# Papel del patólogo en los tumores familiares del tiroides

SEAP, Zaragoza, 19 de Mayo , 2011


## Manuel Sobrinho-Simões

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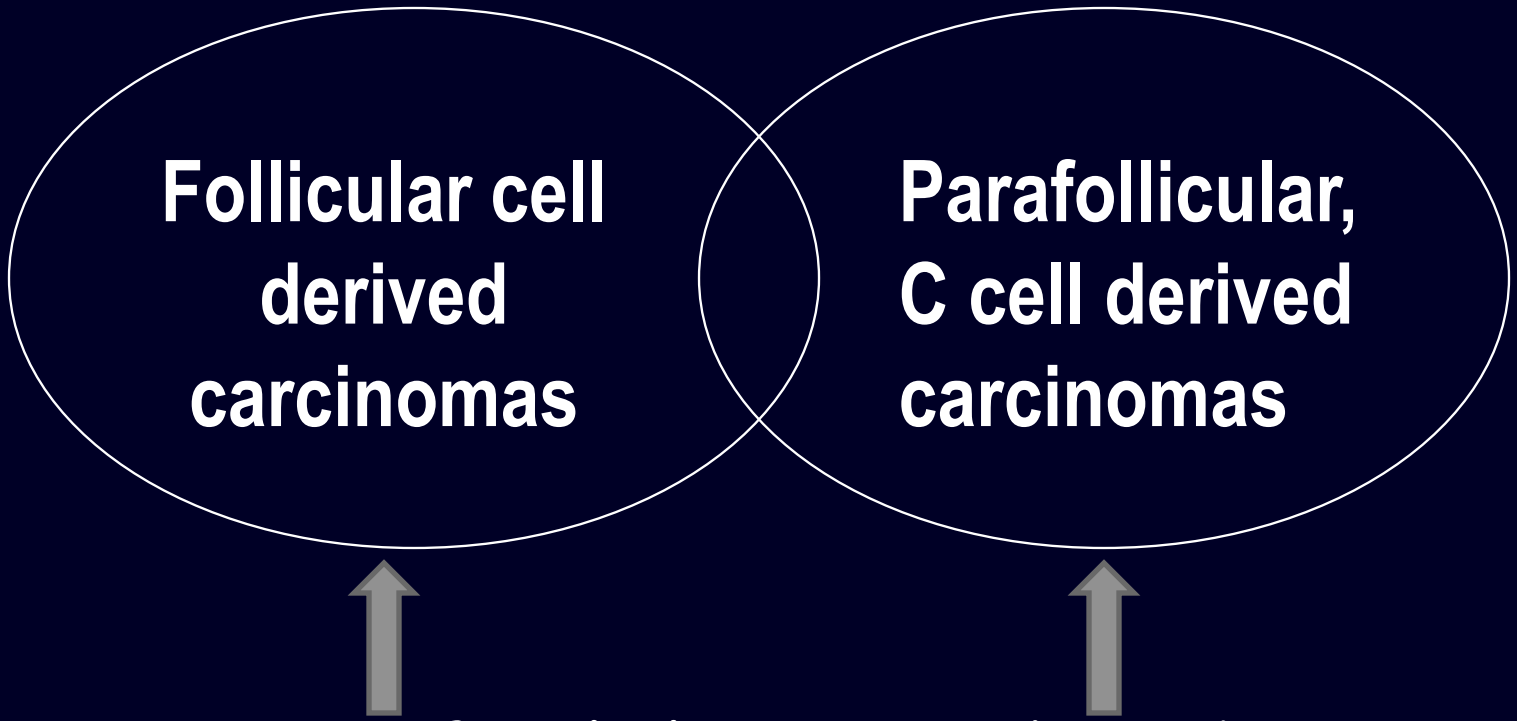
Director, Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP)


Follicular cell derived carcinomas
Parafollicular, C cell derived carcinomas
Prominent familial aggregation (very few known gnes)
Many hereditary tumours (namely RET mutations)

# IDENTIFICATION OF FAMILIAL CASES


**The histopathological features of many Mendelian cancer syndromes such as hereditary breast/ovarian cancer, familial adenomatous polyposis and hereditary non-polyposis colon cancer, hereditary diffuse gastric cancer, von Hippel-Lindau syndrome, familial medullary carcinoma and Krebs-cycle associated tumour syndromes, should be used as triggers for gene searching.**

# Role of pathologists in the identification of hereditary tumours besides the familial history

**Context:** (Very) young patients, multifocality/bilaterality,… - eg. Carcinoma of the adrenal cortex in a 7 year-old patient Li-Fraumeni syndrome ? Search for p53 alterations

**Tumor type:** eg. Retinoblastoma, medullary thyroid carcinoma, haemangioblastoma,… Search for Rb, RET, VHL alterations
Questionable: paraganglioma, phaeochromocytoma, some papillary renal carcinomas. Search for SDHB and other Krebs cycle mutations,…

**Context + Tumour type:** eg. Isolated cell (diffuse) carcinoma of the stomach in a young adult – search for E-cadherin mutations

**Special histotypes and/or co-existence of peculiar histologic features:** eg. Polypotic and non-polypotic lesions of the colon (APC and HNPCC), some breast carcinomas (BRCA 1 and 2), cribriform-morular variant of thyroid carcinoma (APC), pagetoid spread of in situ isolated cell carcinoma of the stomach (HDGC).

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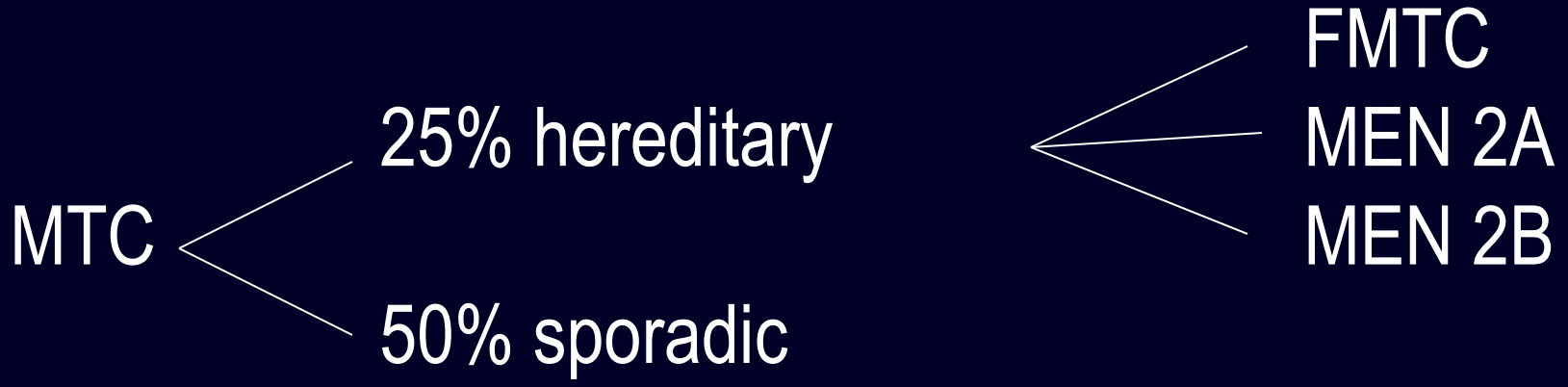
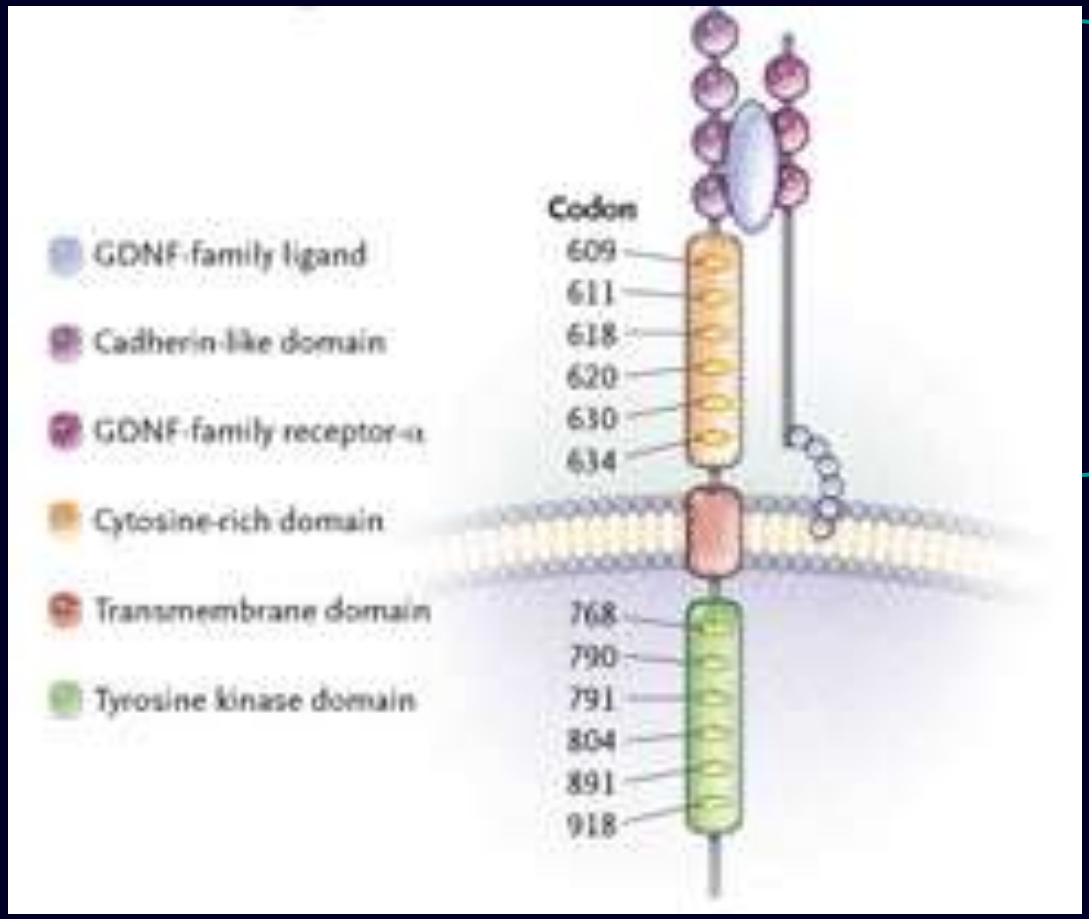
# MEDULLARY THYROID CARCINOMA (MTC)

MTC < 5% of clinically evident thyroid carcinomas

MTC + medullary microcarcinoma – 5 to 10%



# RET




MEN2A

FMTC

MEN2B

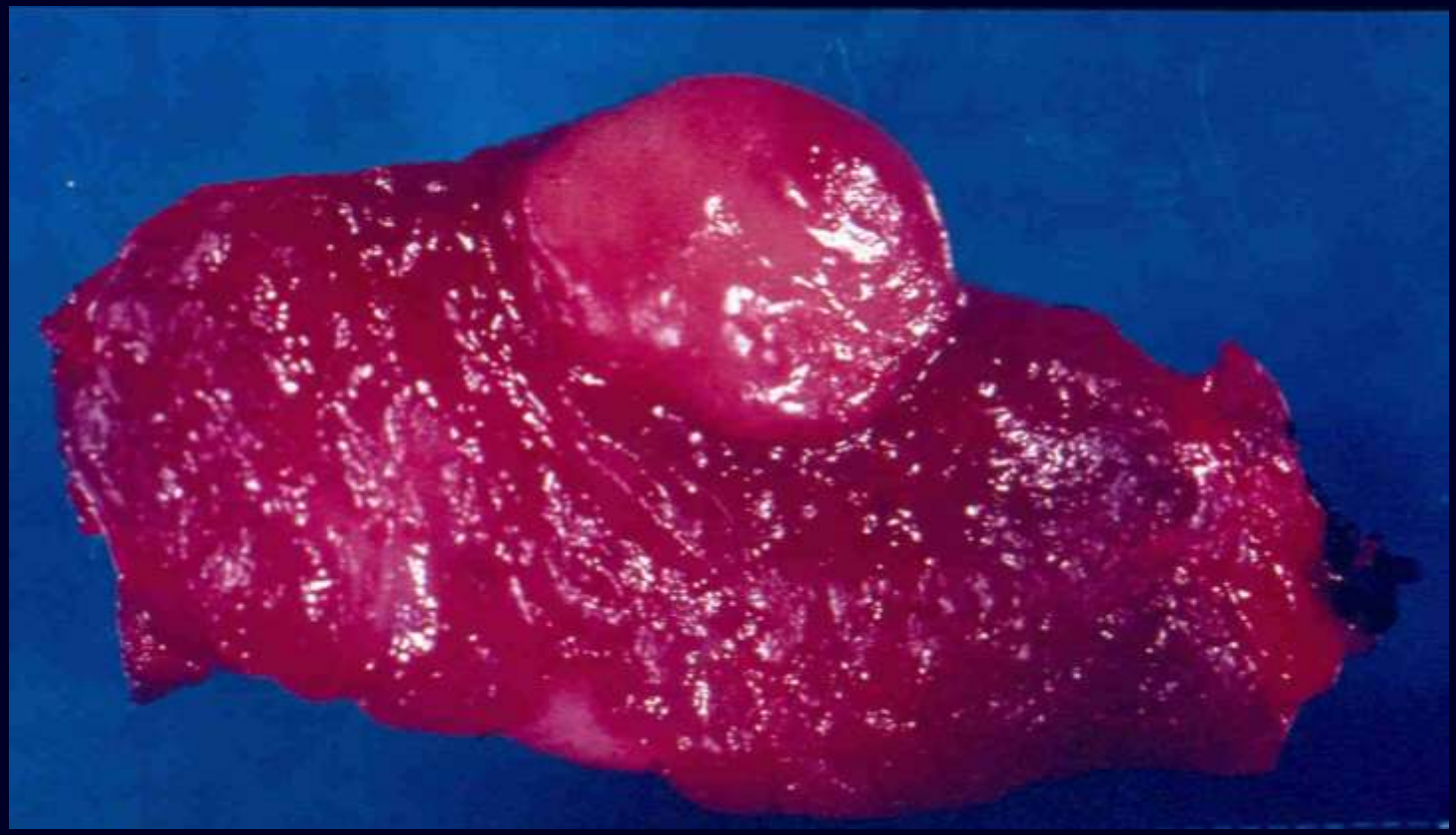
# *Hereditary Medullary Thyroid Carcinoma / Multiple endocrine neoplasia type 2*

| | MTC(%) | PHEO (%) | HPT (%) |
|---|---|---|---|
| MEN 2A | + (~100%) | + (~50%) | + (15-30%) |
| MEN 2B | + (~100%) | + (~50%) | - (0%) |
| FMTC | + (~100%) | - (0%) | - (0%) |

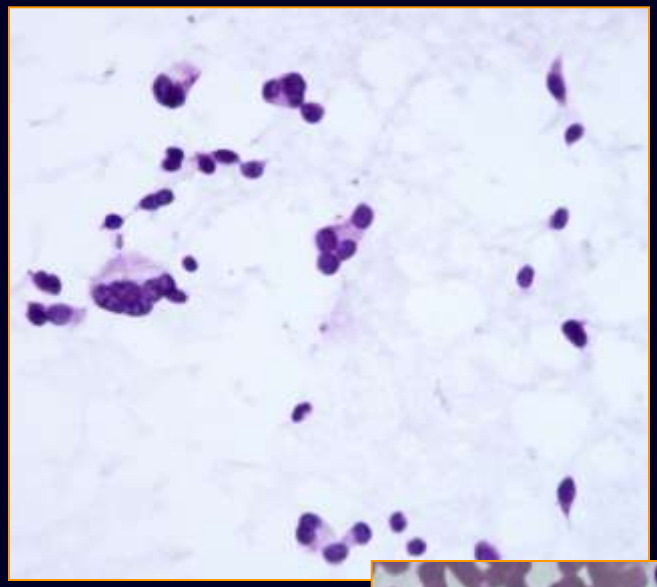
JAMA 1996; 276:1575-1579.

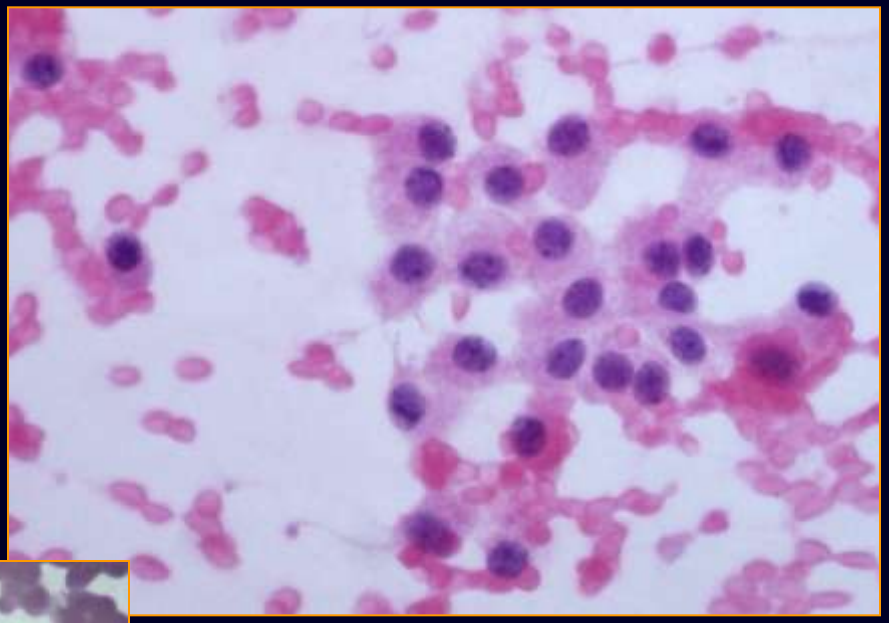
Horm Res 1997; 47:221-226.

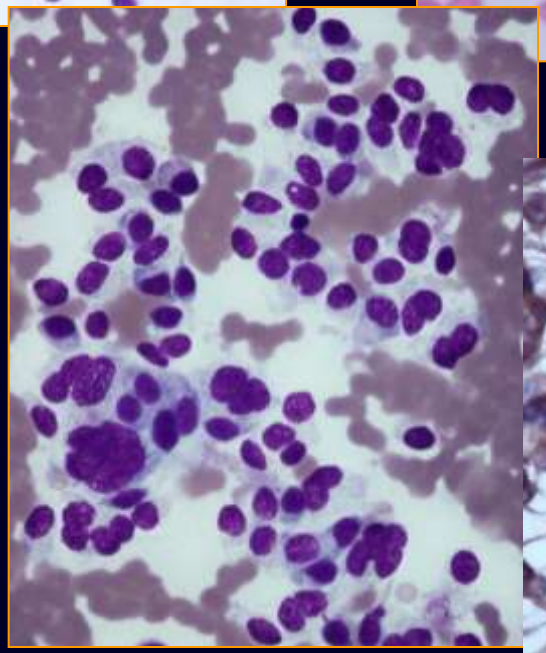
Are there macroscopic or microscopic features of medullary carcinoma that may indicate a familial setting?

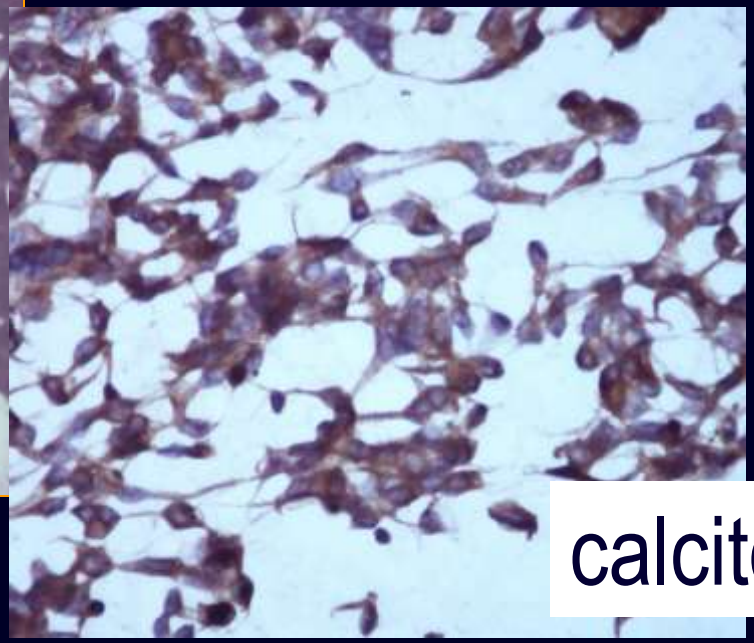


The answer is NO if one excludes multifocality of the cancer and/or C cell hyperplasia









calcitonin

# Medullary ca

# General features of hereditary cancers

- Familial aggregation in a Mendelian transmission pattern
- Syndromic spectrum of primary tumors in the same individual or in the family
- Early onset
- Bilateral tumors
- Multifocal tumors
- Precursor hyperplastic lesions in the remaining organ

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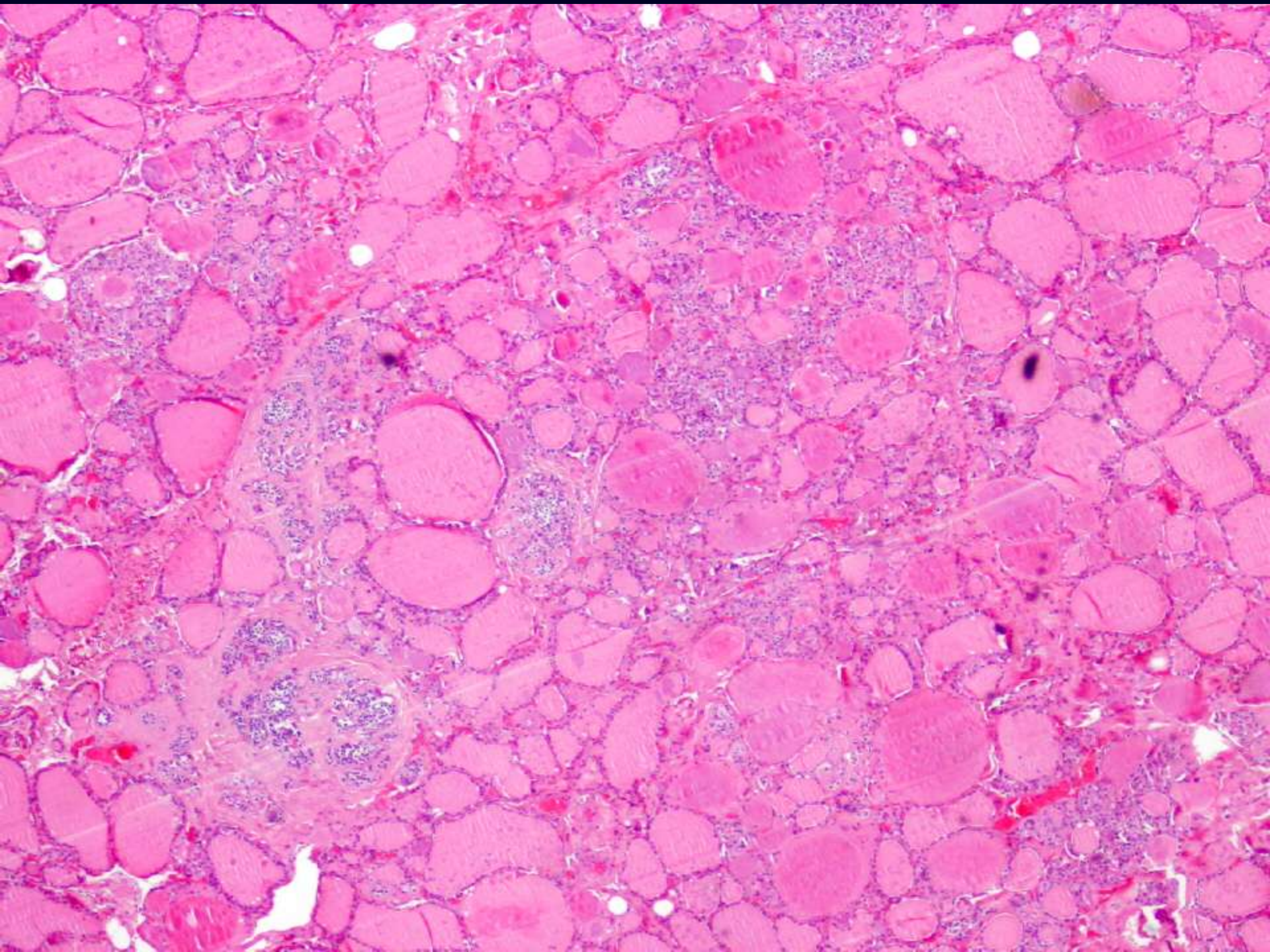
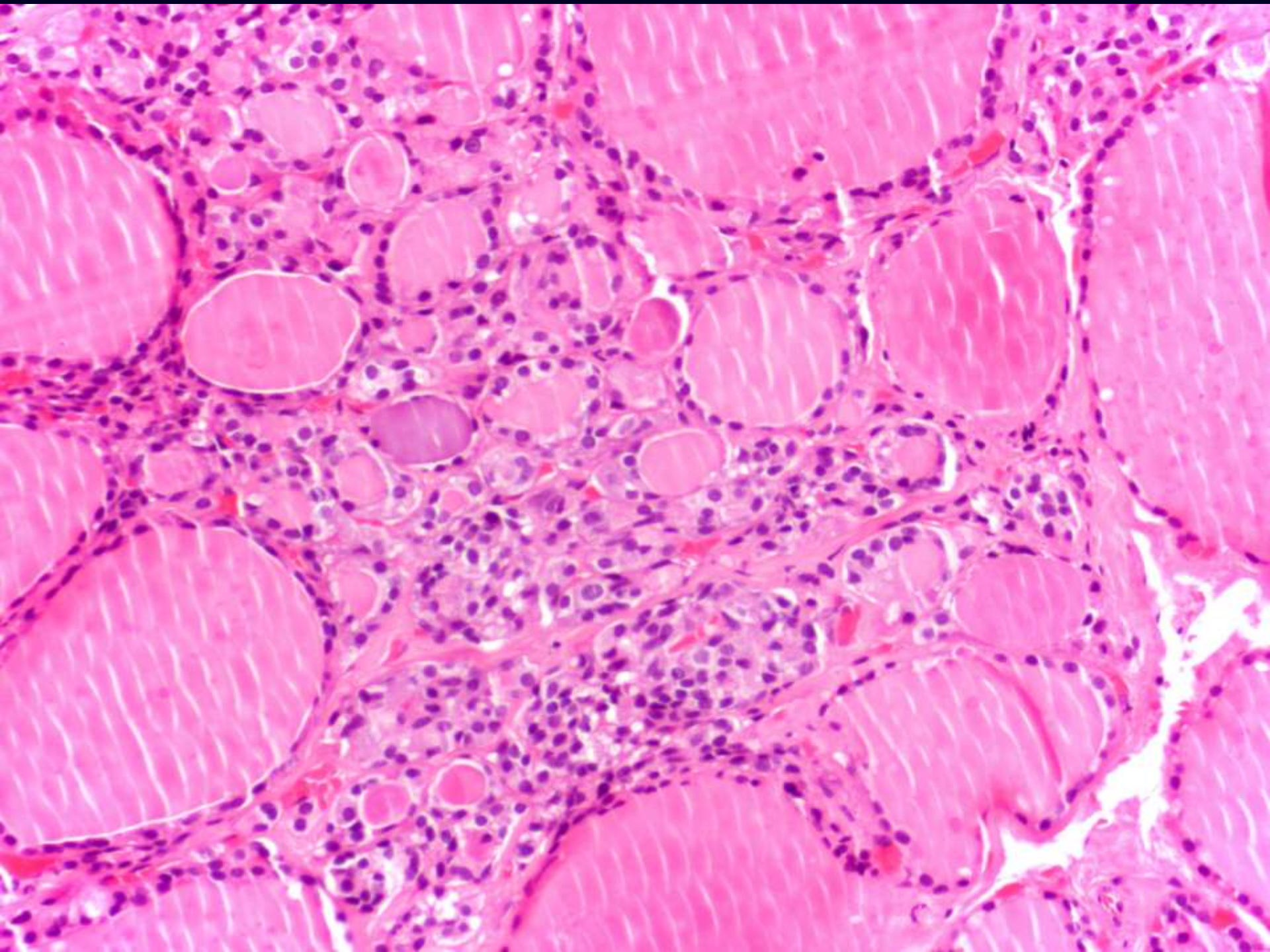
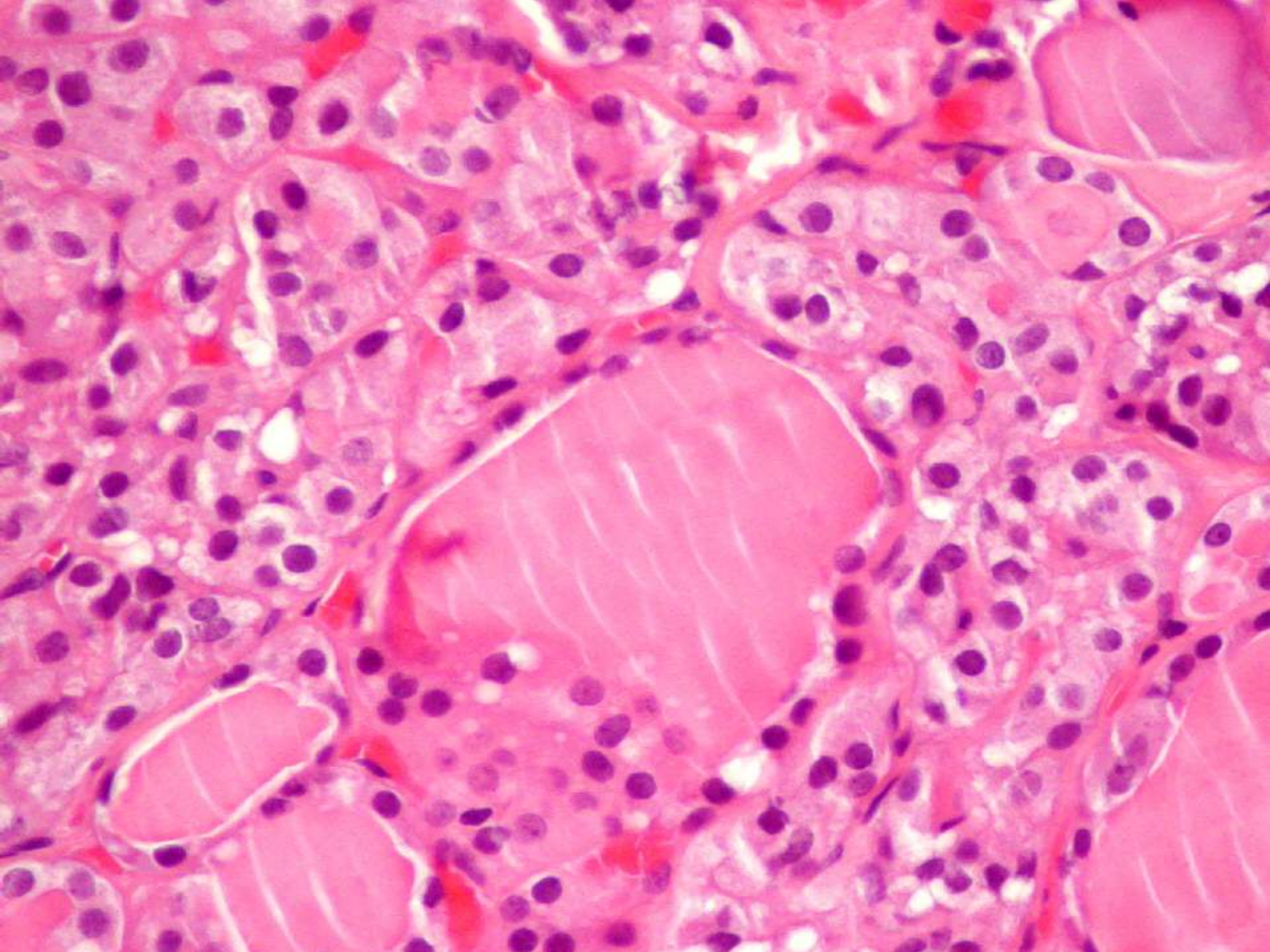
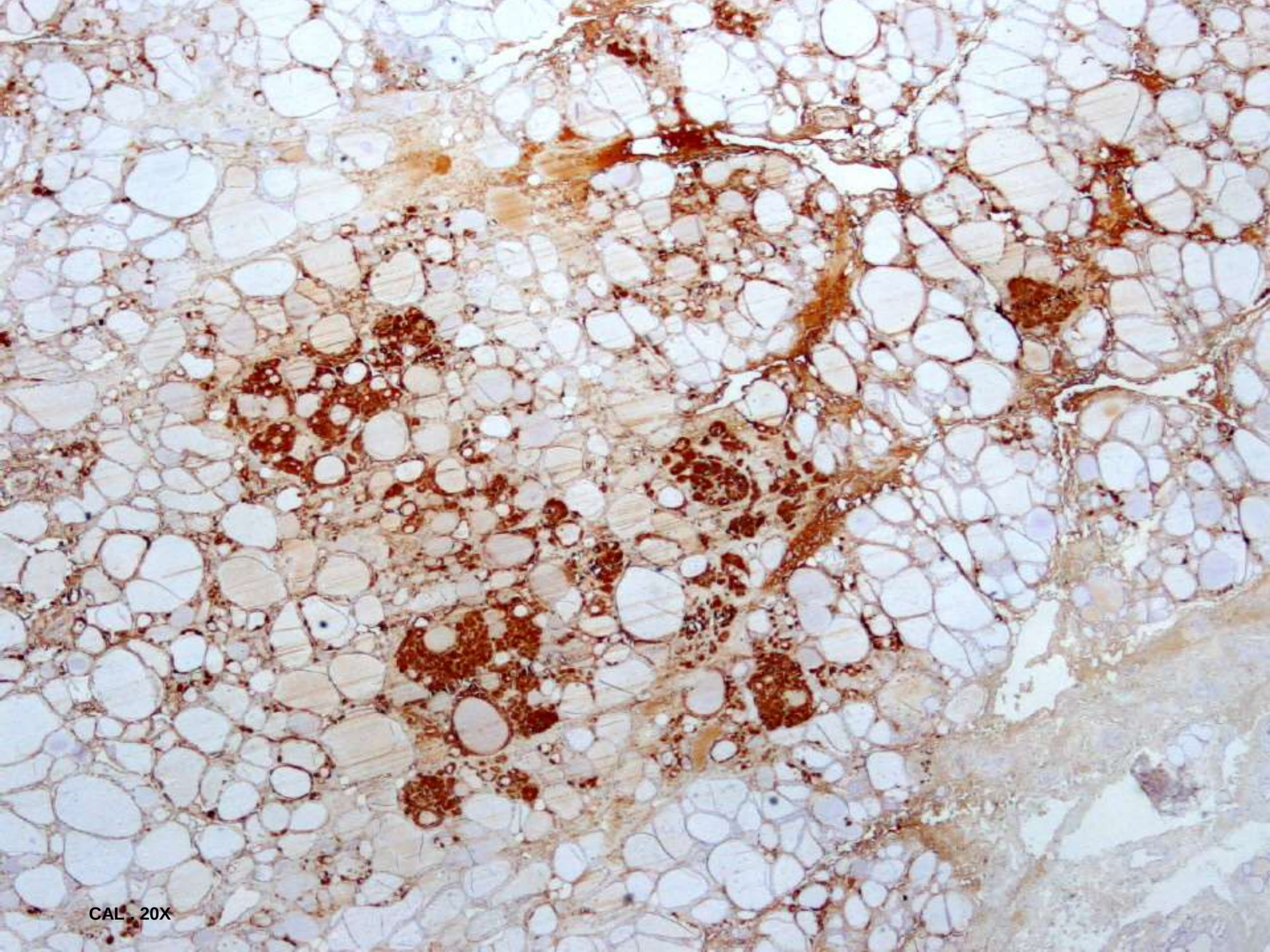
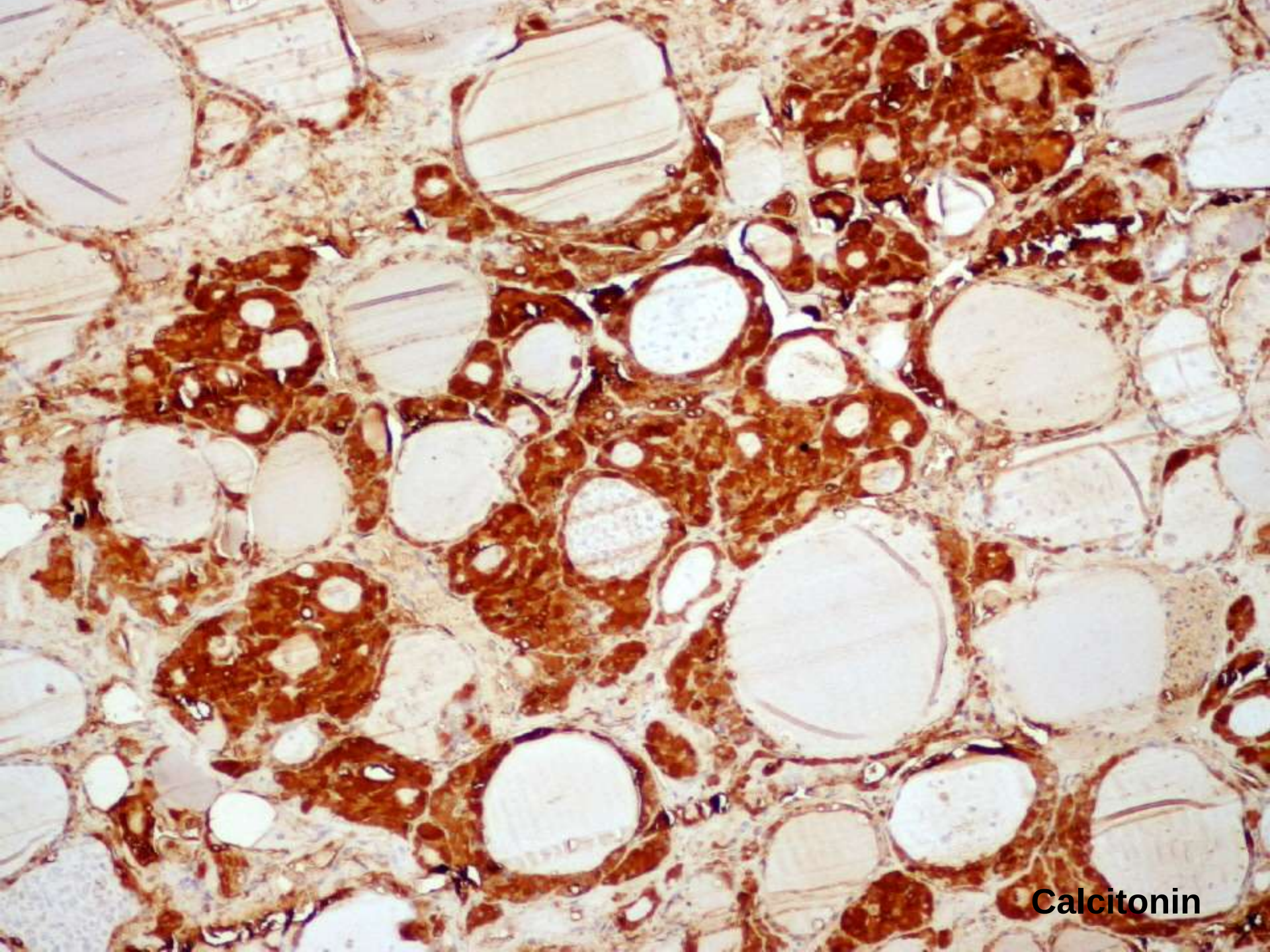




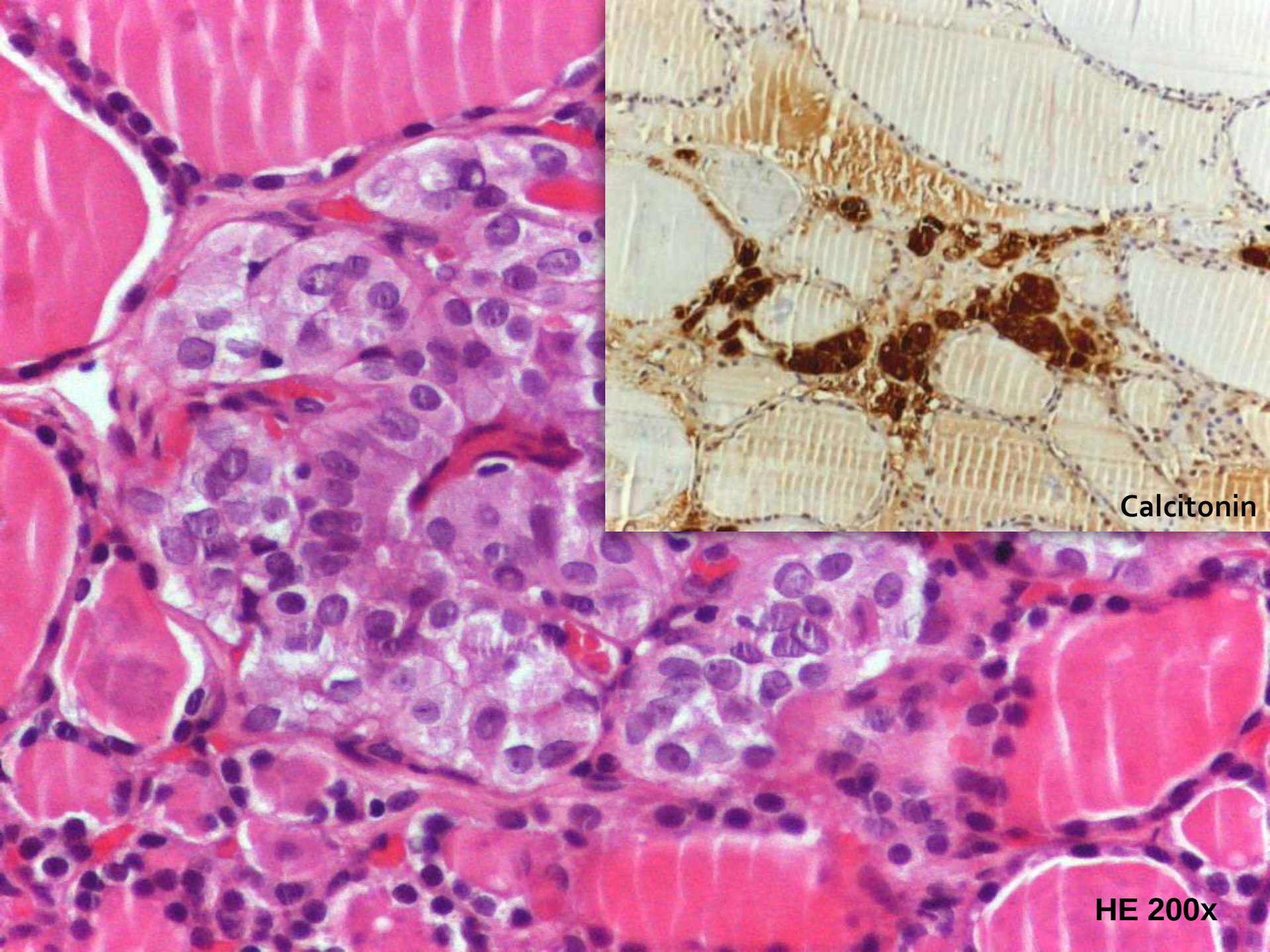


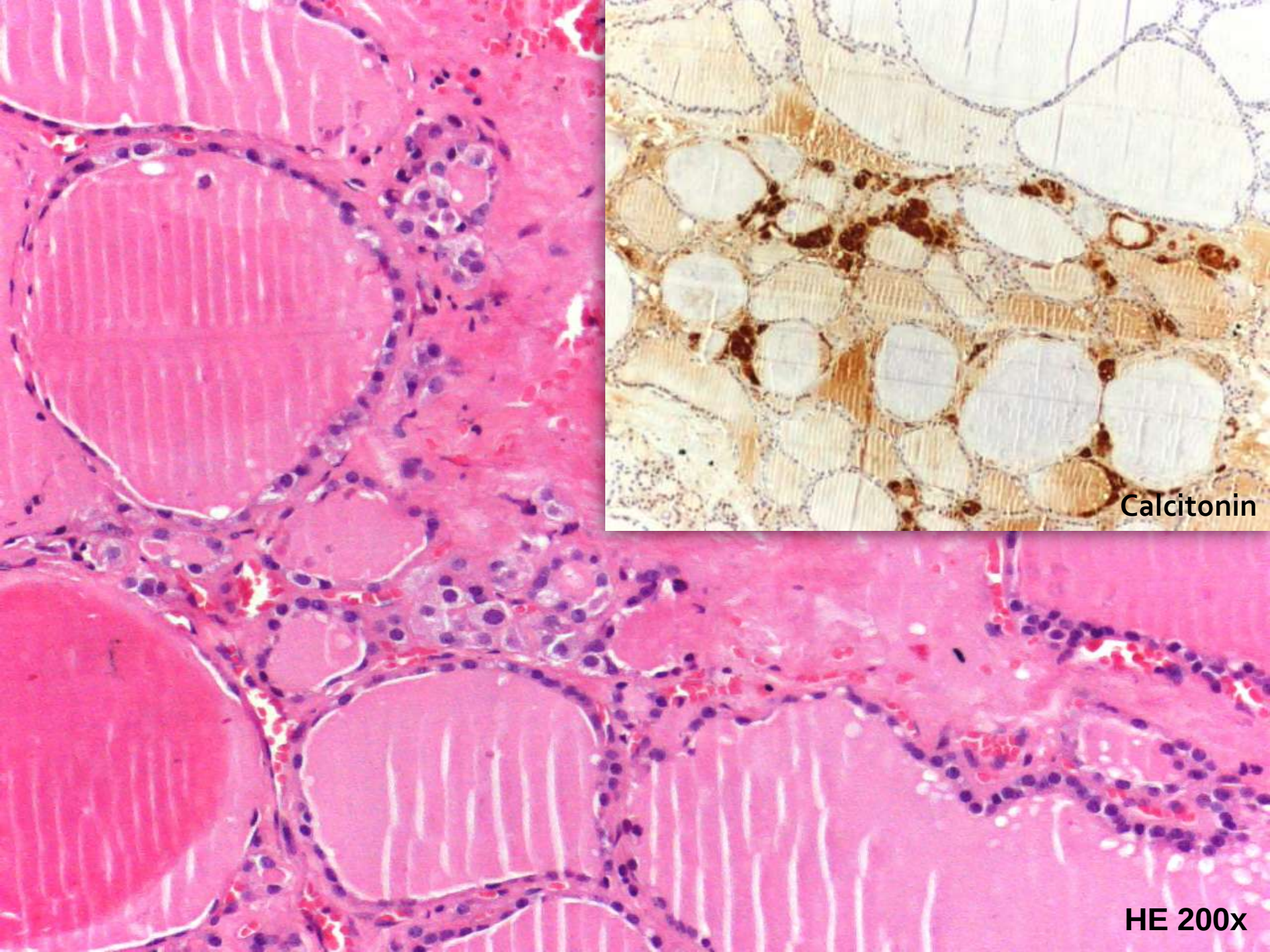

CAL , 20X

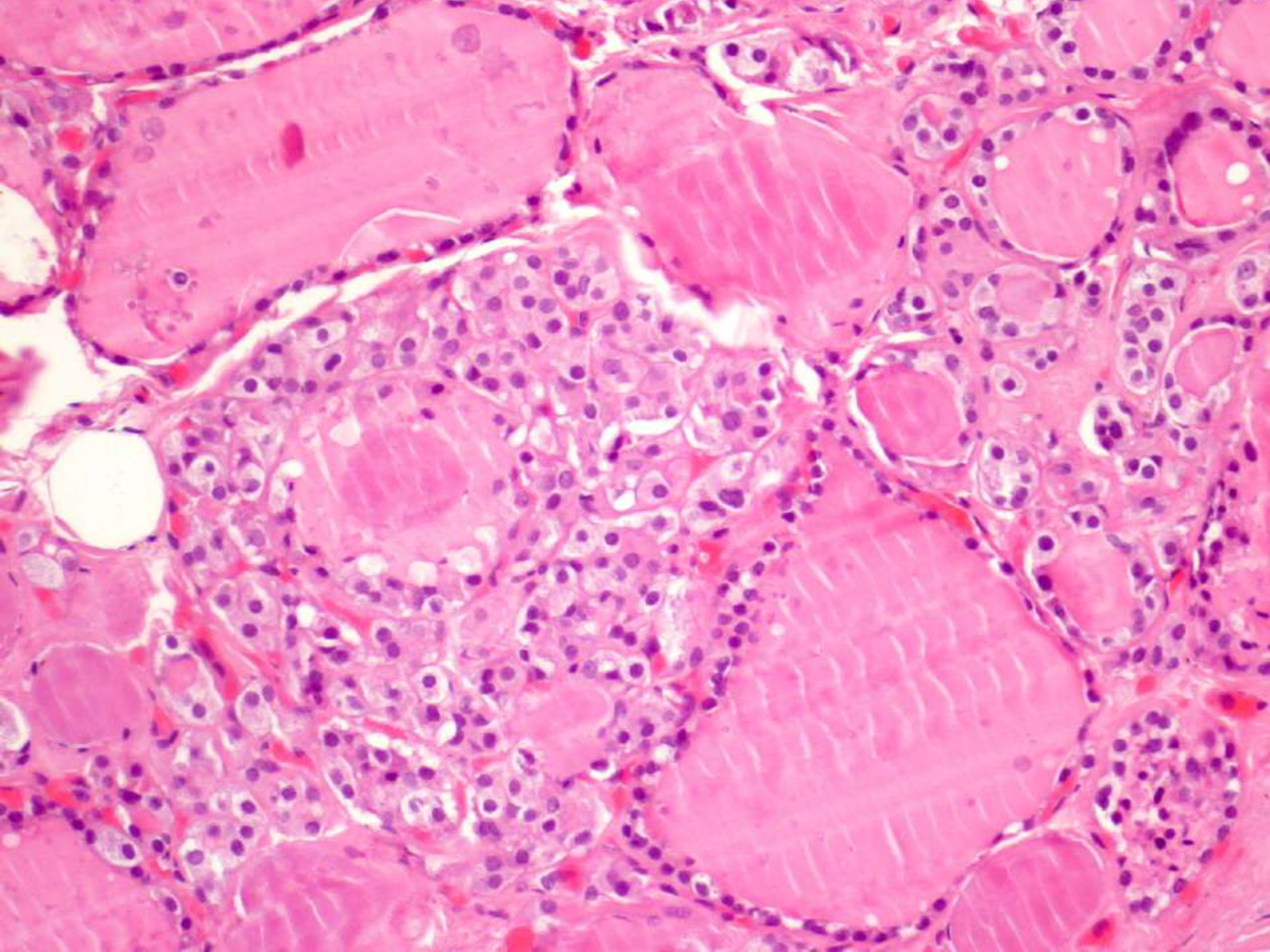

Calcitonin

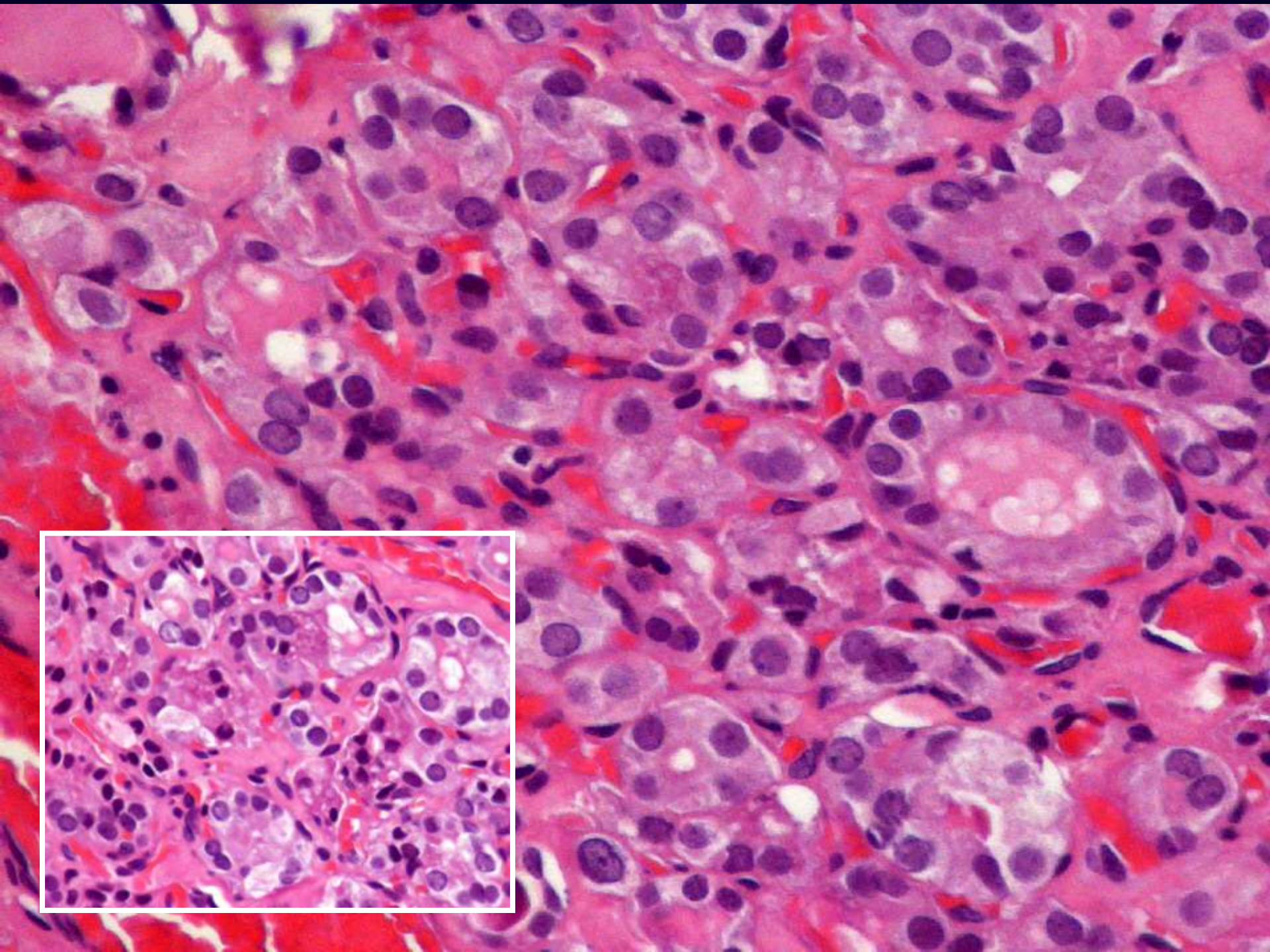
# Differential diagnosis of reactive and neoplastic C cell hyperplasia

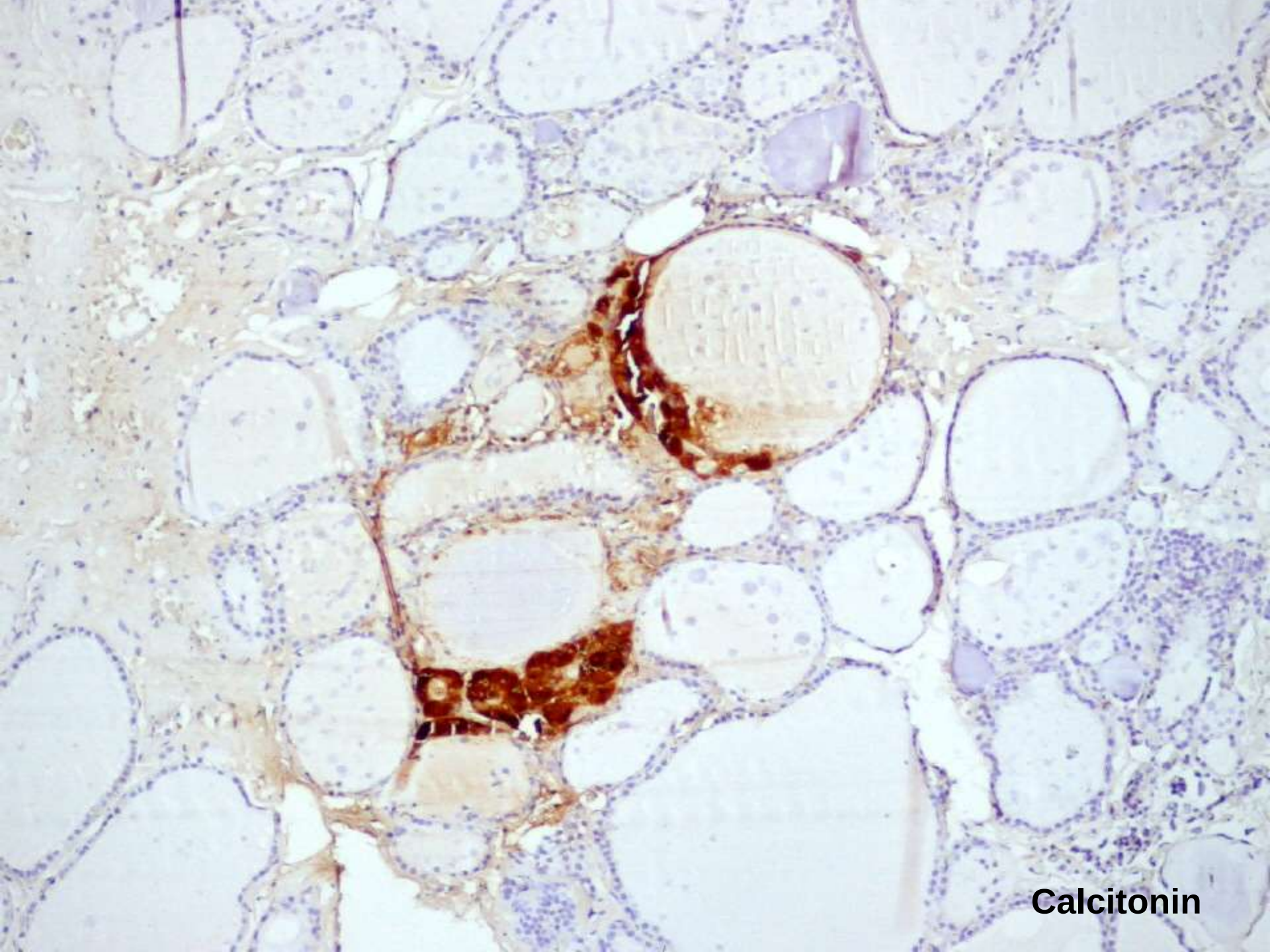
# Differential diagnosis of nodular C cell hyperplasia and medullary microcarcinoma


Calcitonin
HE 200x


Calcitonin
HE 200x

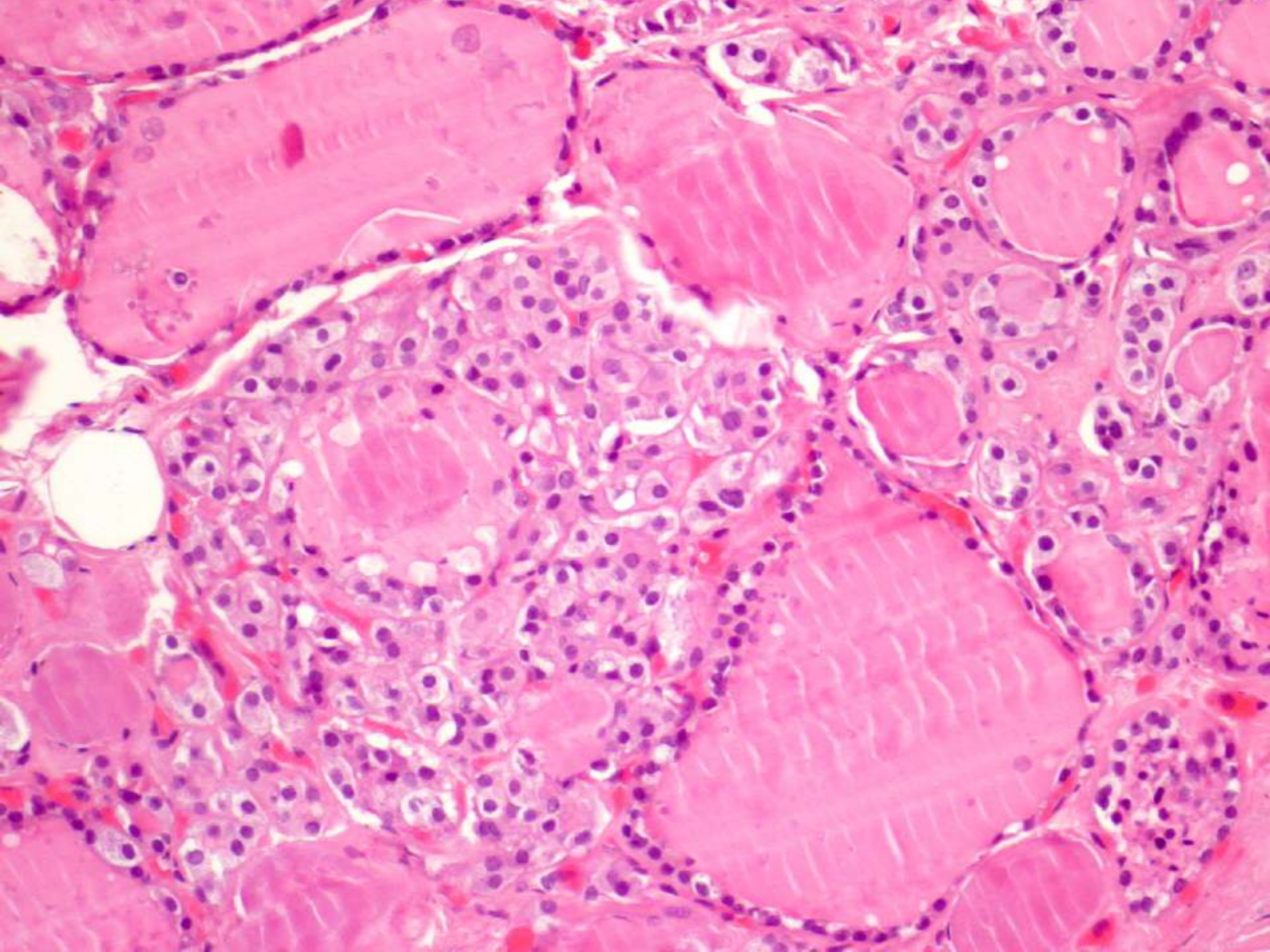




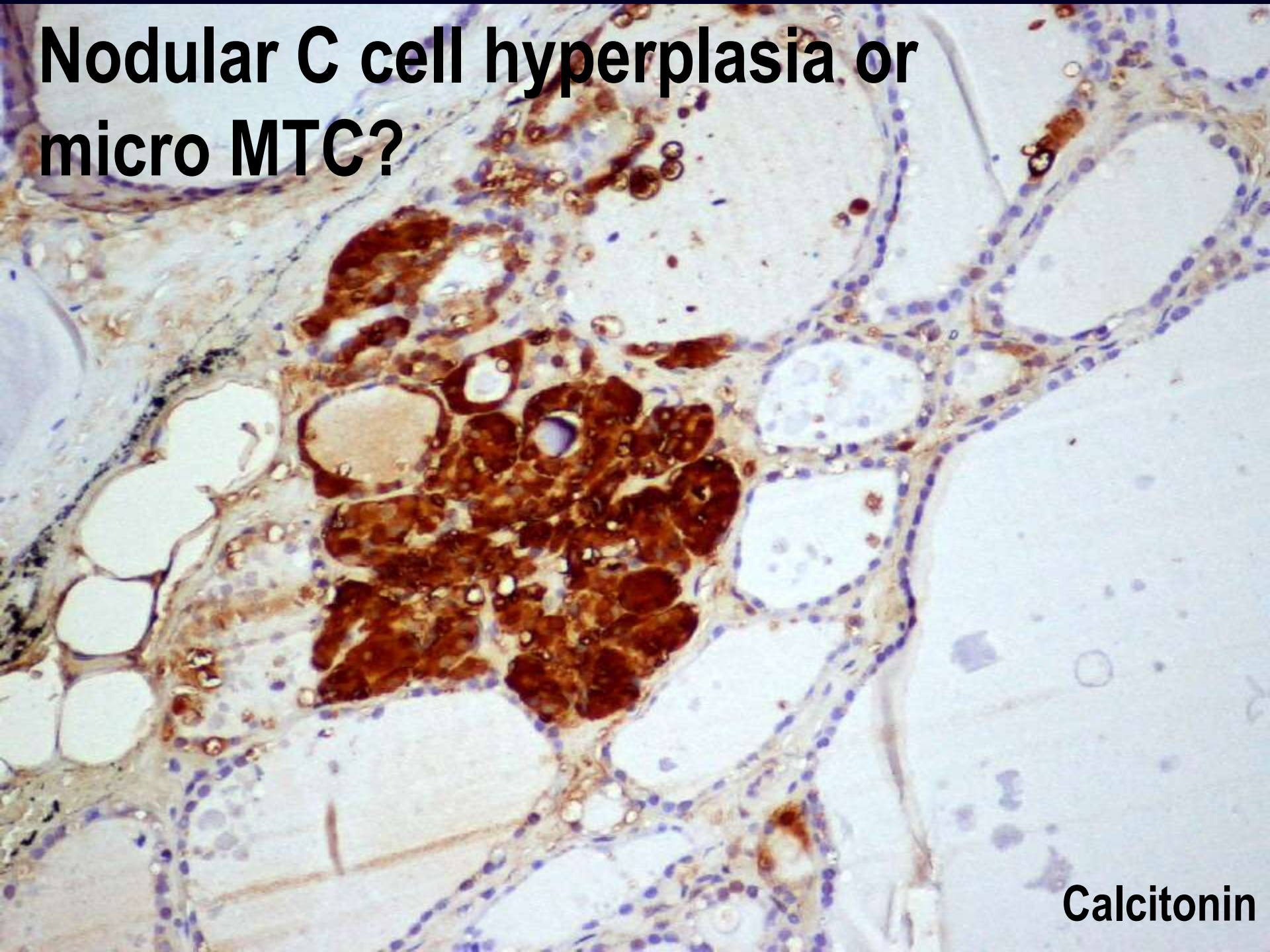

Calcitonin

Differential diagnosis of reactive and neoplastic C cell hyperplasia

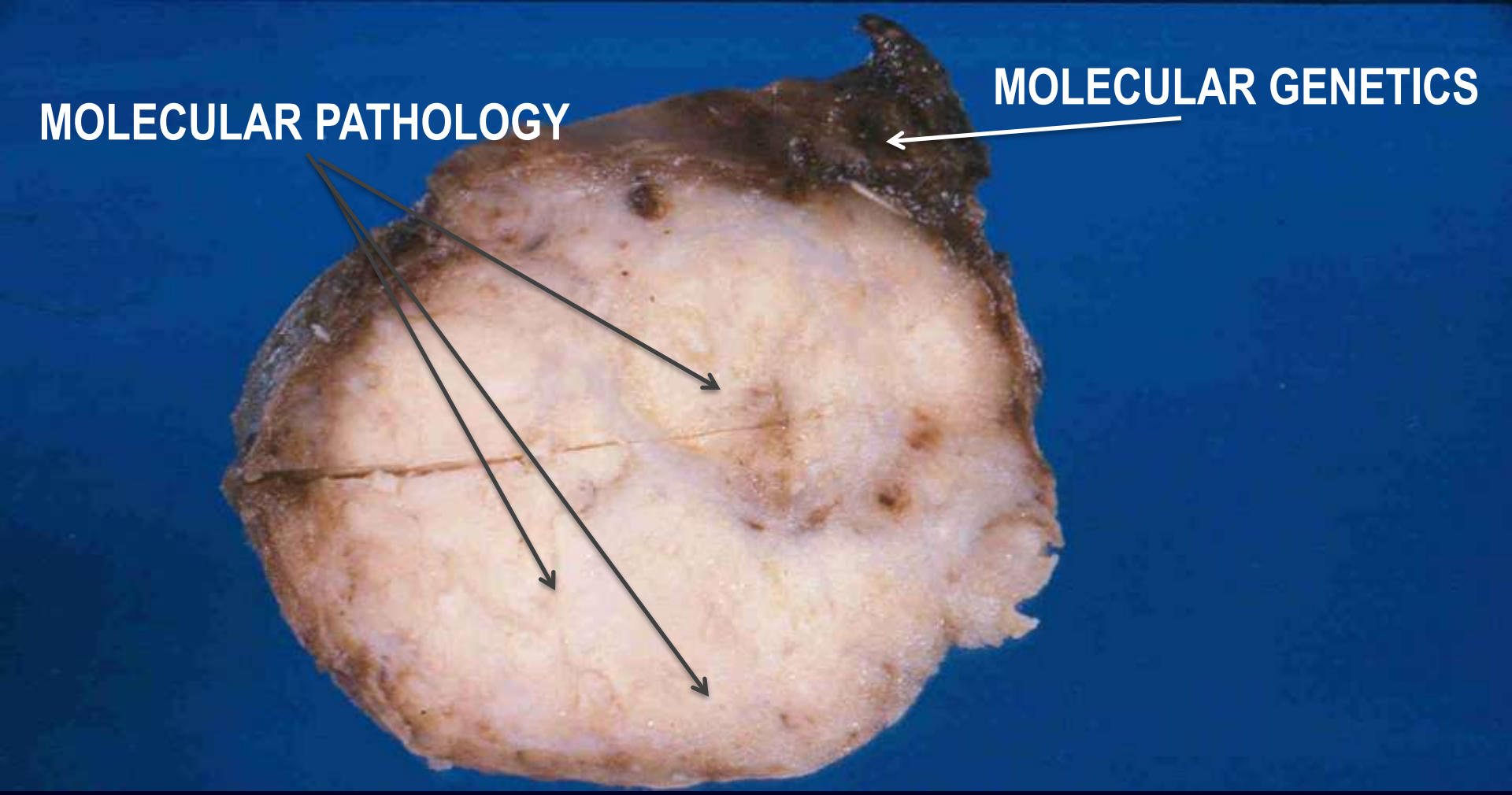
Differential diagnosis of nodular C cell hyperplasia and medullary microcarcinoma



# Nodular C cell hyperplasia or micro MTC?



Calcitonin




# MOLECULAR MEDICINE

MOLECULAR GENETICS - germline DNA alterations

MOLECULAR PATHOLOGY - somatic, non-hereditary genetic alterations

Sobrinho-Simões M, American Board of Pathology, S. Francisco, 2001

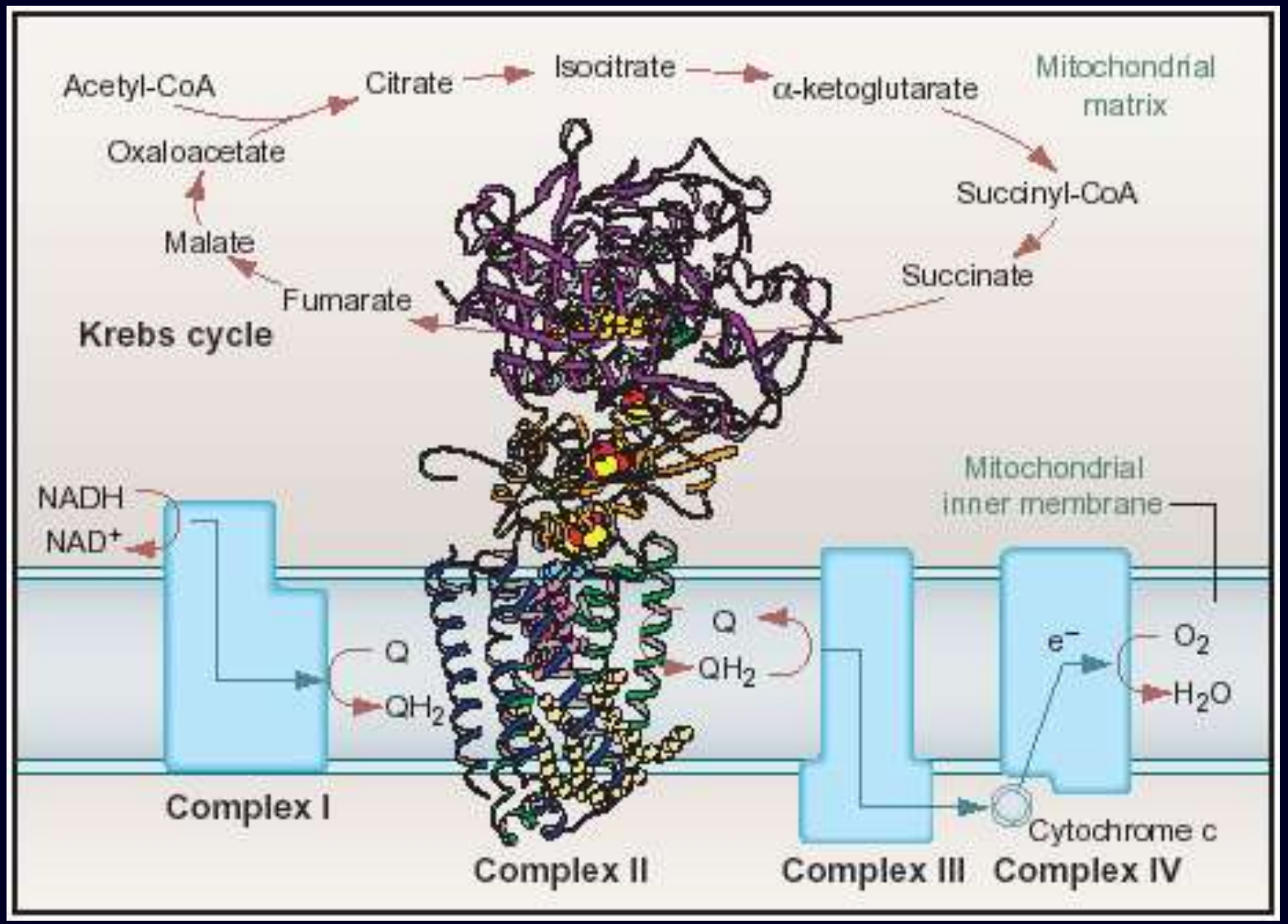
# Medullary carcinoma & C cell hyperplasia

More than 10% of hereditary forms do not have a known RET mutation

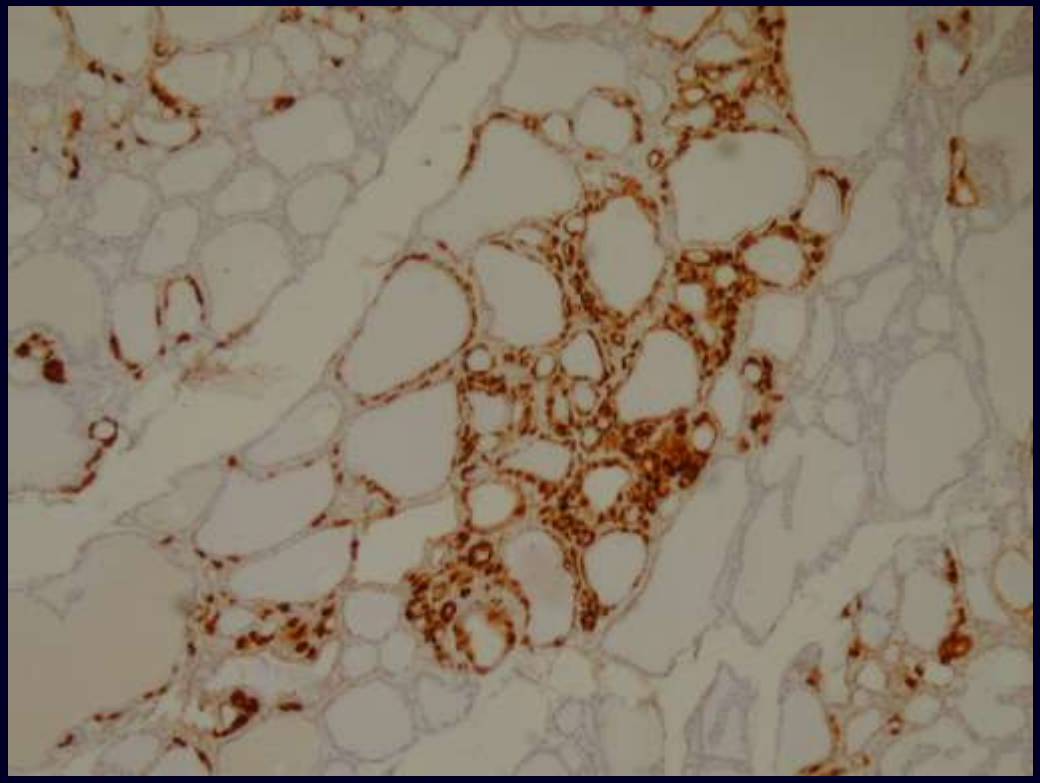
New RET mutations…

Role of modulator (landscaper) genes: SDHs,…

# Succinate dehydrogenase (SDH)



C-cell hyperplasia in individual II.1



Germline SDHD  mutation segregating with familial non-RET C cell hyperplasia

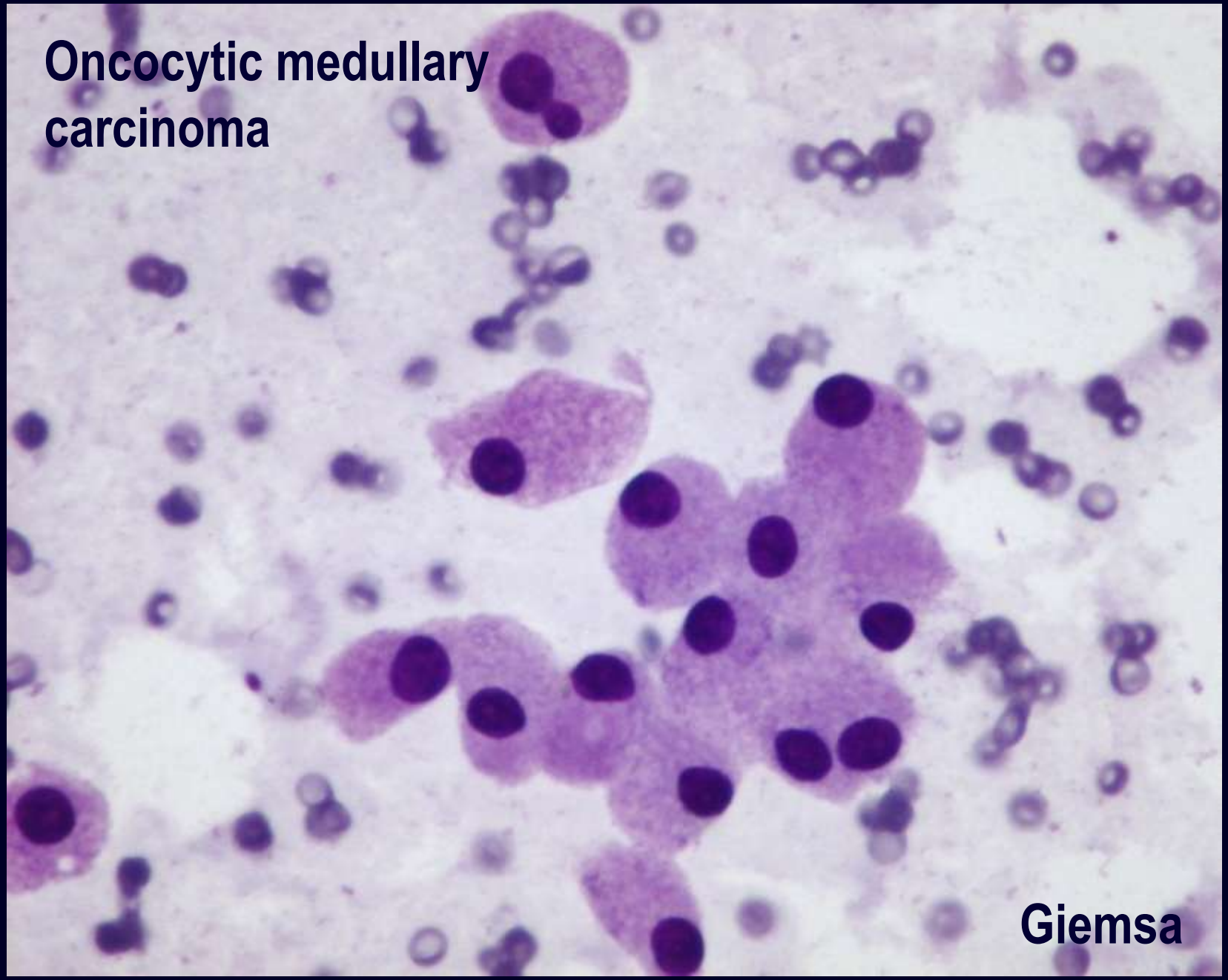
Lima et al, JCEM, 2003

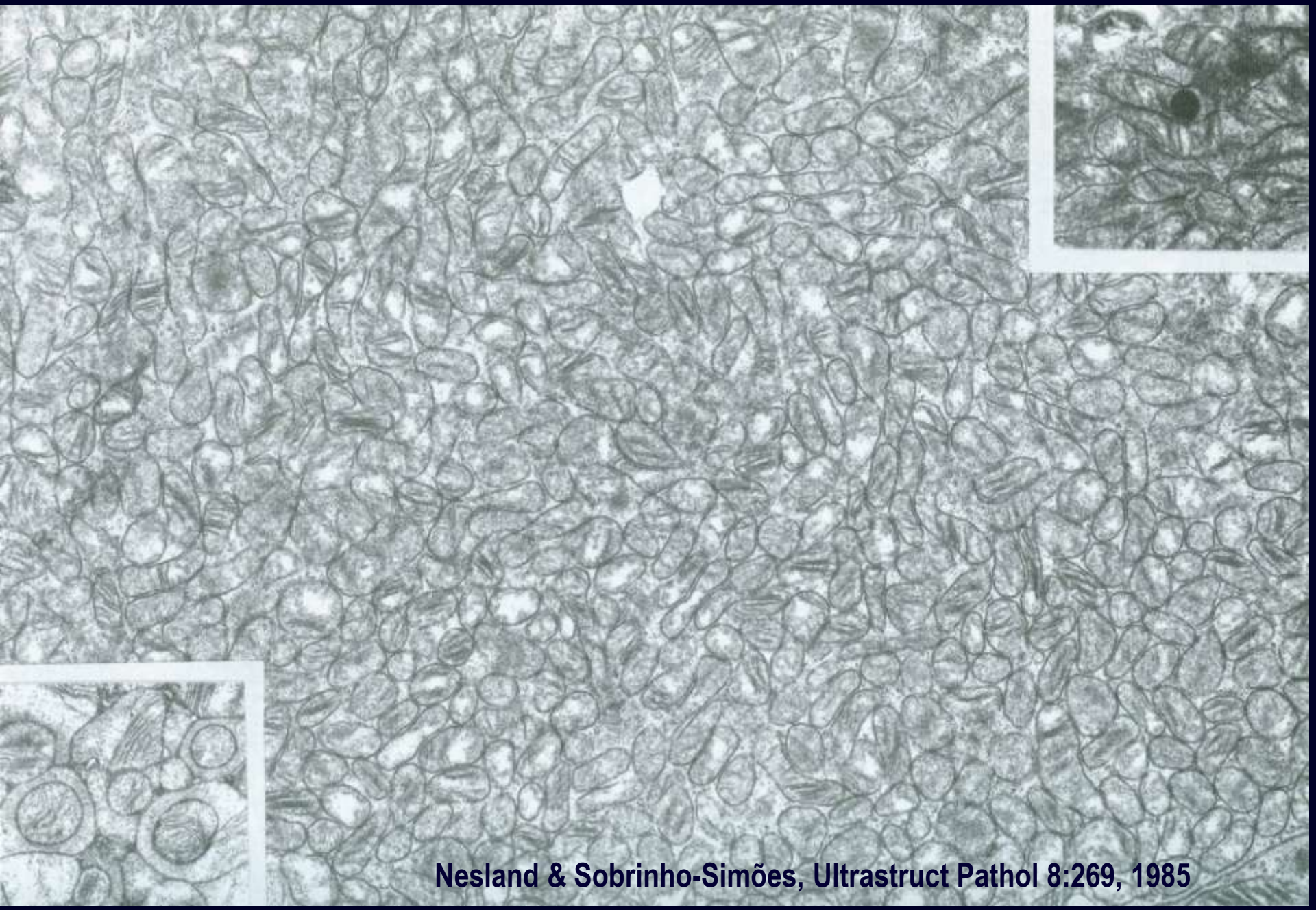
# FAMILIAL TUMOURS

PARAGANGLIOMAS
&
C-CELL HYPERPLASIA

SDHD
germline
polymorphism

Baysal et al, Science 287:848, 2000
Lima et al, JCEM 88:4932, 2003


Oncocytic medullary carcinoma
Giemsa



Nesland & Sobrinho-Simões, Ultrastruct Pathol 8:269, 1985

# FNMTC

## Familial Non-Medullary Thyroid Cancer

Epidemiological studies show a five to ten fold relative risk of developing thyroid cancer in first-degree relatives of thyroid cancer patients

*Int J Cancer* **85**:201-205.

*J Clin Endocrinol Metab* **86**:5307-5312.

*Cancer Epidemiol Biomarkers Prev* **10**:113-7.

*J Clin Endocrinol Metab. 2005* ***10****:5747-53..*

*Int. J. Cancer*: **92**, 144–150 (2001)


Publication of the International Union Against Cancer

# MODIFICATION OF CANCER RISKS IN OFFSPRING BY SIBLING AND PARENTAL CANCERS FROM 2,112,616 NUCLEAR FAMILIES

Chuanhui DONG and Kari HEMMINKI*

*Department of Biosciences at Novum, Karolinska Institute, Huddinge, Sweden*

| *Offspring cancer site* | *Parent cancer site* | *SIR Parent only* | *SIR Sibling only* | *SIR Parent and sibling* |
|---|---|---|---|---|
| Colon | Colon | 1,89 | 4,05 | 27,64 |
| Rectum | Rectum | 1,77 | 2,24 | 32,76 |
| Skin | Skin | 2,2 | 1,5 | |
| Breast | Breast | 1,85 | 1,98 | 2,39 |
| Ovary | Ovary | 2,81 | 1,94 | 25,54 |
| Prostate | Prostate | 2,91 | 4,91 | 23,72 |
| Thyroid | Thyroid | 6,94 | 6,97 | 292 |

Syndromic forms are rare

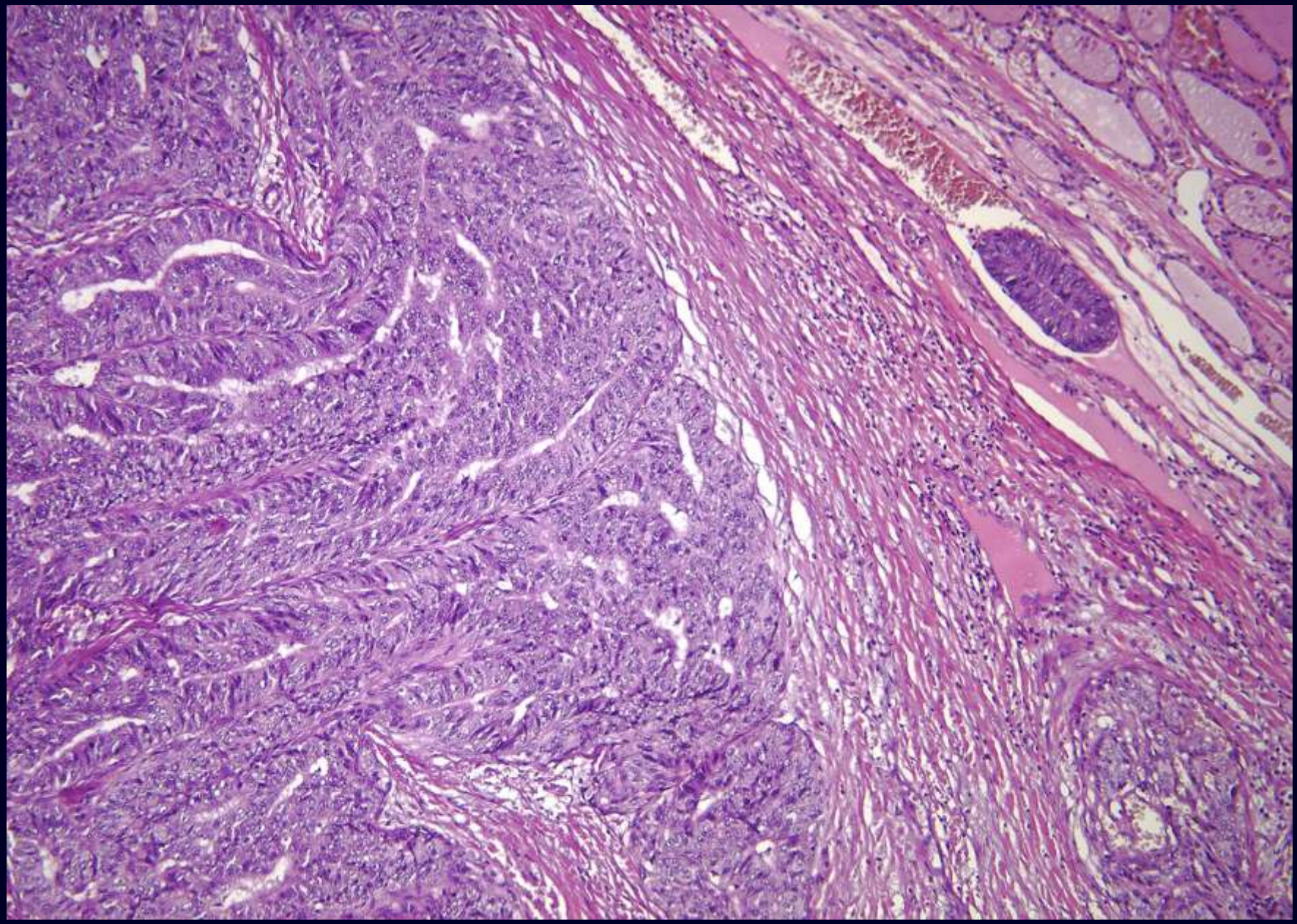
Site-specific forms are frequent

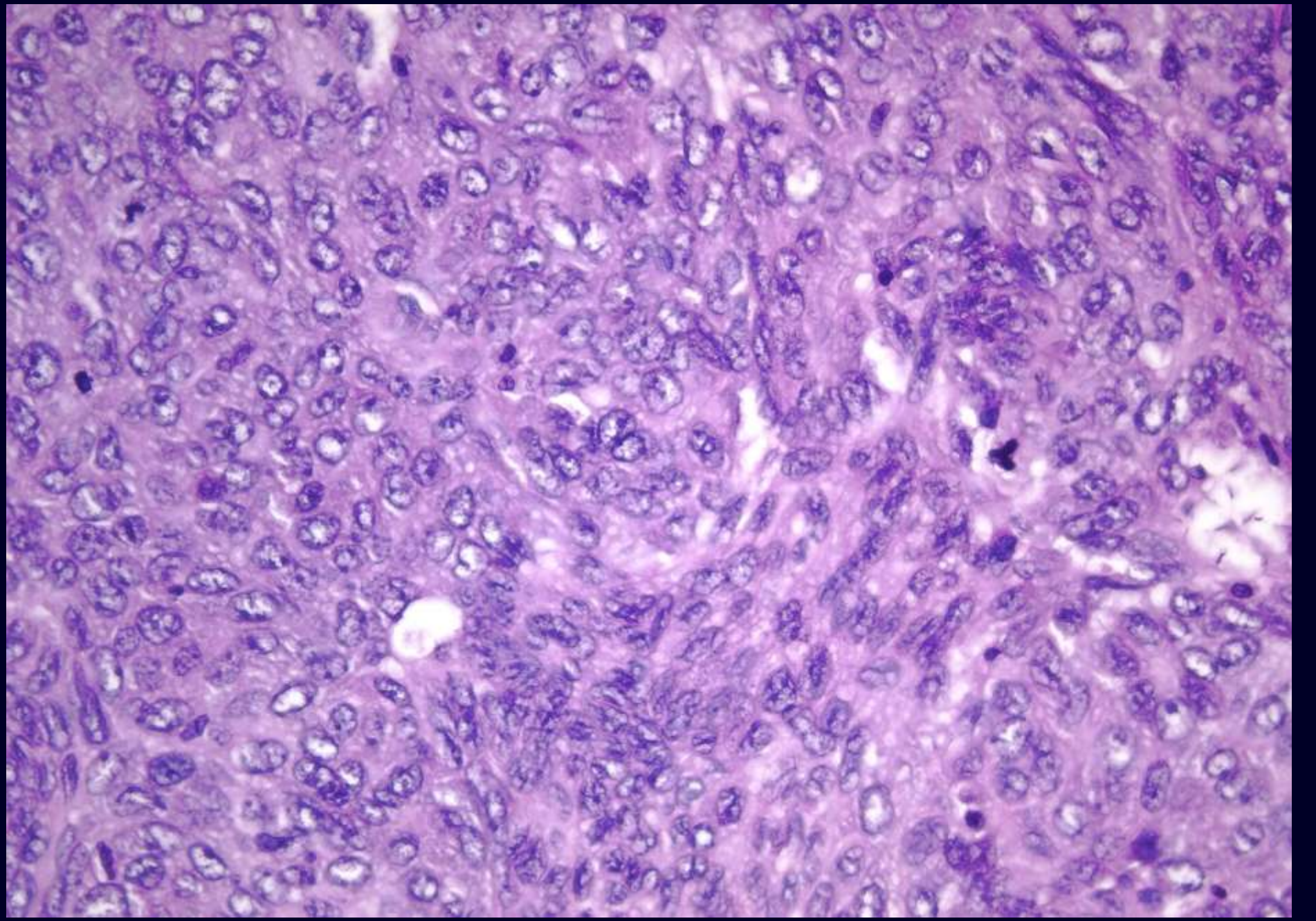
**Table 1.** Summary of Morphological Patterns and Somatic Molecular Genetics in Syndromic and Site-Specific FNMTCs

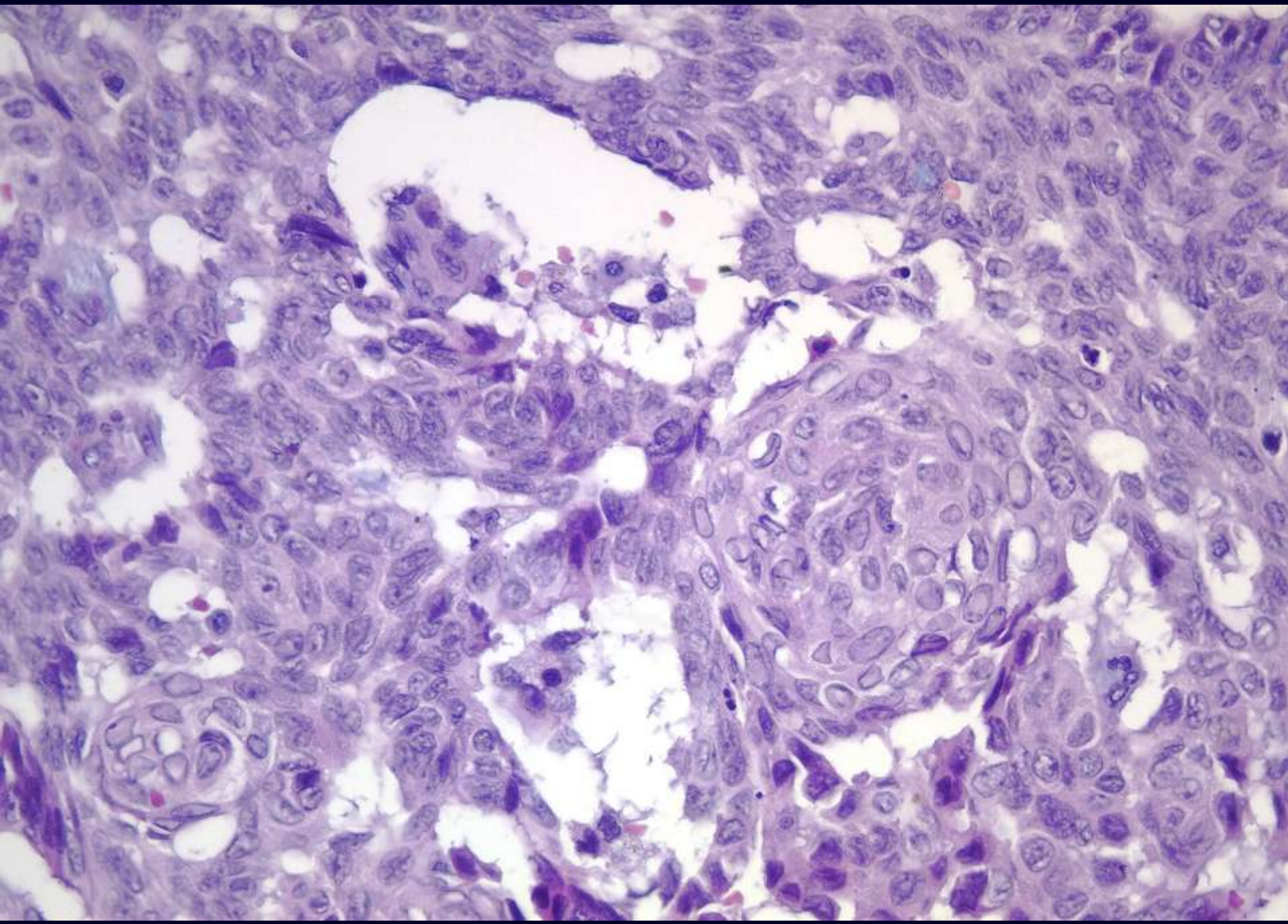
| | Chromossomal Location | Predisposing Gene | Morphological Patterns | Somatic Pathology |
|---|---|---|---|---|
| Syndromic FNMTCs | | | | |
| Familial adenomatous polyposis | 5q21 | *APC* | Cribriform-morular variant of PTC | RET/PTC1[68] |
| Cowden syndrome (multiple hamartoma) | 10q23.3 | *PTEN* | Multiple adenomatous nodules; FTA, FTC | Not assessed |
| Cowden-like syndromes | 11q23 and 1p36 | *SDHB* and *SDHD* | PTC | Not assessed |
| Carney complex type 1 | 17q22-24 | *PRKAR1alpha* | Multiple adenomatous nodules; FTA, PTC, FTC | Not assessed |
| Werner syndrome | 8p11-21 | *WRN* | PTC, FTC, ATC | Not assessed |
| McCune-Albright syndrome | 20q13.2 | *GNAS1* | Nodular and diffuse goiter; FA, FC, PTC, clear-cell carcinoma | Not assessed |
| Site-specific FNMTCs | | | | |
| TCO—tumors with cell oxyphilia | 19p13.2 | Unknown | Hurthle cell variants | 19p13.2 LOH[72]; *GRIM-19*[73] |
| Papillary thyroid and renal neoplasia—fPTC/PRN1 | 1p13.2-1q22 | Unknown | Conventional PTC; papillary renal neoplasia | Not assessed |
| NMTC1 | 2q21 | Unknown | Follicular variant of PTC | LOH at 2q21[71] |
| MNG1 | 14q32, Xp22 | Unknown | PTC in background of multinodular goiter | Not assessed |
| FNMTC | 8p23.1-p22 | Unknown | Benign thyroid disease, PTC, FTA, FTC without distinctive features | BRAF V600E[39] |
| FNMTC | 8q24 | Unknown | Benign thyroid disease, PTC, and melanoma | Not assessed |
| FNMTC | 1q21 and 6q22 | Unknown | No distinctive features | Not assessed |

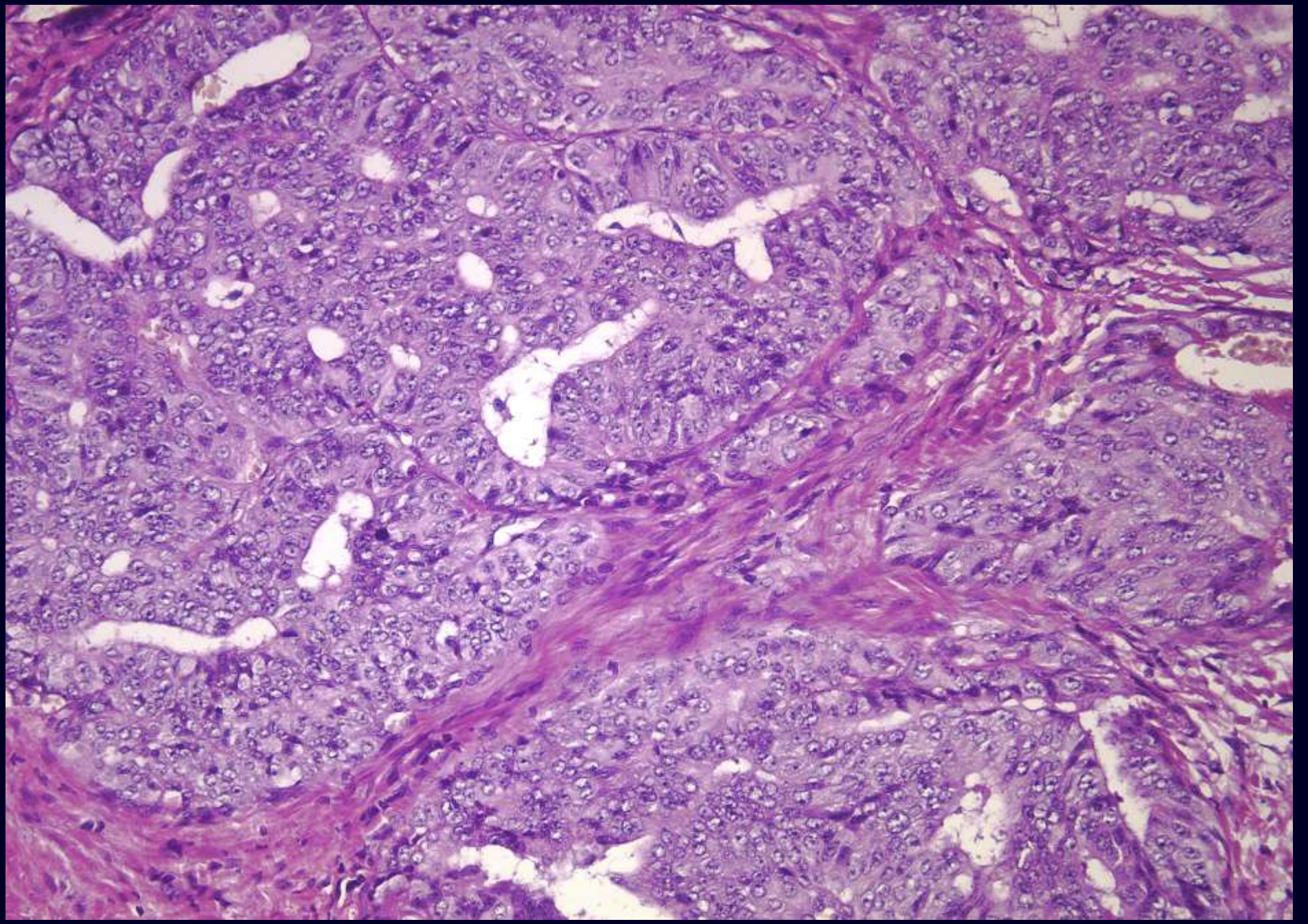
Abbreviations: NMTC, nonmedullary thyroid cancer; FNMTC, NMTC in familial aggregation; FTA, follicular thyroid adenoma; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

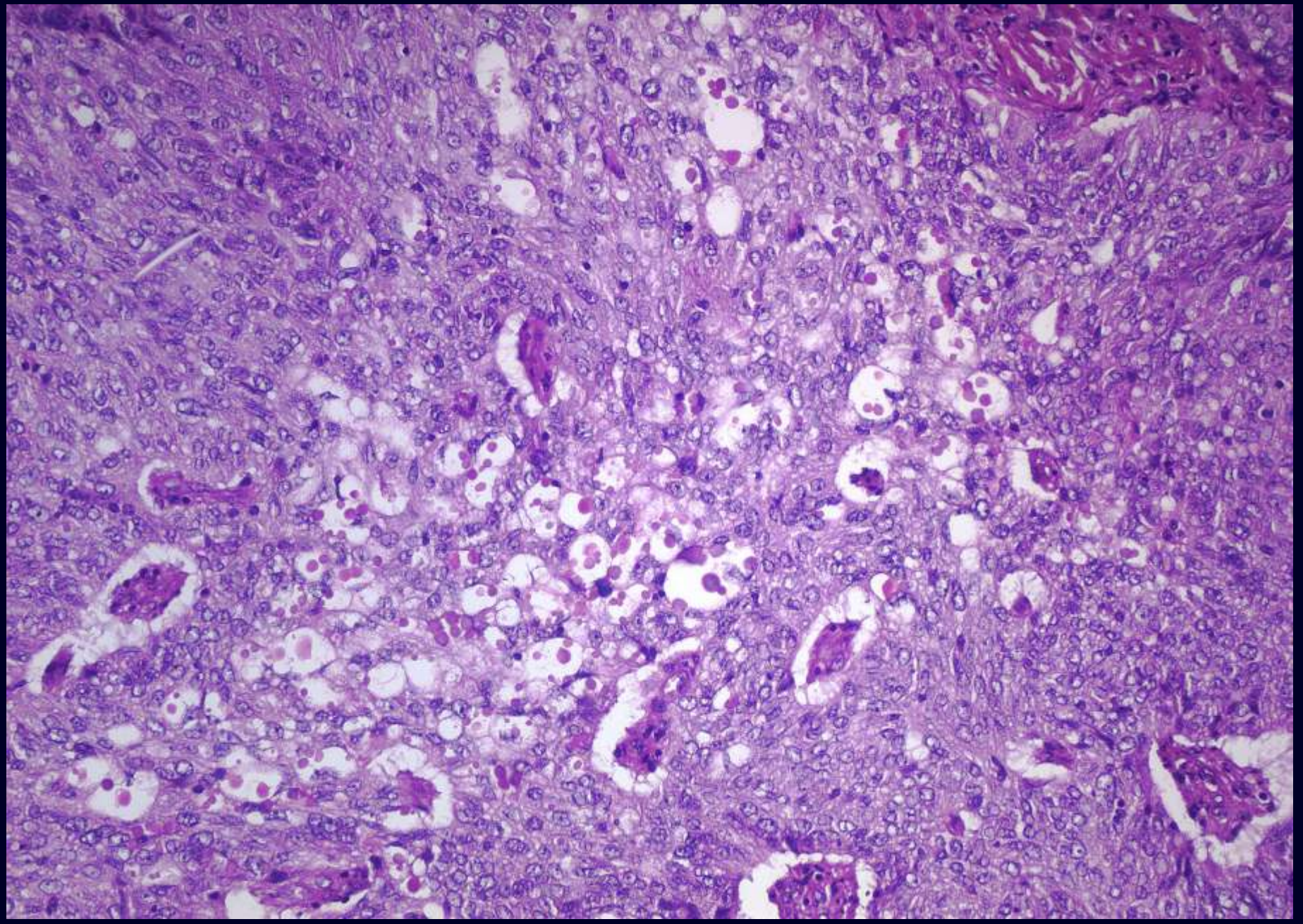
# Cribriform-morular variant – Associated or not to APC





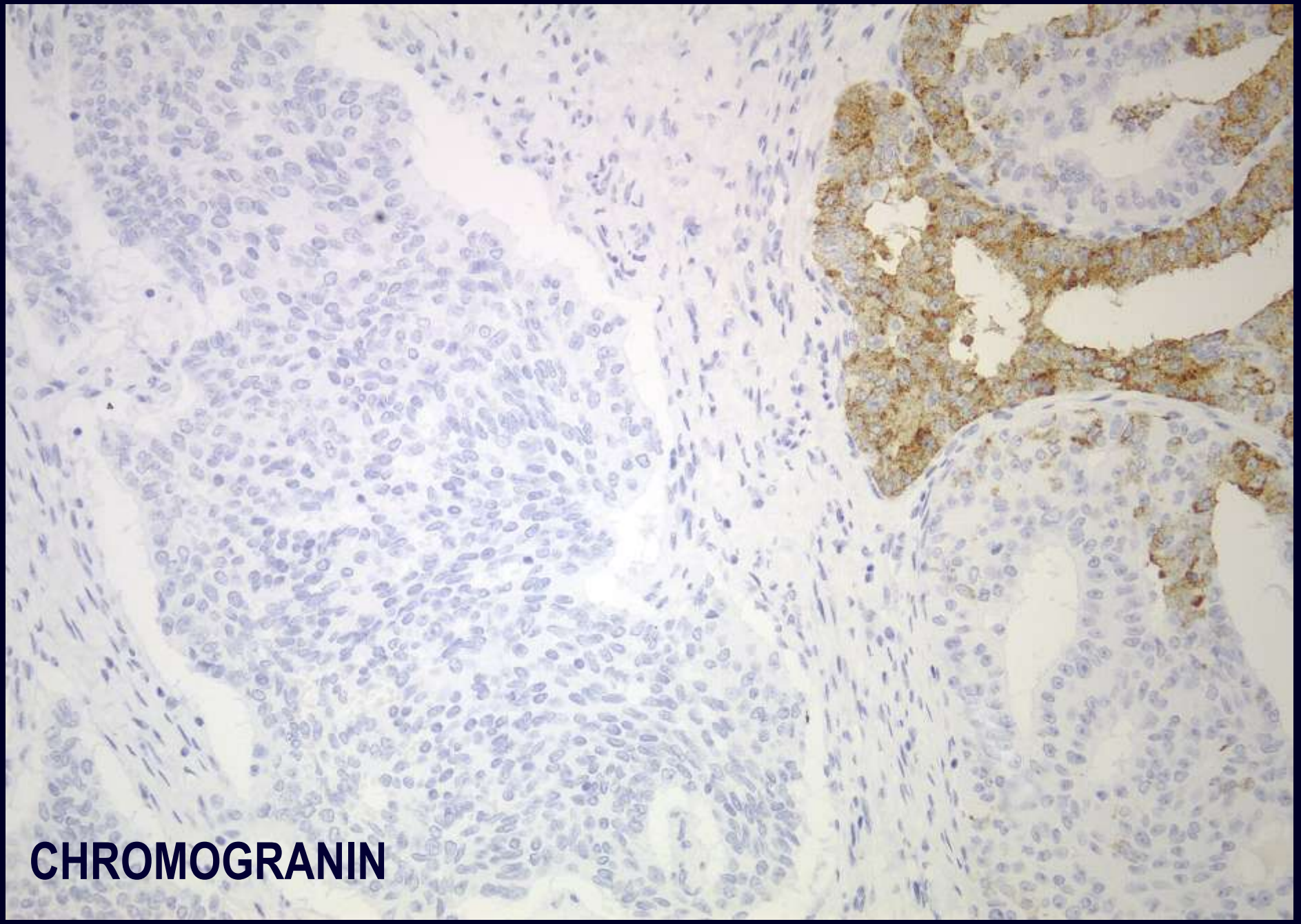


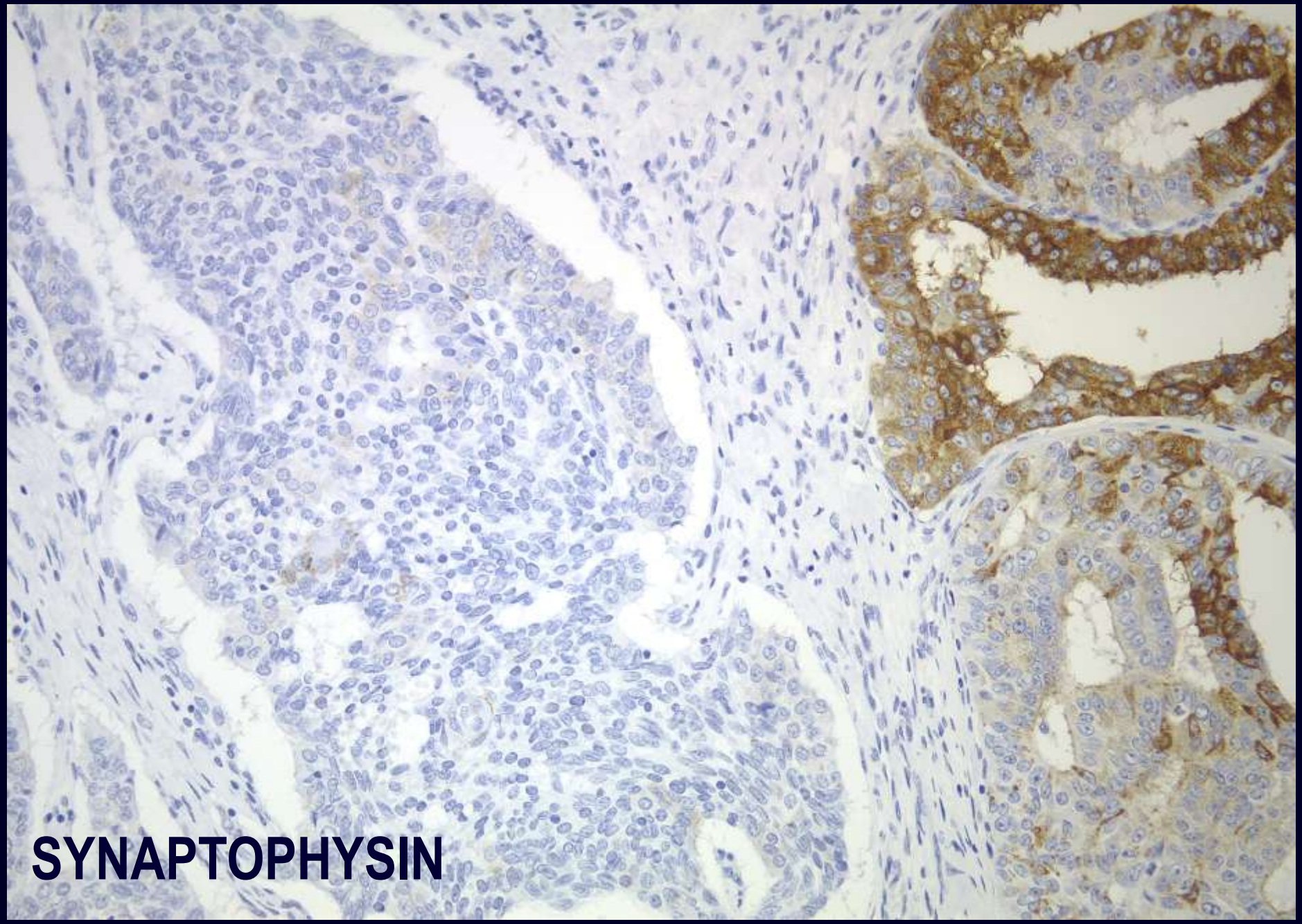




# Cribriform-morular variant of papillary thyroid carcinoma: molecular characterization of a case with neuroendocrine differentiation

Cameselle-Teijeiro et al. Am J Clin Pathol 131:134, 2009


CHROMOGRANIN


SYNAPTOPHYSIN

13th European Congress of Endocrinology
Rotterdam, The Netherlands
30 April - 4 May 2011
POSTER : P454

# Estrogen receptors and progesterone receptor expression and their relationship to types of thyroid cancer

José Cameselle-Teijeiro , Lara Alberte-Lista , Diego Peteiro-González , Miguel Melo , Ihab Abdulkader , Paula Soares , Pilar Gayoso-Diz , Manuel Sobrinho-Simões

# FNMTC

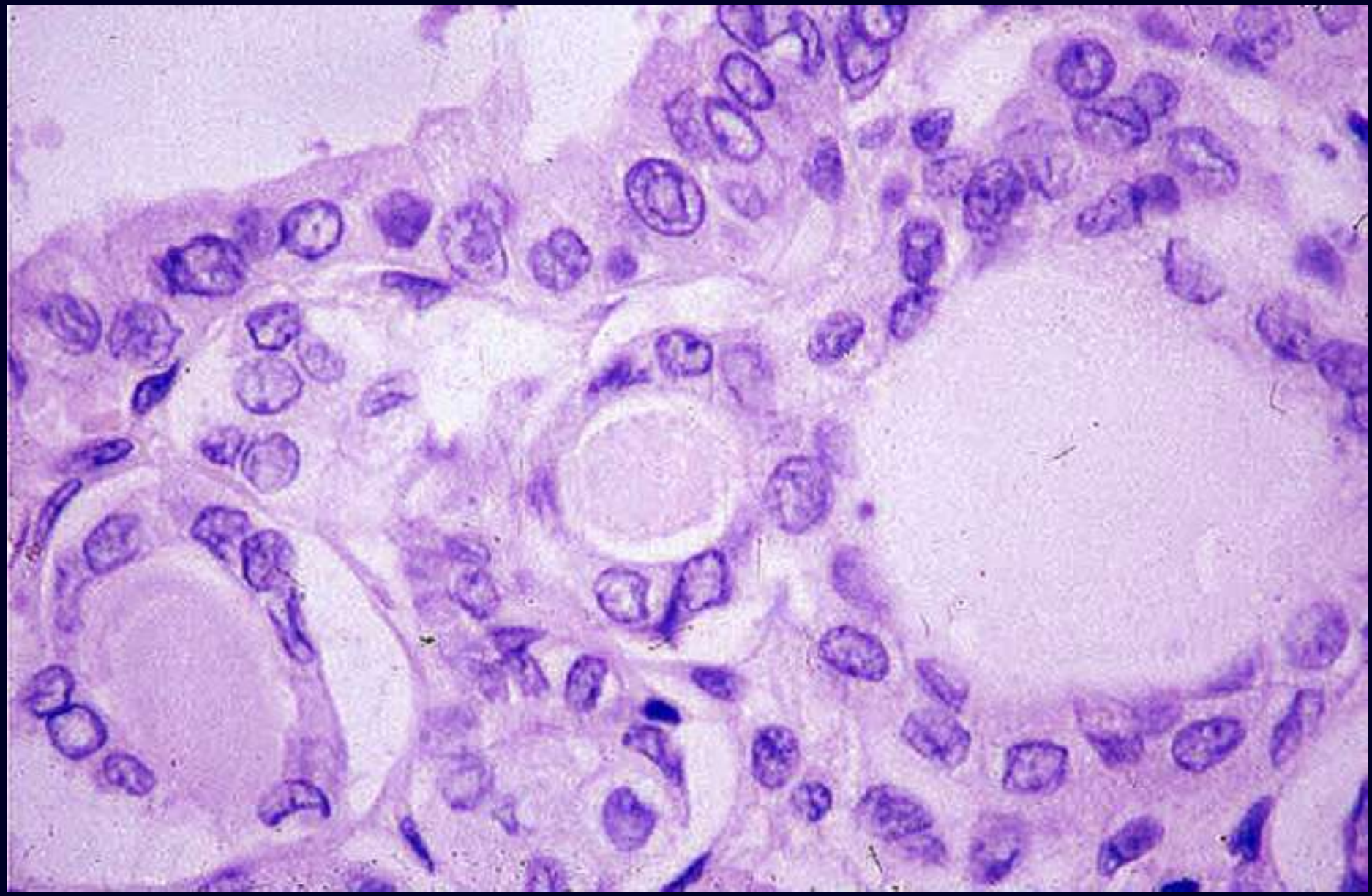
## Familial Non-Medullary Thyroid Cancer

Familial PTC, the most common form of FNMTC, is characterized by increased incidence of multifocality and greater recurrence rate than its sporadic counterpart, suggesting that FPTC may constitute a distinct clinical entity, with a more aggressive behaviour.

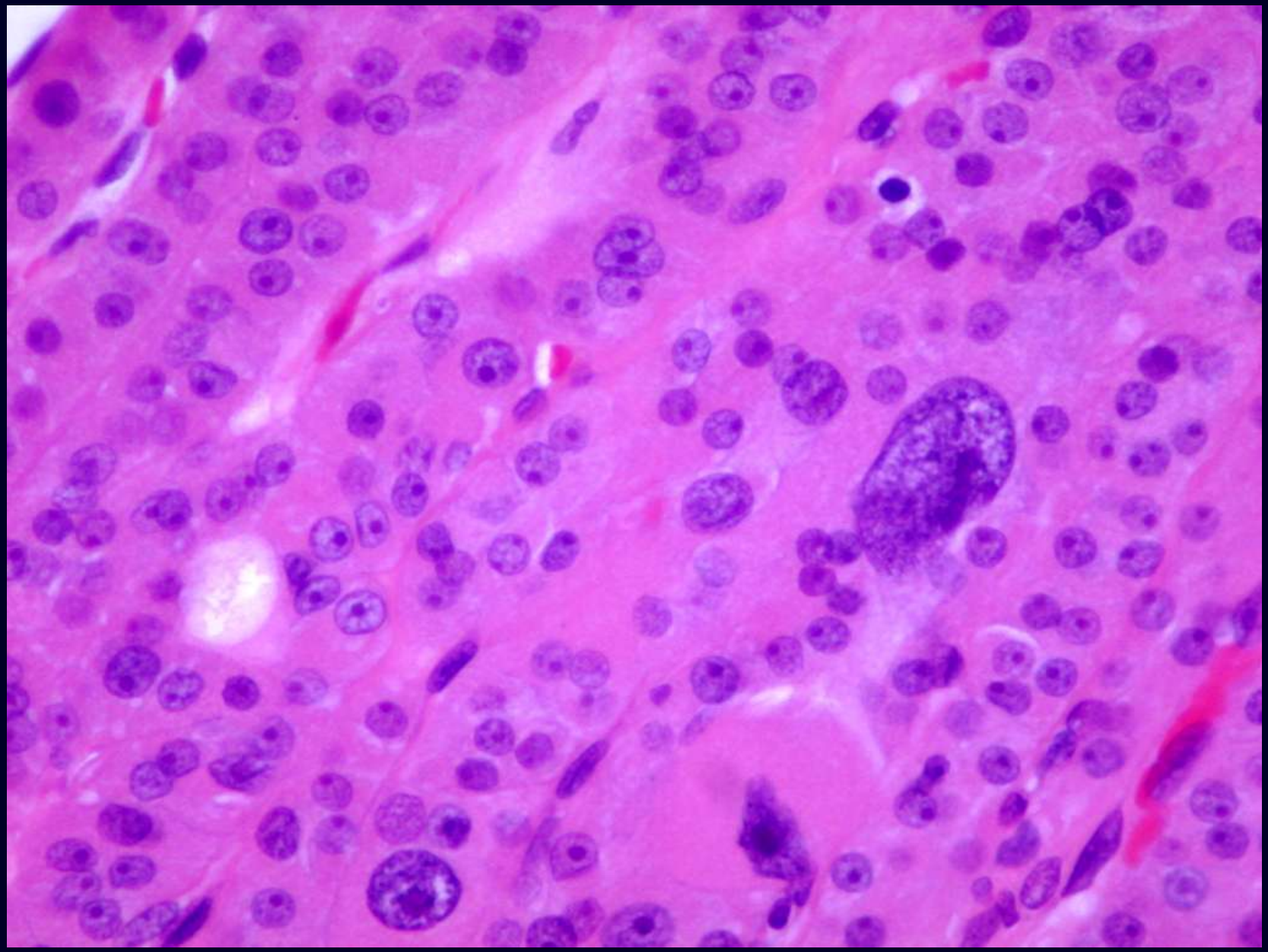
Most familial PTCs are either cases of Follicular variant PTC or Hurthle cell PTC.

*Arch Surg* **130**:892-897.
*Surgery* **128**:1043-1050.
*World J Surg* **26**:897-902.

# Follicular variant of PTC



# Hürthle cell (oncocytic) tumours

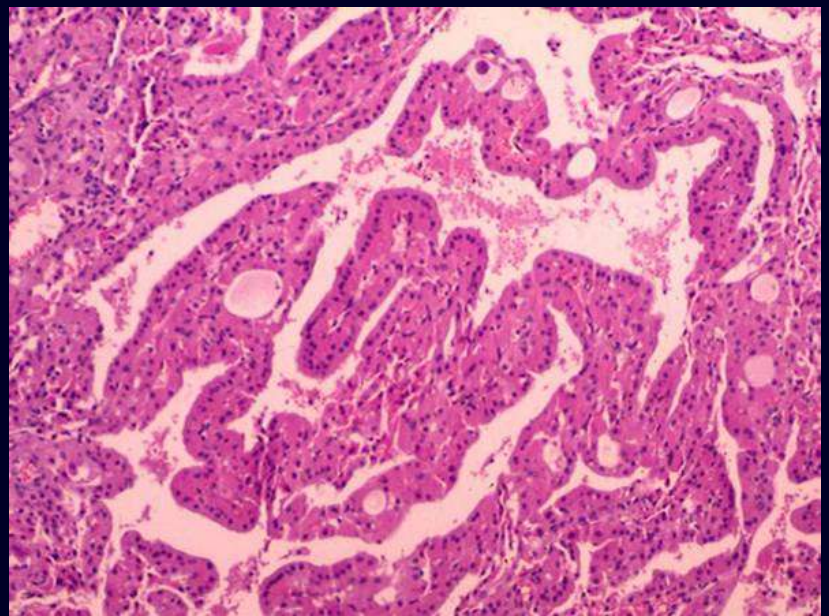


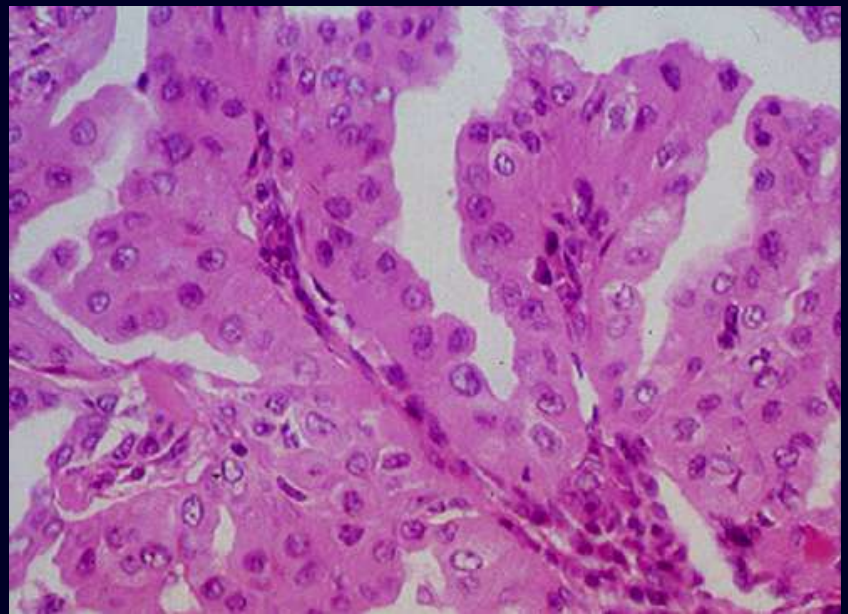
British Journal of Cancer (2005) 92, 1892 – 1898

www.bjcancer.com

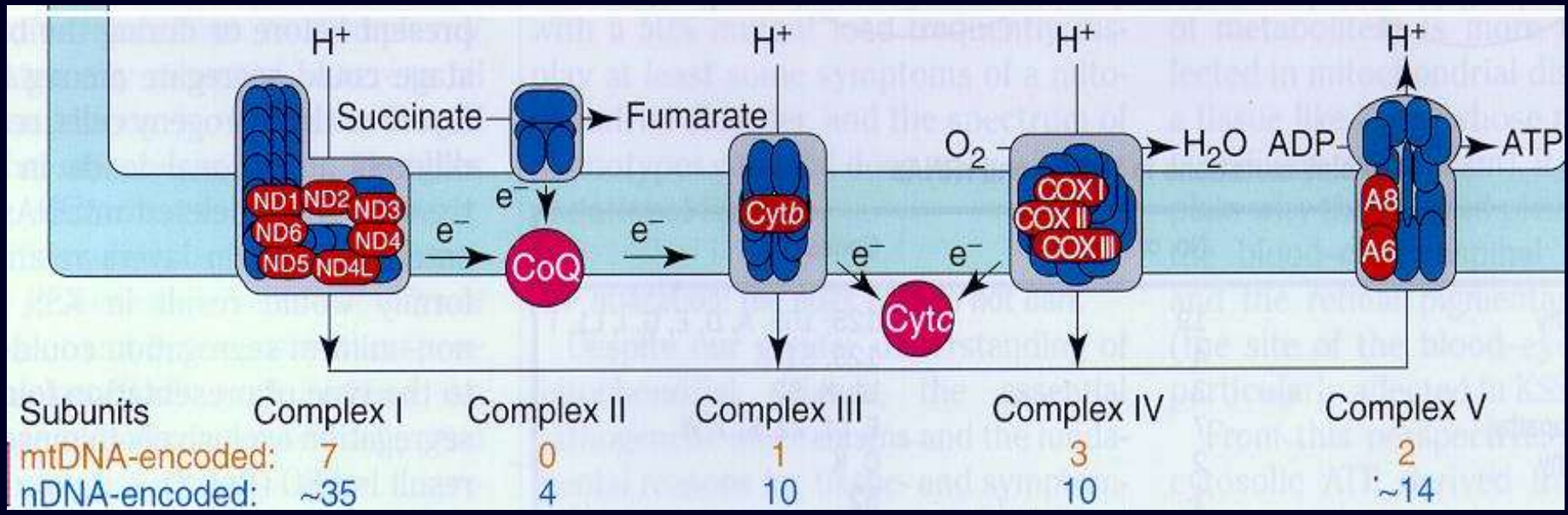
# Somatic and germline mutation in *GRIM-19*, a dual function gene involved in mitochondrial metabolism and cell death, is linked to mitochondrion-rich (Hürthle cell) tumours of the thyroid

V Máximo[1], T Botelho[1], J Capela[2], P Soares[1,3], J Lima[1], A Taveira[1,2], T Amaro[4], AP Barbosa[5], A Preto[1], HR Harach[6], D Williams[7] and M Sobrinho-Simões[*,1,3,8]



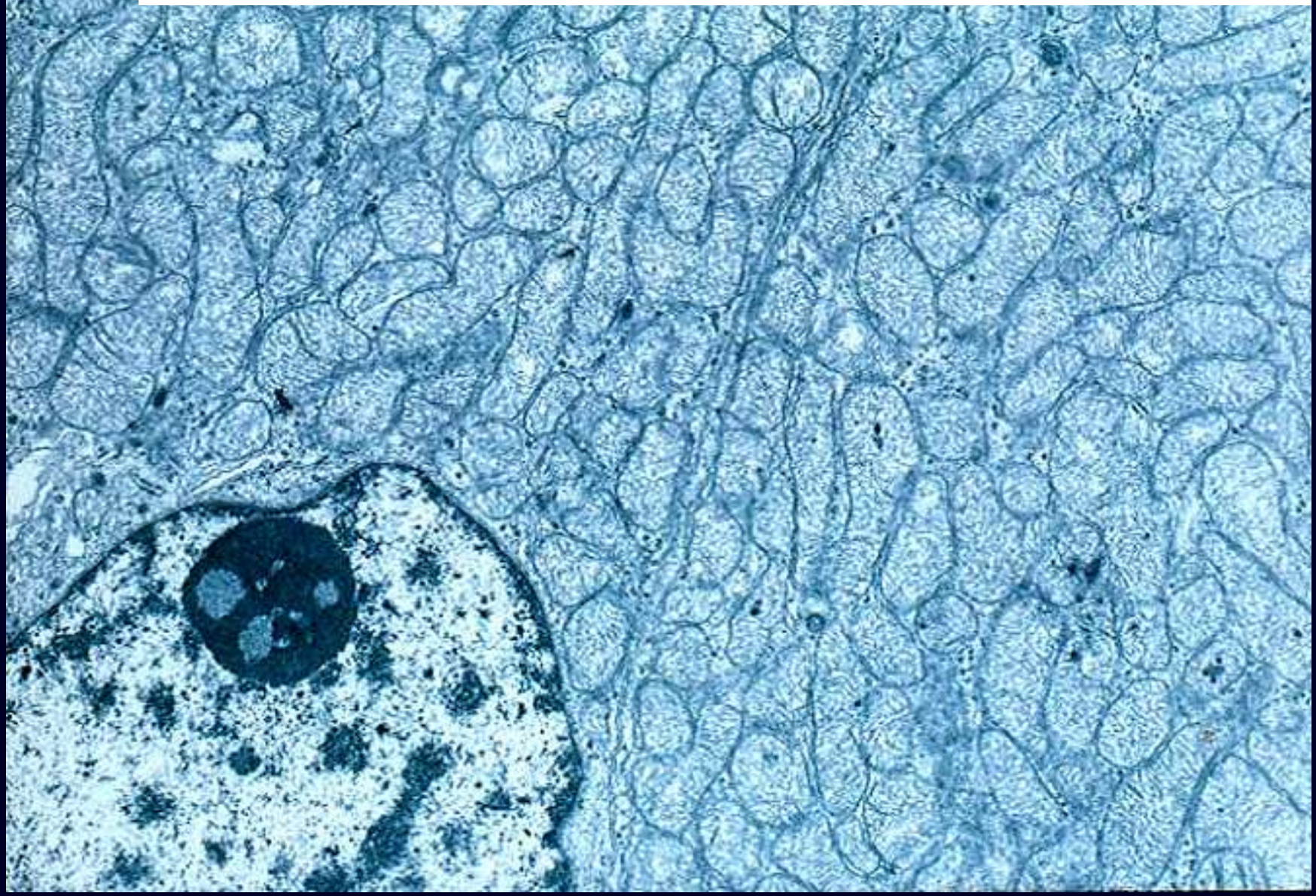


# Mitochondrial oxidative phosphorylation (OXPHOS) system



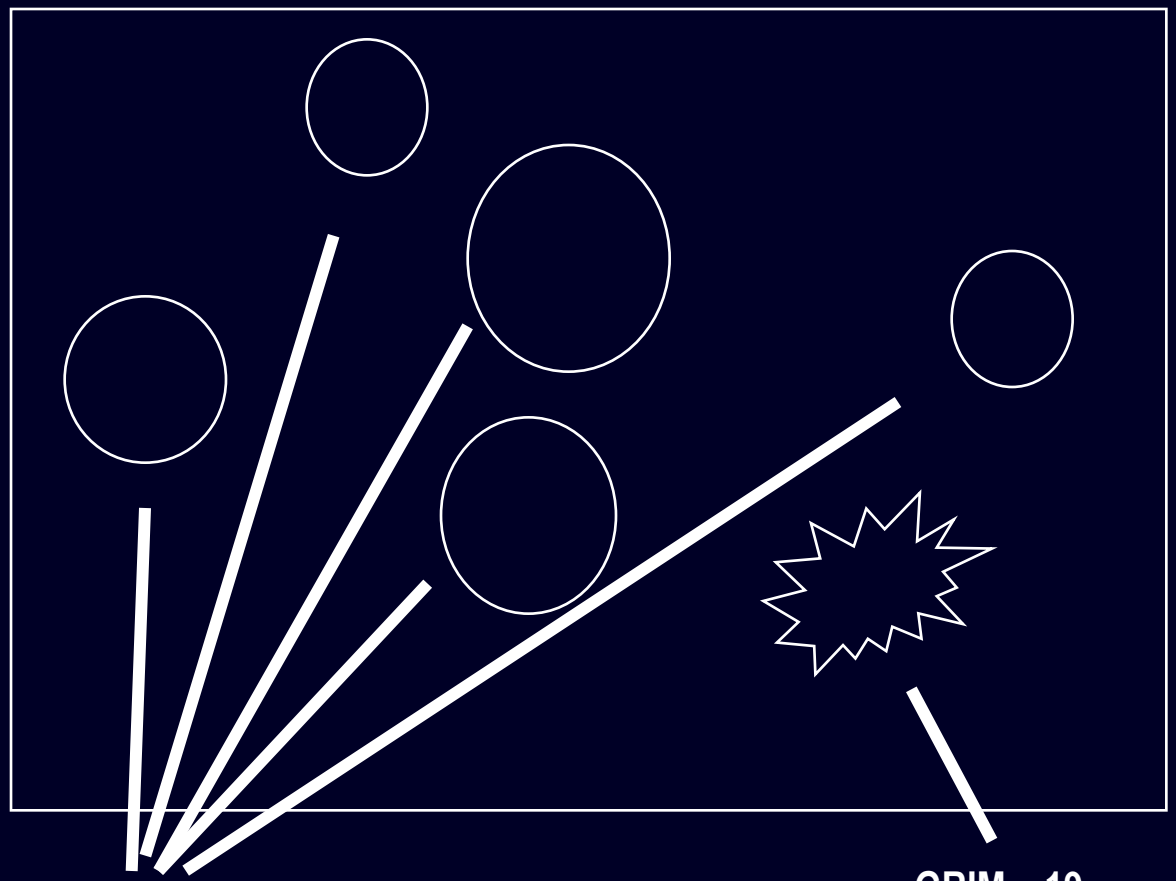
**Hürthle cell lesions of the thyroid: a combined study using transmission electron microscopy, scanning electron microscopy and immunocytochemistry.**

Nesland & Sobrinho-Simões, Ultrastruct Pathol 8:269, 1985.



# Familial nodular goiter with oncocytic features

Máximo V et al, Br J Cancer 2005



GRIM – 19
germline mutation

GRIM – 19
germline mutation
+
RET/PTC rearrangement

# FNMTC

Concentration of cases of Follicular variant PTC and Hurthle cell (oncocytic ) variant PTC

But

The large majority of cases of Follicular variant PTC and of oncocytic tumours (adenomas, FTC and PTC) are not familial

# Familial clustering of thyroid tumours

## (Outside hereditary MTC and syndromic forms)

Oncogenes
Tumour suppressor genes
Landscaper (modulator) genes

OXPHOS & Krebs cycle genes

GRIM-19 in familial Hürthle cell tumours
Maximo et al, Br J Cancer, 2005

SDHD in familial C-cell hyperplasia
Lima J et al, JCEM, 2003

Familial follicular cell-derived thyroid tumors.
Prazeres H et al, Int J Surg Pathol, 2010

# CANCER GENES

Oncogenes

Tumour-supressor genes

“Secondary” genetic alterations

Driver genes

Passenger genes (Different qualities of the passengers...)

Gatekeepers
Caretakers

Landscapers

Forerunners

# WHAT ABOUT THE STROMA?

# Chromosomal, epigenetic and microRNA-mediated inactivation of LRP1B, a modulator of the extracellular environment of thyroid cancer cells.

Prazeres H, Torres J, Rodrigues F, Pinto M, Pastoriza MC, Gomes D, Cameselle-Teijeiro J, Vidal A, Martins TC, Sobrinho-Simões M, Soares P.

Oncogene 2011;30:1302-17

# Identification of hereditary tumours

**C cell (medullary) carcinoma – RET, SDHD,…**

**Follicular cell derived carcinomas**

- **APC – Cribriform morular ca (variant of PTC?)**
- **PTEN – Different types of benign and malignant tumours**
- **GRIM-19 – Oncocytic variant of adenoma and papillary carcinoma**
- **……..**

- Familial aggregation in a Mendelian transmission pattern
- Syndromic spectrum of primary tumors in the same individual or in the family
- Early onset
- Bilateral tumors
- Multifocal tumors
- Precursor hyperplastic lesions in the remaining organ

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