	Usually unilateral pheochromocytomas [433] or rarely sympathetic paragangliomas [452]. Other manifestations: <i>cafe au lait</i> macules, neurofibromas, freckling in the axillary/inguinal regions, optic gliomas, iris hamartomas, sphenoid dysplasia or thinning of long bone cortex [453].	<10% [433, 452]; however some kindreds harbour a higher risk

Could this be a neuroendocrine tumor?

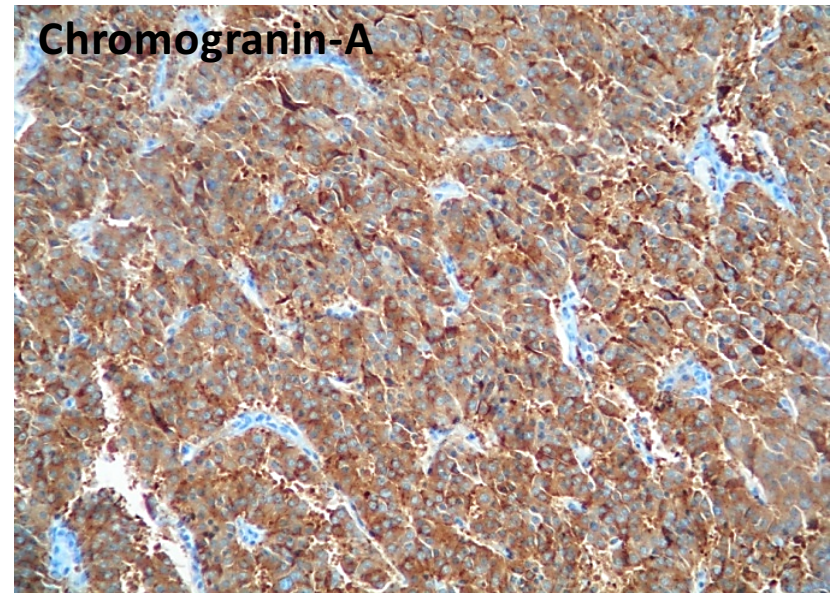




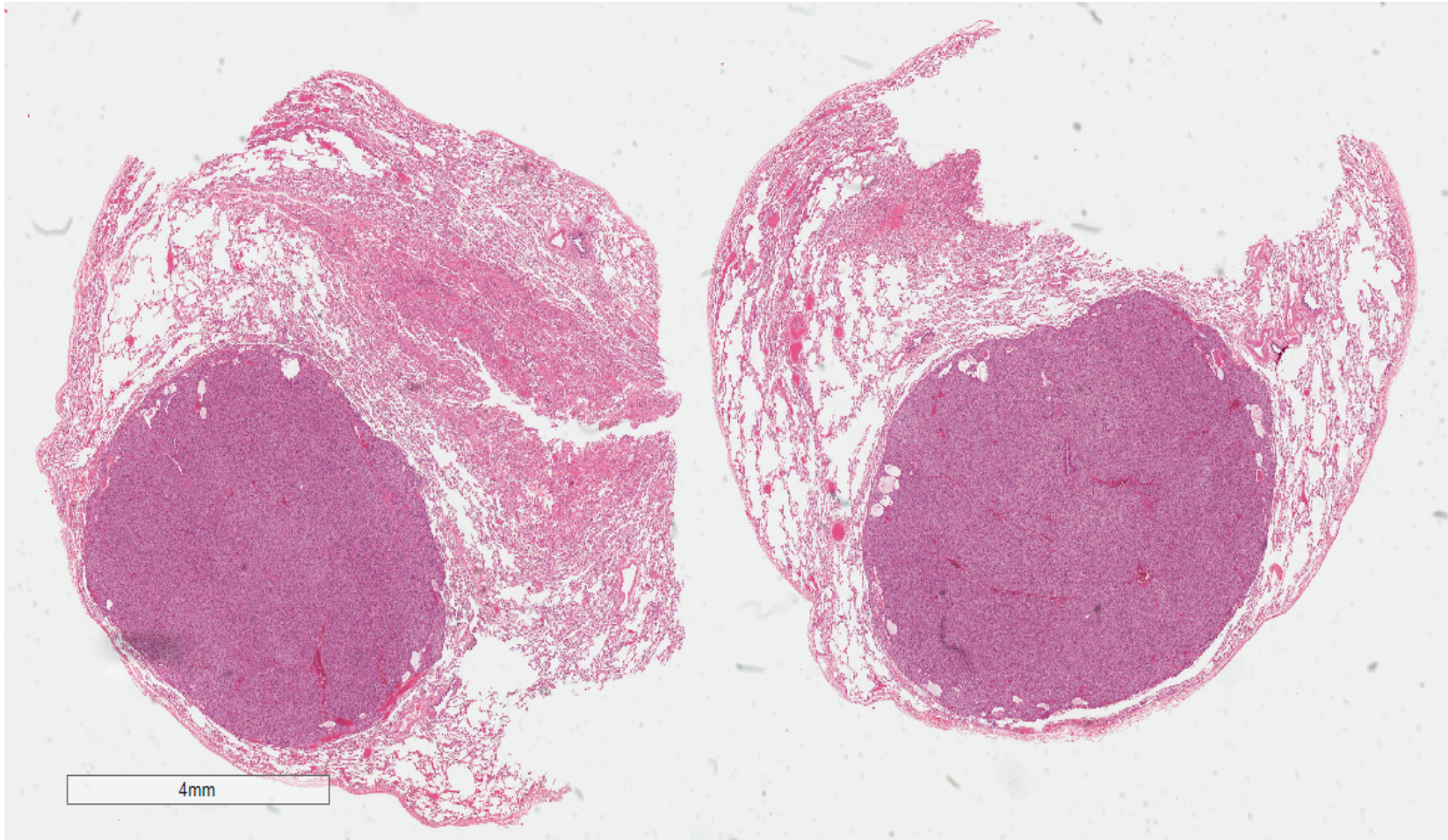
# Confirm Neuroendocrine Differentiation

## Neuroendocrine Differentiation

- Synaptophysin
- Chromogranins
  - \*poorly differentiated can be negative
- NSE
- PGP 9.5
- CD56
- CD57
- NESP-55
- Histidine decarboxylase



**Positive for chromogranin-A and synaptophysin**  
**Negative for TTF-1, CDX-2, CAM5.2, AE1/AE3, CK7**  
**Mitotic activity is <1/10HPF, no necrosis**



A keratin- and transcription factor-  
negative tumor showing  
neuroendocrine differentiation

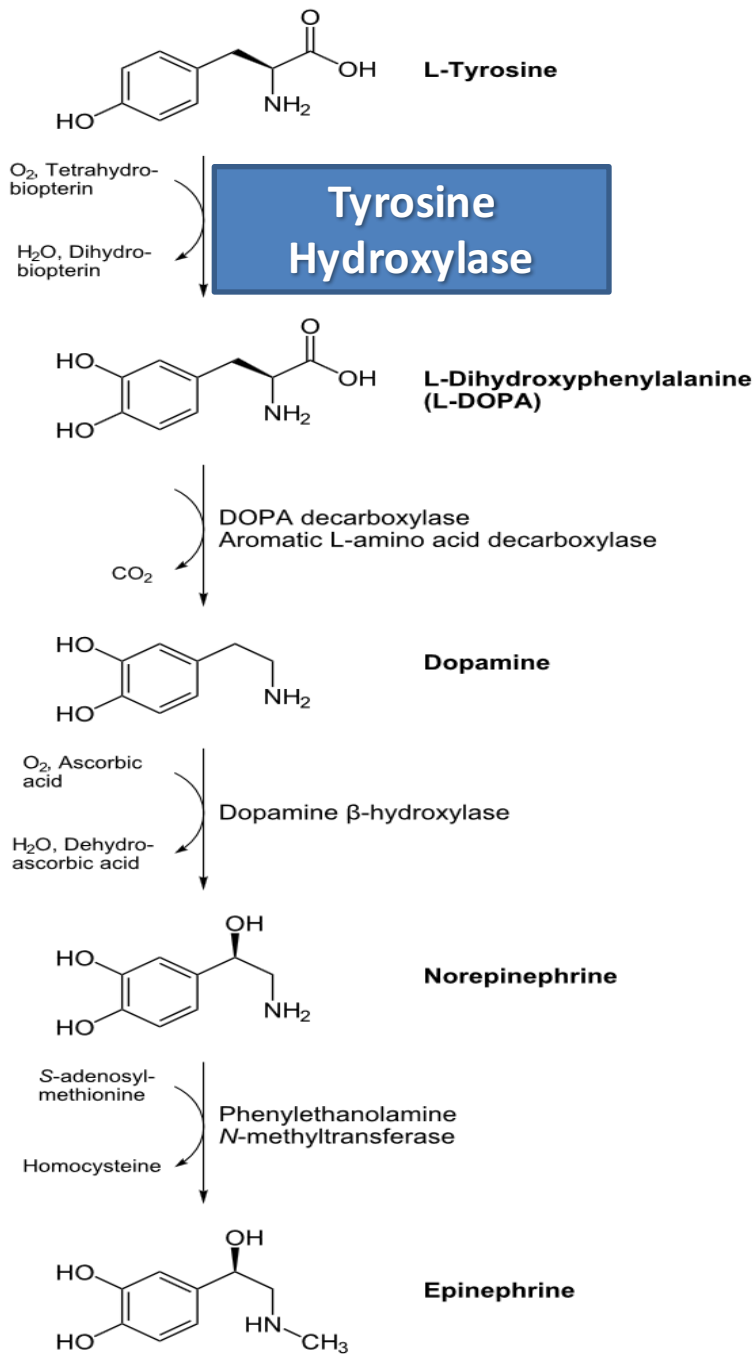
Paraganglioma should be excluded in a keratin- and transcription factor- negative neuroendocrine tumor

Pulmonary NET (*“carcinoid” tumor*)

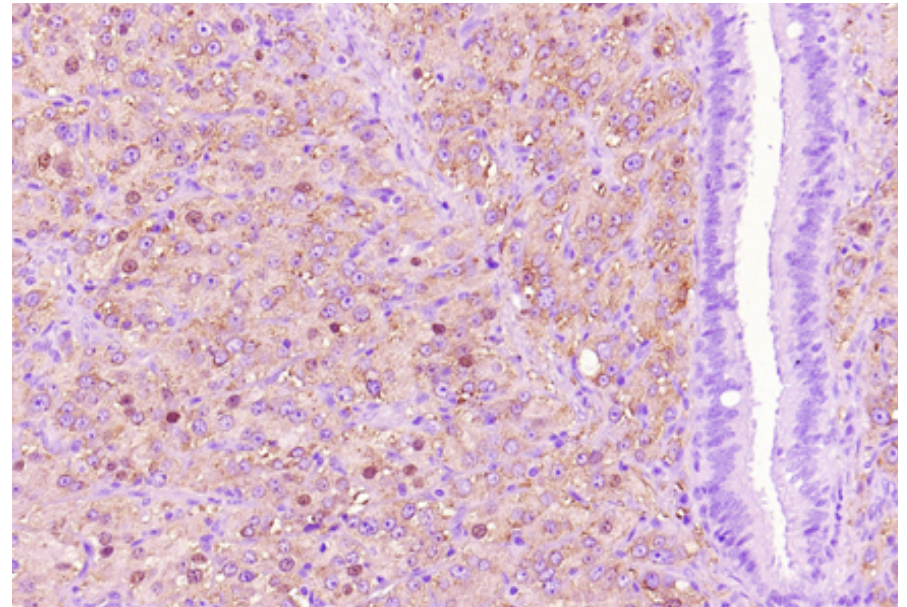
or

Paraganglioma

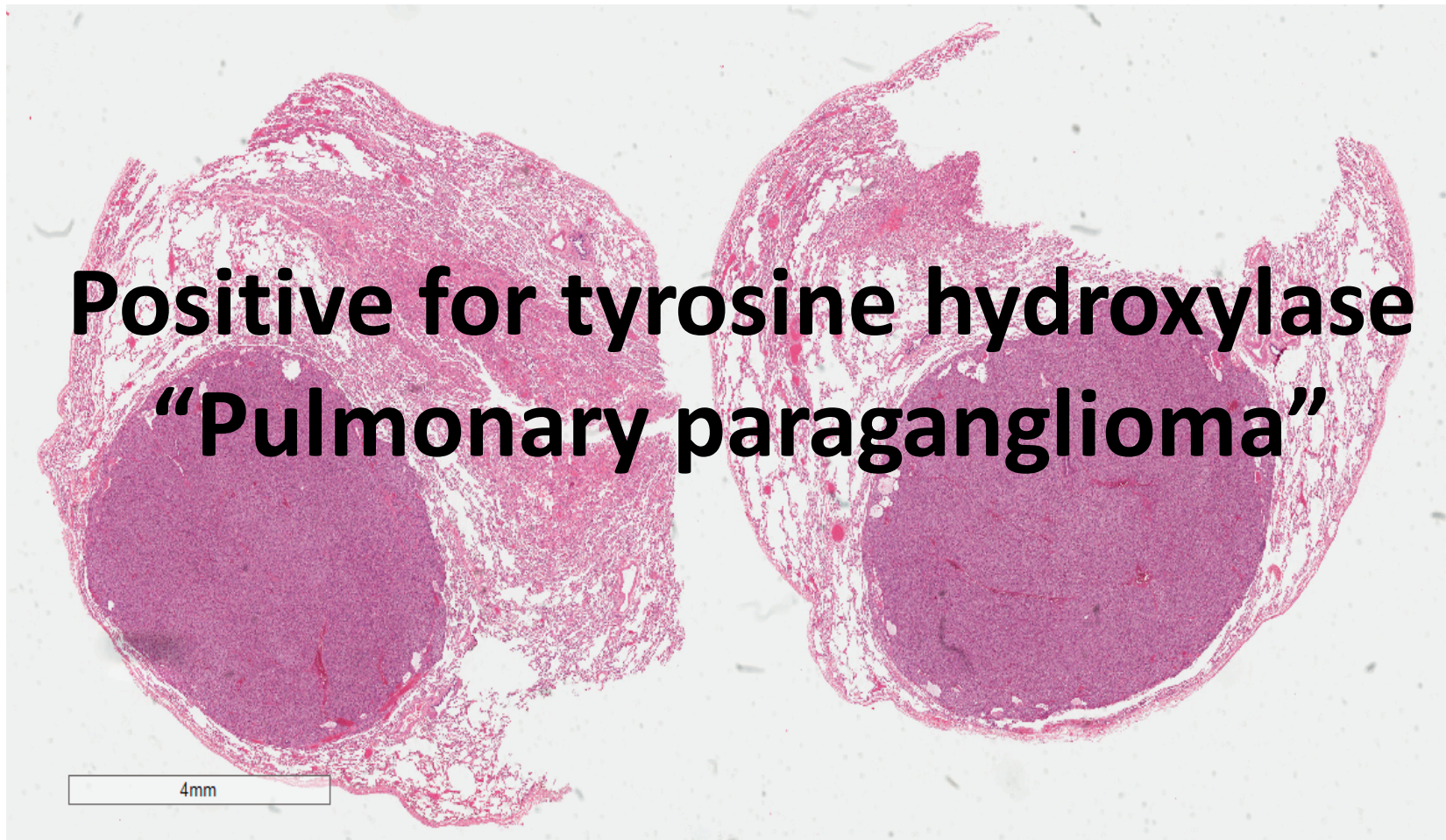
- Clinical management is different for paragangliomas
- Unlike other NETs, paragangliomas are MIBG-avid
- Criteria of malignancy in paragangliomas



**This tumor was positive for tyrosine hydroxylase**

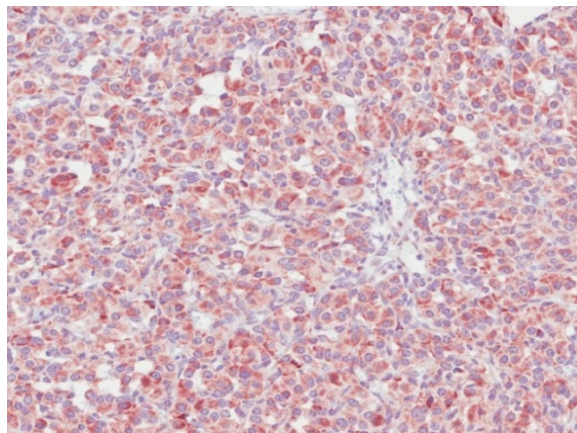
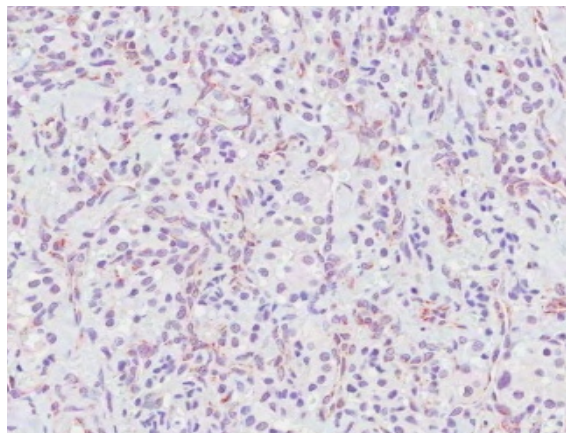


Positive for chromogranin-A and synaptophysin  
Negative for TTF-1, CDX-2, CAM5.2, AE1/AE3, CK7  
Mitotic activity is <1/10HPF, no necrosis



# Familial Paraganglioma

- *SDHA, SDHB, SDHC, SDHAF2, SDHD* genes mutations
- *RET, NF-1, VHL, TMEM127, MAX, KIF1B- $\beta$ , HIF2 $\alpha$ , FH, PHD2/EGLN1, PHD1* genes mutations
- **At least 30-40% of paragangliomas are associated with familial syndromes**
- **At least 50% of SDHB gene mutations are associated with malignancy**
- **Use an antibody against SDHB**
  - Sporadic tumors and normal tissue elements are positive
  - SDHx-related tumors show loss of SDHB expression
  - Genetic testing is required when SDHB stain is negative

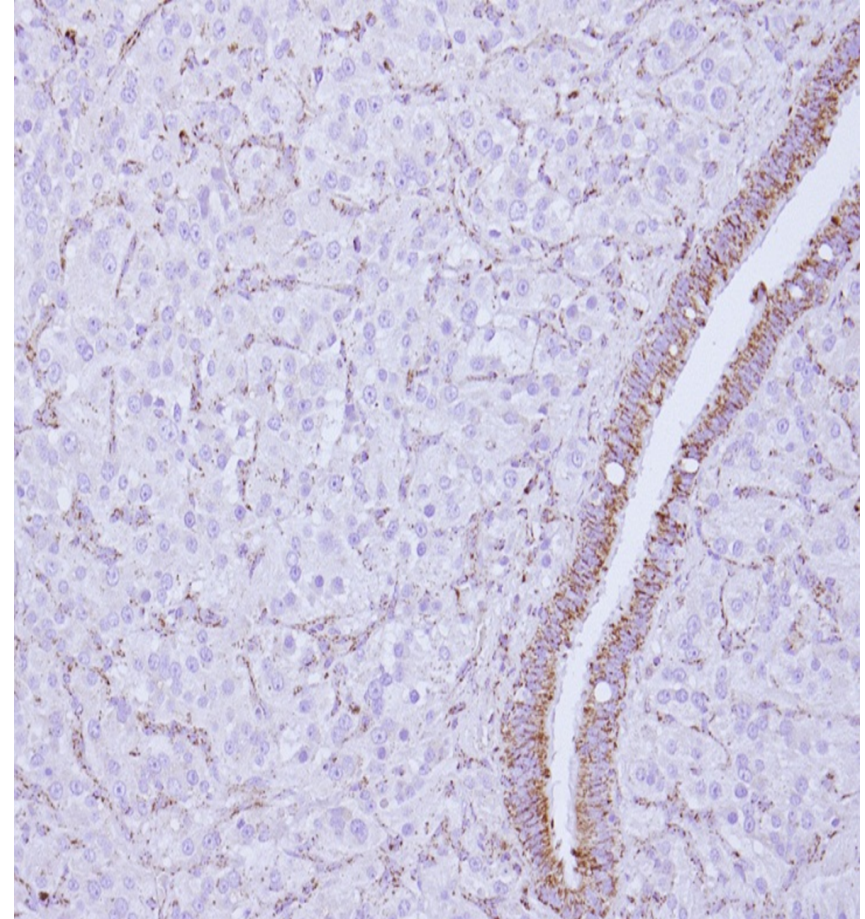
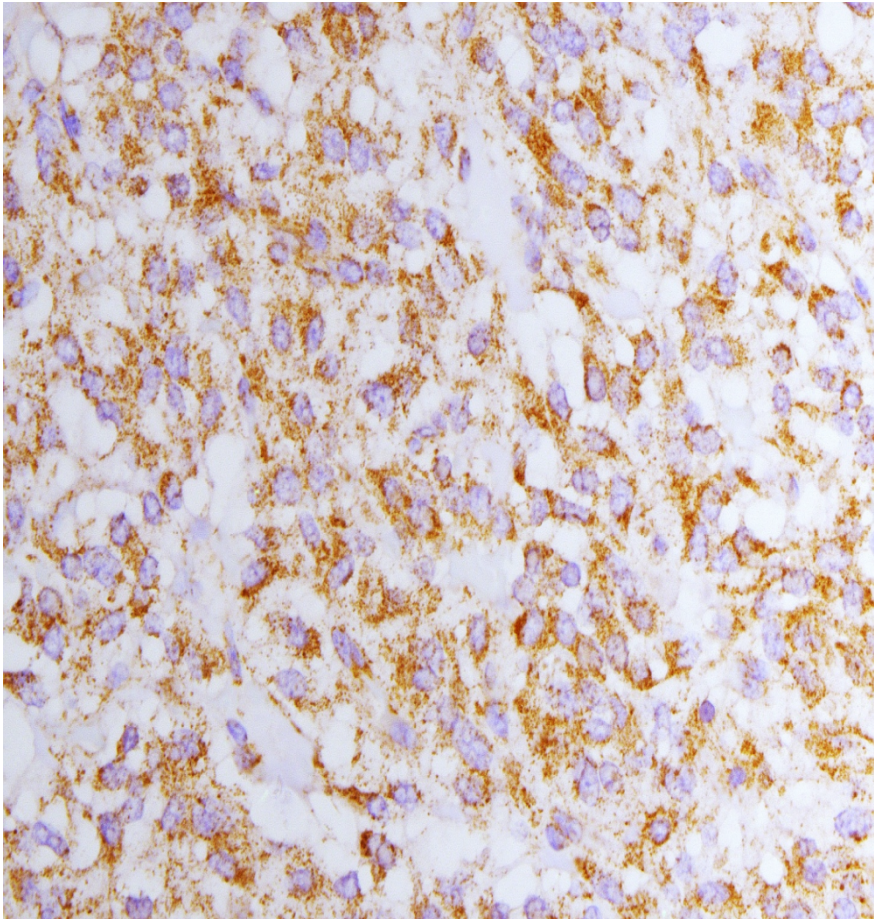


# ***SDHx*-related Paraganglioma Syndromes**

<b>PGL</b>	<b>Gene</b>	<b>Pheochromocytoma</b>	<b>Paraganglioma Sympathetic</b>	<b>Paraganglioma Parasympathetic</b>
<b>PGL 1</b>	<b><i>SDHD</i> (11q23)</b>	+/-	-/+	++
<b>PGL 2</b>	<b><i>SDHAF2</i> (11q12.2)</b>	-	-	++
<b>PGL 3</b>	<b><i>SDHC</i> (1q23.3)</b>	+/-	+/-	++
<b>PGL 4</b>	<b><i>SDHB</i> (1p36.13)</b>	+	++	+
<b>PGL 5</b>	<b><i>SDHA</i> (5p15)</b>	+	++	+



Intact SDHB expression is characterized by cytoplasmic granular positivity



Loss of SDHB immunoreexpression can be seen in  
*ANY* SDH gene mutations

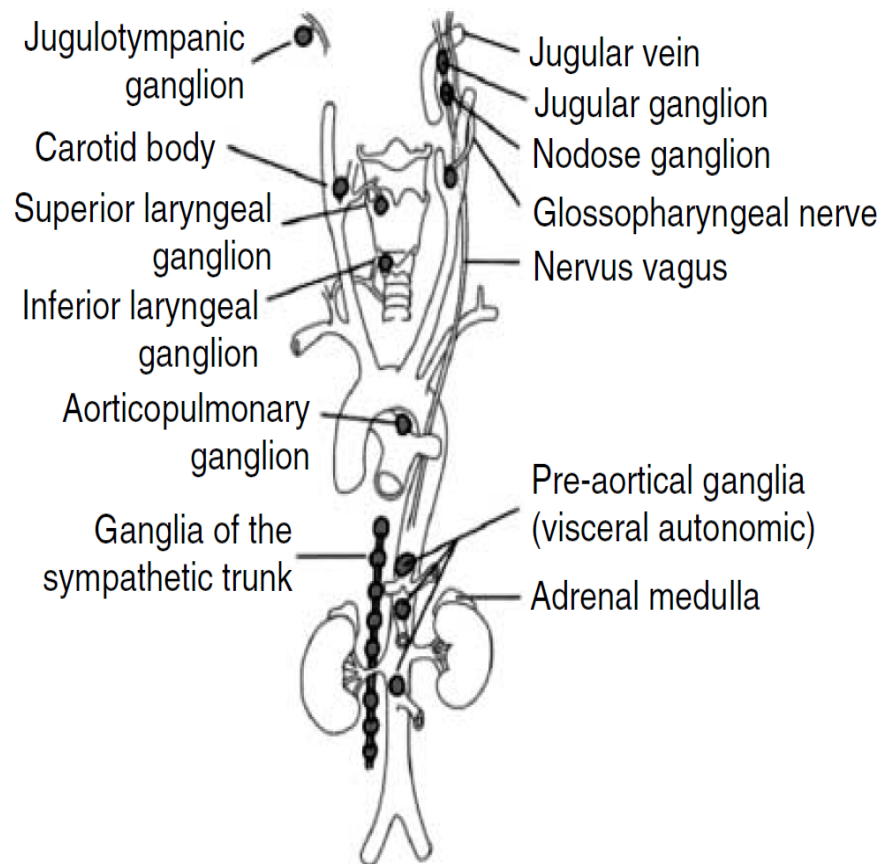
The mediastinal mass is a cardiac paraganglioma  
that shows loss of SDHB expression

In this case, germline SDHC mutation is identified

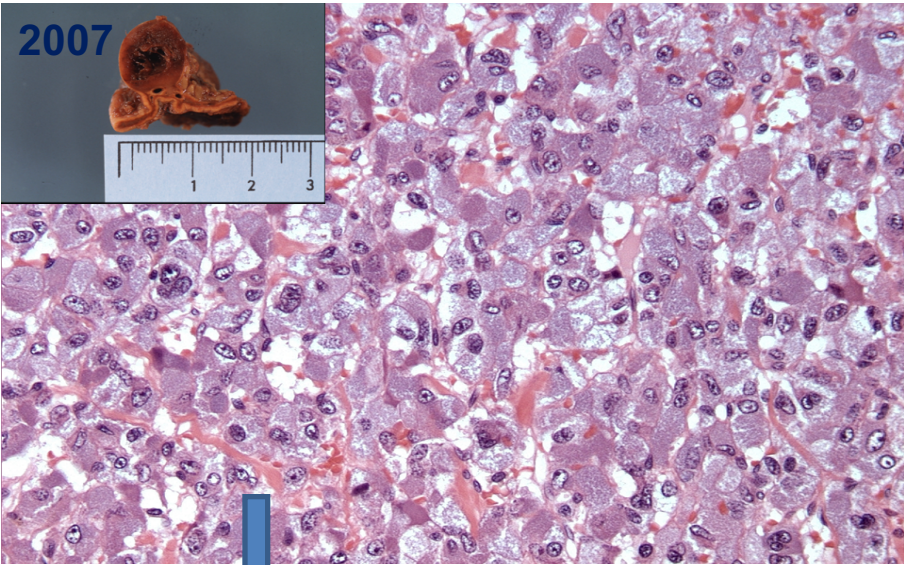
# Criteria of Malignancy (WHO 2004)

## Paraganglioma-Pheochromocytoma

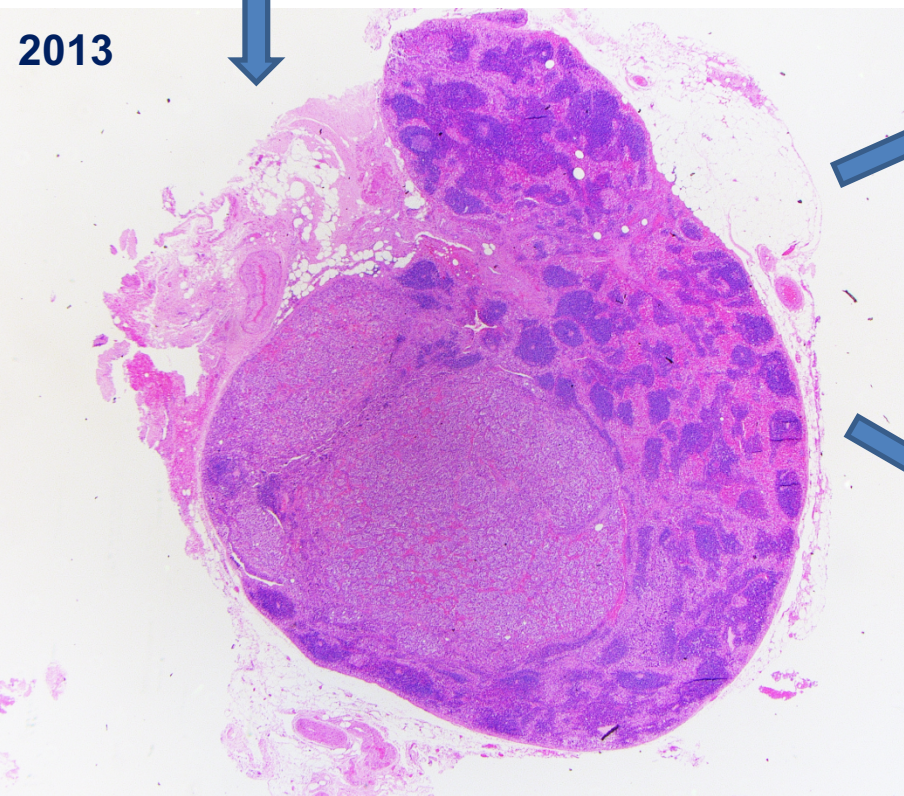
Malignancy is defined by the presence of *metastases* to sites where paraganglial tissue is not normally found



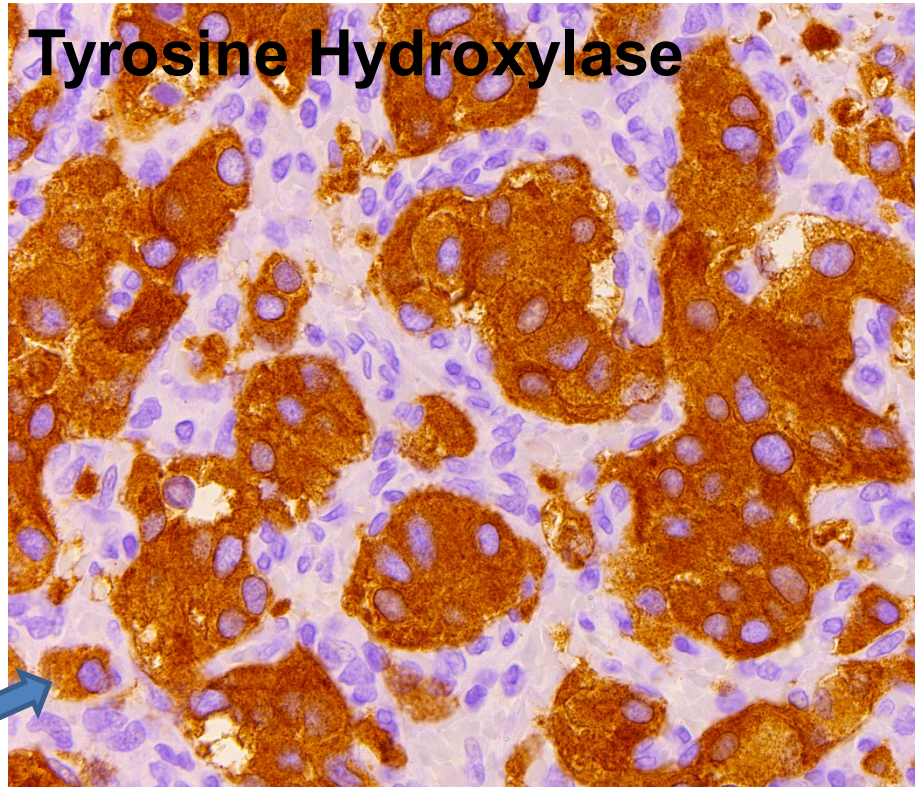
2007



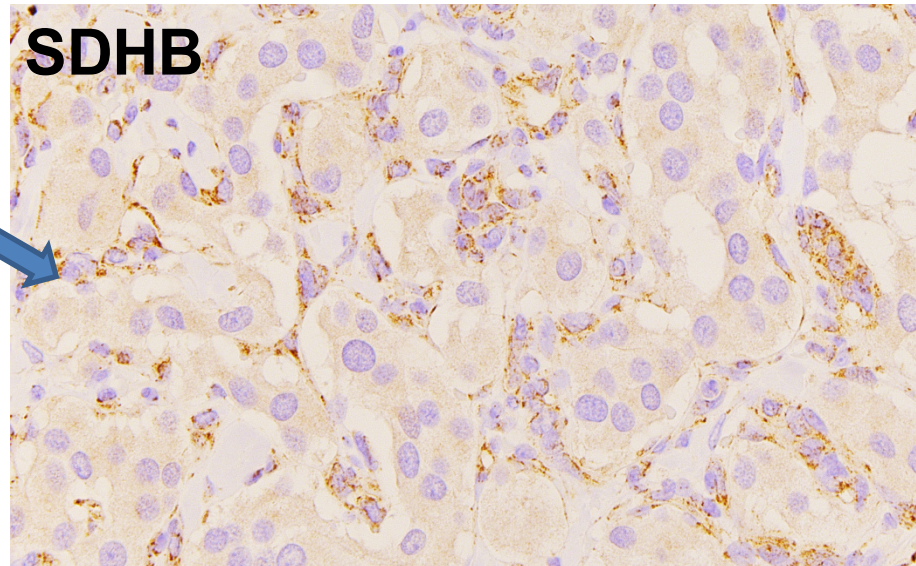
2013



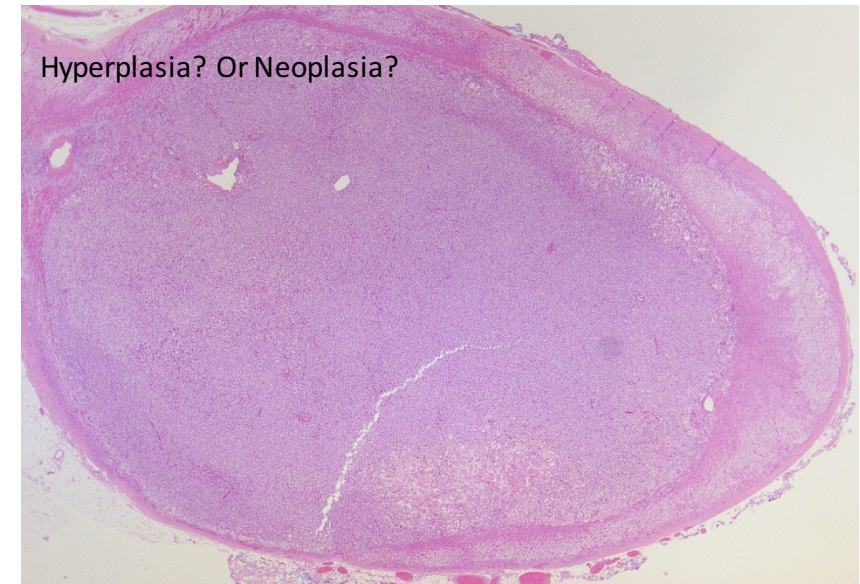
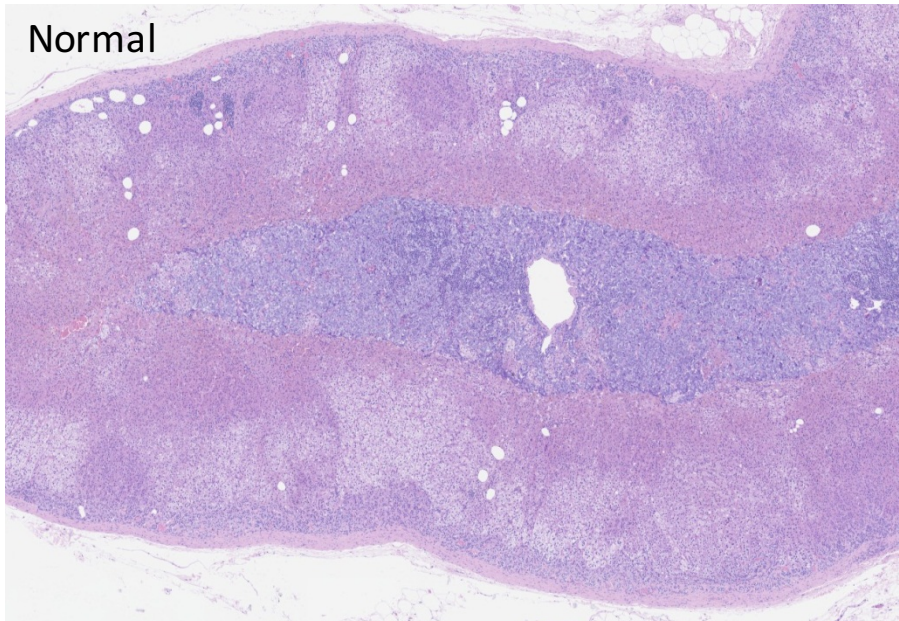
**Tyrosine Hydroxylase**



**SDHB**



# Hereditary Pheochromocytoma: The Importance of Nontumorous Medulla



MEN2 patients have  
medullary hyperplasia

# Protocol for the Examination of Specimens From Patients With Pheochromocytomas and Extra-adrenal Paragangliomas

*Ozgur Mete, MD; Arthur S. Tischler, MD; Ronald de Krijger, MD, PhD; Anne Marie McNicol, MD; Graeme Eisenhofer, MD, PhD; Karel Pacak, MD, PhD; Shereen Ezzat, MD; Sylvia L. Asa, MD, PhD*

• During the last decade there have been revolutionary breakthroughs in understanding the biology of pheochromocytomas and extra-adrenal paragangliomas. Discoveries of new susceptibility genes and genotype-phenotype correlations have led to the realization that appropriate patient care requires a complete integration of clinical, genetic, biochemical, imaging, and pathology findings. Clinical practice has in many cases not kept pace with the rate of discovery, underscoring a need for updated procedures for evaluation of patient specimens and reporting of data. We therefore propose a new synoptic reporting approach for pheochromocytomas and extra-adrenal paragangliomas that will provide clear and uniform information to pathologists and clinicians, in order to advance the diagnosis of these neoplasms and optimize patient care.

*Arch Pathol Lab Med. 2014;138:182–188*

**Classification of Pheochromocytomas and Extra-adrenal  
Parangliomas  
Adrenal Gland**

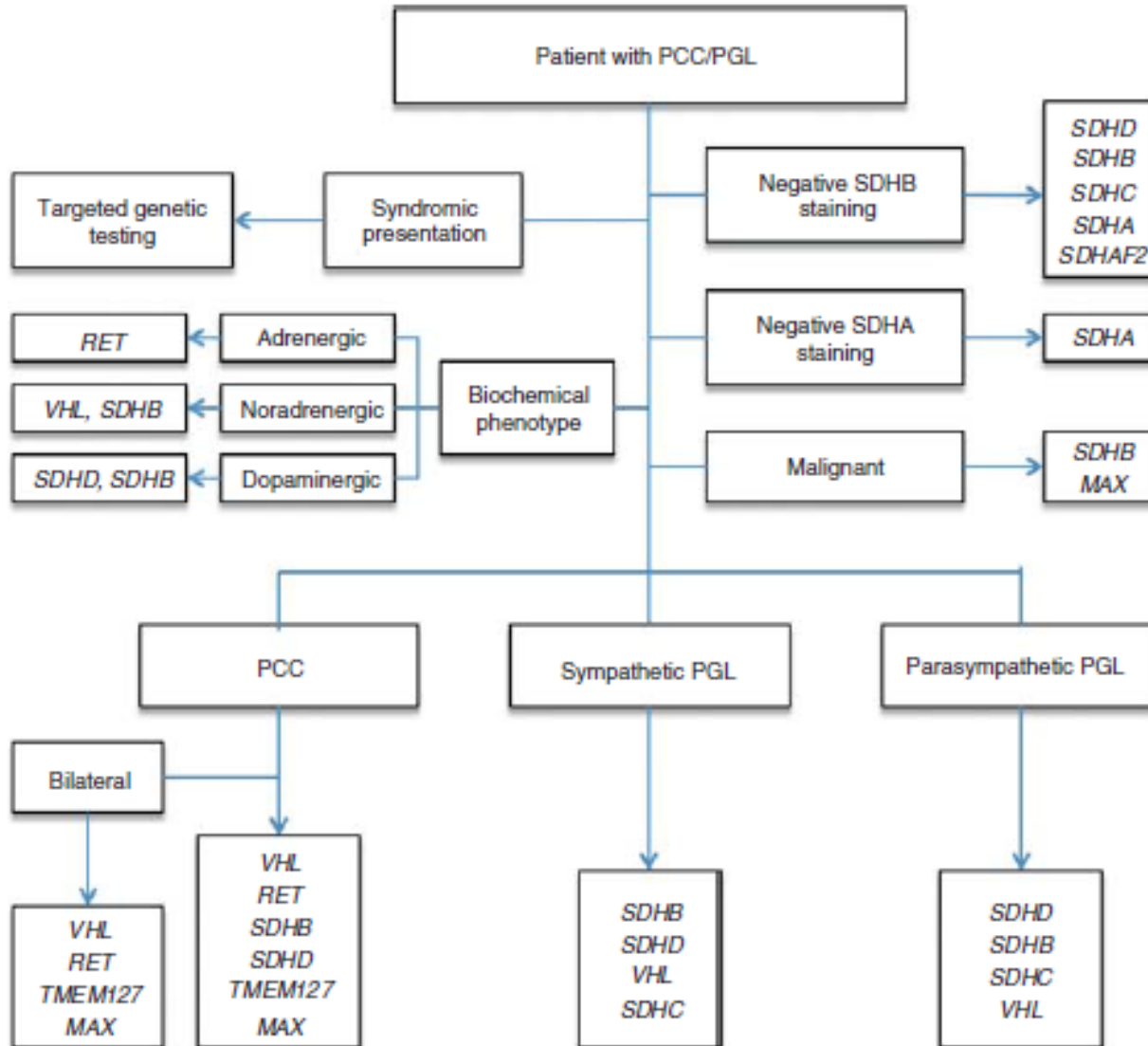
- Pheochromocytoma
- Metastatic pheochromocytoma
- Composite pheochromocytoma (specify components): \_\_\_\_\_

**Extra-adrenal Localizations**

- Carotid body paraganglioma
- Jugulotympanic paraganglioma
- Vagal paraganglioma
- Laryngeal paraganglioma
- Aorticopulmonary paraganglioma
- Gangliocytic paraganglioma
- Cauda equina paraganglioma
- Orbital paraganglioma
- Nasopharyngeal paraganglioma
- Extra-adrenal sympathetic paraganglioma
- Superior and inferior para-aortic paraganglioma
- Urinary bladder paraganglioma
- Intrathoracic and cervical paravertebral paraganglioma
- Metastatic paraganglioma
- Composite paraganglioma (specify site and components): \_\_\_\_\_
- Others (specify): \_\_\_\_\_

# Current Algorithms

## Clinicopathologic Correlations





# Overall Clinical Management

- Accurate diagnosis is CRITICAL
- Surgery requires appropriate pre-medication to avoid potential medical crises
- No currently proven role for adjuvant/neo-adjuvant therapy
- Chemotherapy generally ineffective
- Potential role for Sunitinib

# Special Scans

- MIBG is a nuclear scan test that uses injected radioactive material (radioisotope) and a special scanner to locate or confirm the presence of pheochromocytoma/paraganglioma
- Generally, widely available
- Potential radiopharmaceutical therapy
  - Type of PRRT

# Take Home Messages

- **The 10% rule is no longer valid!**
  - At least 30-40% familial,
  - At least 15 genes
  - At least 50% of *SDHB*-driven paragangliomas are malignant
- **Genotype-Phenotype correlations**
  - Biochemistry-Genotype correlations
  - Clear cells-*VHL* disease
  - *SDHB* antibody-any *SDH* gene mutations
  - Medullary hyperplasia-*RET* gene mutations (MEN2)
- **Normal anatomic distribution** of paraganglia should be remembered when distinguishing *multifocal* disease from *metastatic* disease