Presented by Dr. Susan Richter

HEAD AND NECK PARAGANGLIOMAS –

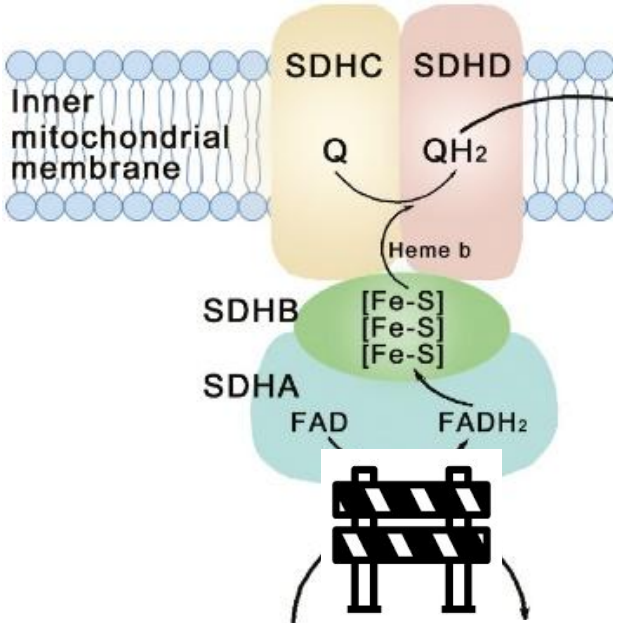
Biology and Management

ABOUT

- 14 years in PPGL research
- Senior scientist at the University of Auckland, New Zealand
- Before 12 years in Germany, laboratory of Prof. Eisenhofer
- Special interest in HN-PGL biology

HN-PGL DIFFER FROM OTHER PGL

Succinate dehydrogenase (SDH)



SUCCINATE

Fumarate

Succinate:fumarate ratios to identify *SDHx* mutations

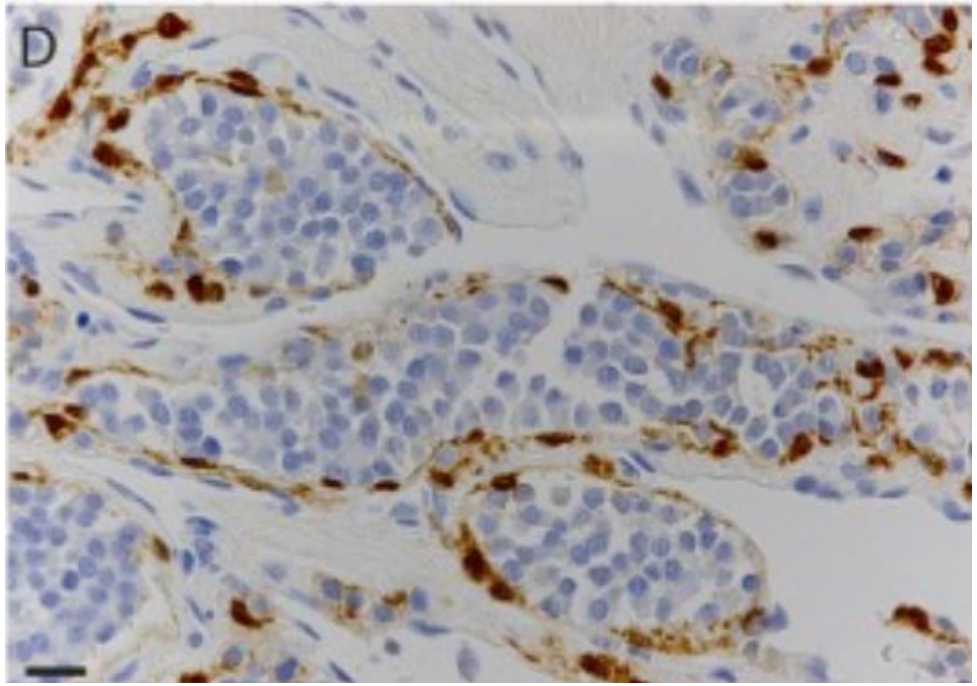
	All PPGLs	PPGLs excl. HNPGL	HNPGL
Sensitivity [%]	93.2	100	84.2
Specificity [%]	96.8	97.3	80.0

MORPHOLOGY OF HN-PGL

Tumor cells

Support cells (not cancerous)

Typical arrangement of tumor cells in clusters



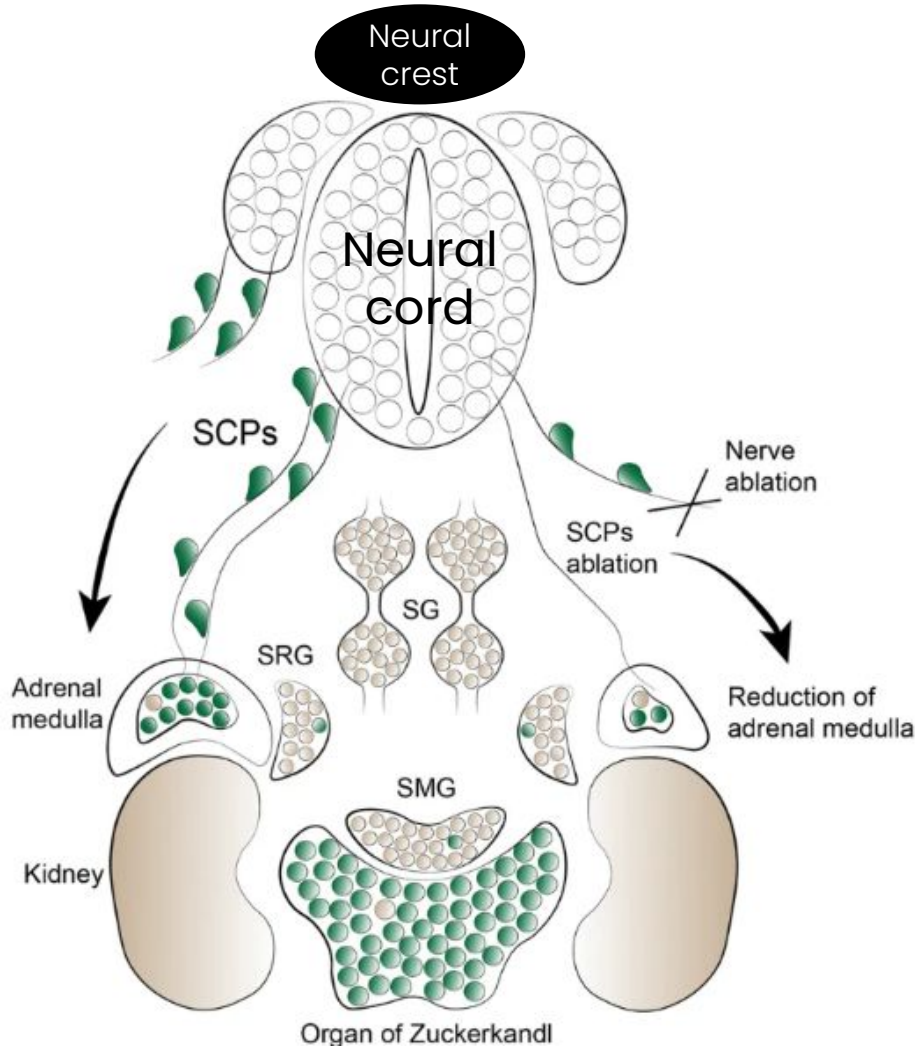
Derive from oxygen-sen sing glomus cells

Multipotent □ develop into glomus cells

Immune cells

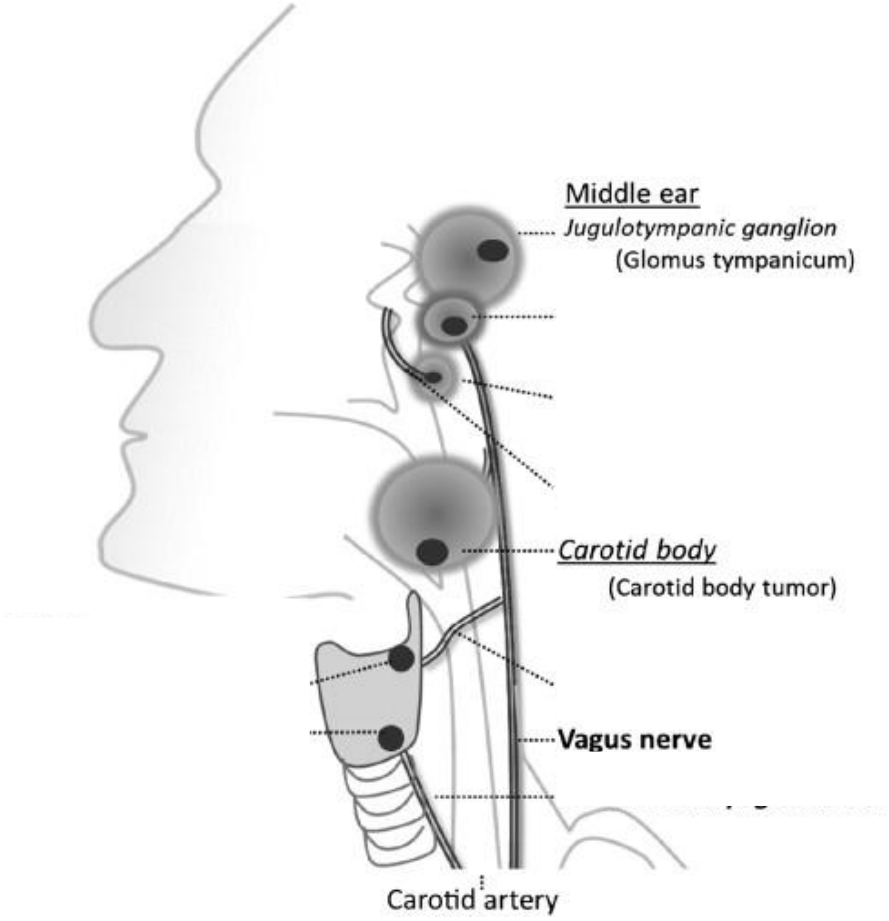
DEVELOPMENTAL ORIGIN OF HN-PGL

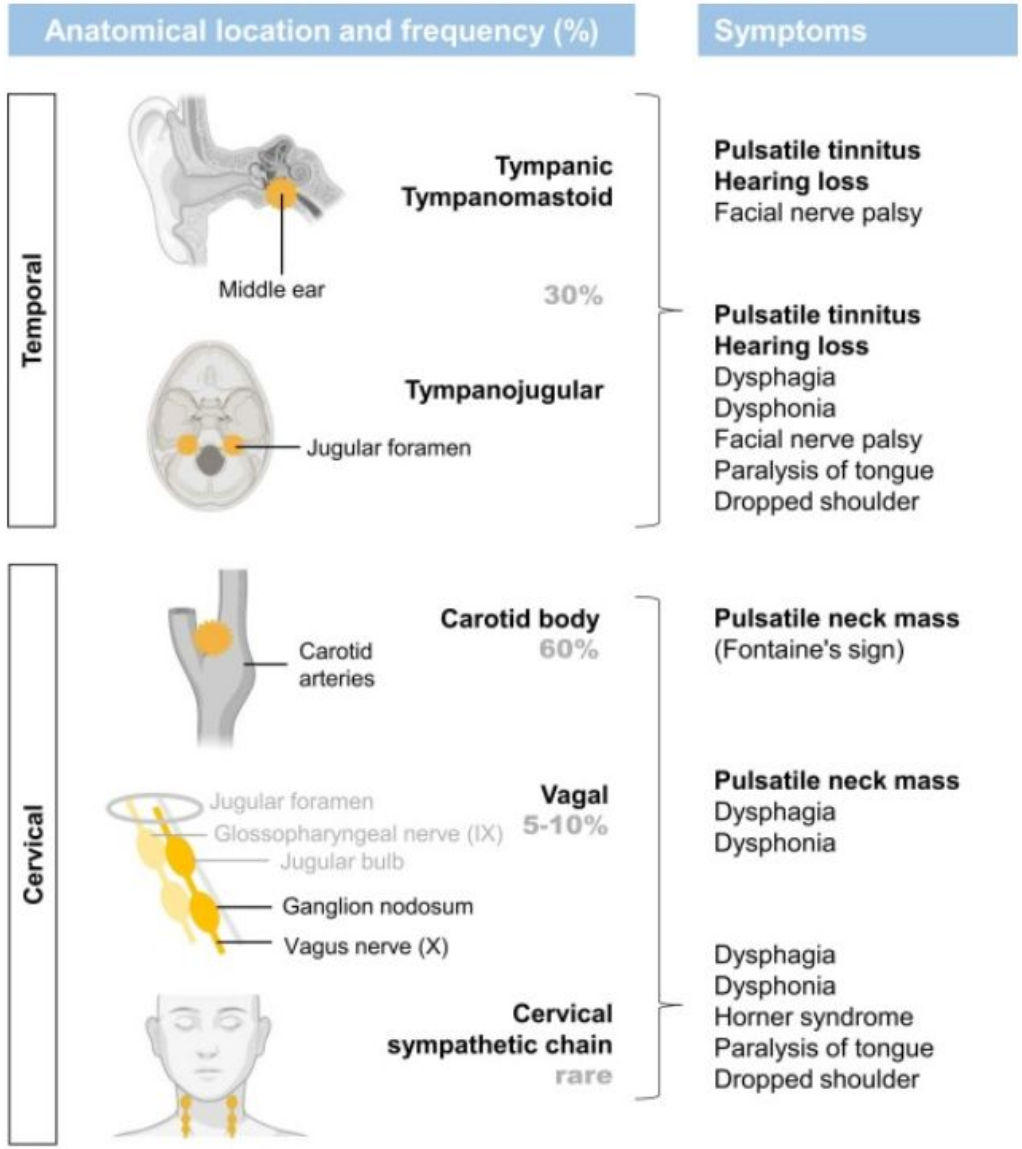
- All PGL types arise from neural crest
- Sympathetic ganglia (SG) from migrating trunk neural crest cells (earlier population) => **sympathetic paraganglioma (chest, abdomen)**
- Head and neck ganglia arise from nerve-associated Schwann cell precursors (SCPs)
  - Migrate along nerves, form ganglia at the end and gain their specific functions
  - They become glomus cells or support cells
  - Adrenal medulla cells with similar origin



Kameneva et al.. https://doi.org/10.1007/s00018-020-03609-5

LOCATION AND SYMPTOMS OF HN-PGL





Williams and Rich. https://doi.org/10.1016/j.path.2014.08.007

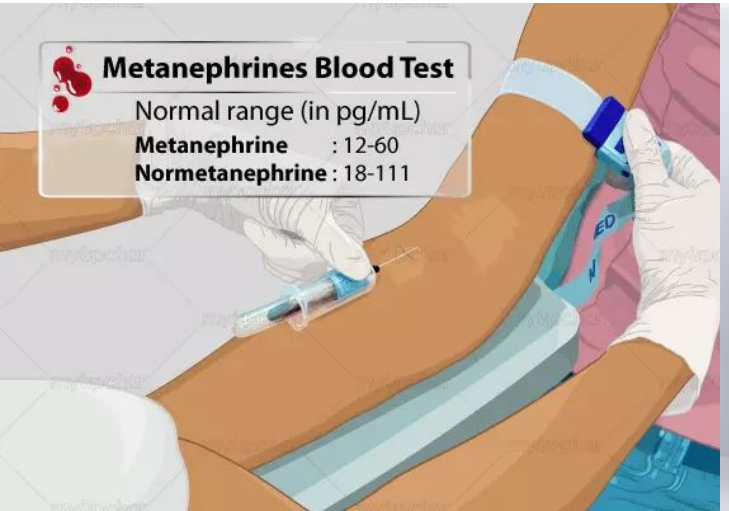
Richter et al.. https://doi.org/10.1016/j.beem.2024.101951

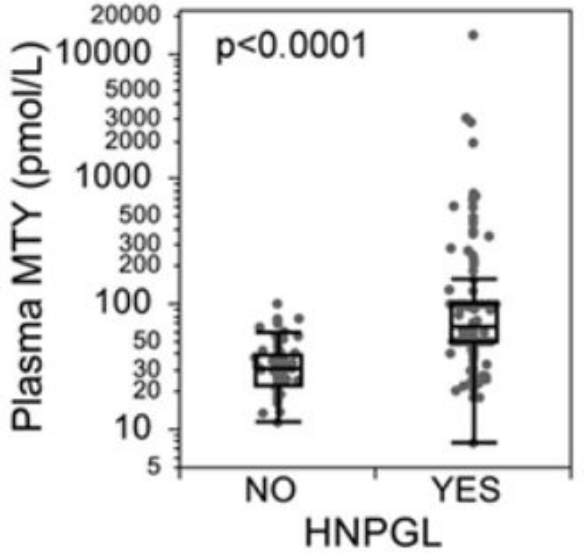
CATECHOLAMINES AND HN-PGL SCREENING RELATED IMPLICATIONS

L-Tyrosine → L-DOPA → Dopamine → ~~Norad… …drenalin~~

HN-PGL

Screening test for PGL



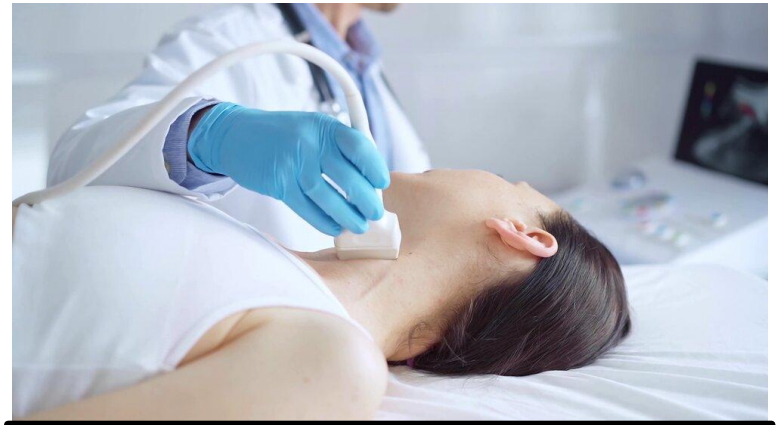


Richter et al.. https://doi.org/10.1530/ERC-21-0359

Plasma metanephrines may not pick up HN-PGL

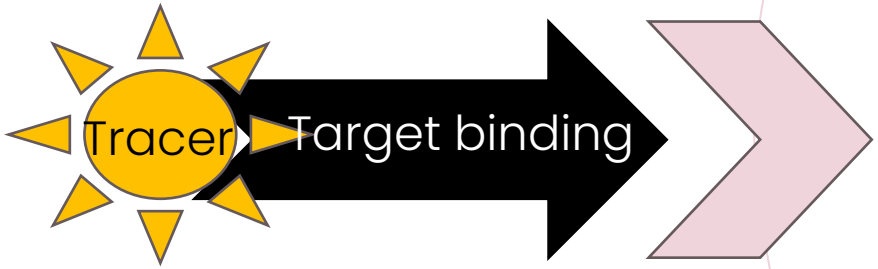
MEDICAL IMAGING – ANATOMICAL

- Ultrasound: initial testing on tumor suspicion
- Best for screening and diagnosis: contrast-enhanced magnetic resonance imaging (MRI) OR computed tomography (CT)
- Classification and treatment plan based on anatomic location
- High-resolution CT with bone windows for temporal HNPGL (ear region)



MEDICAL IMAGING – FUNCTIONAL

- Positron emission tomography (PET) CT



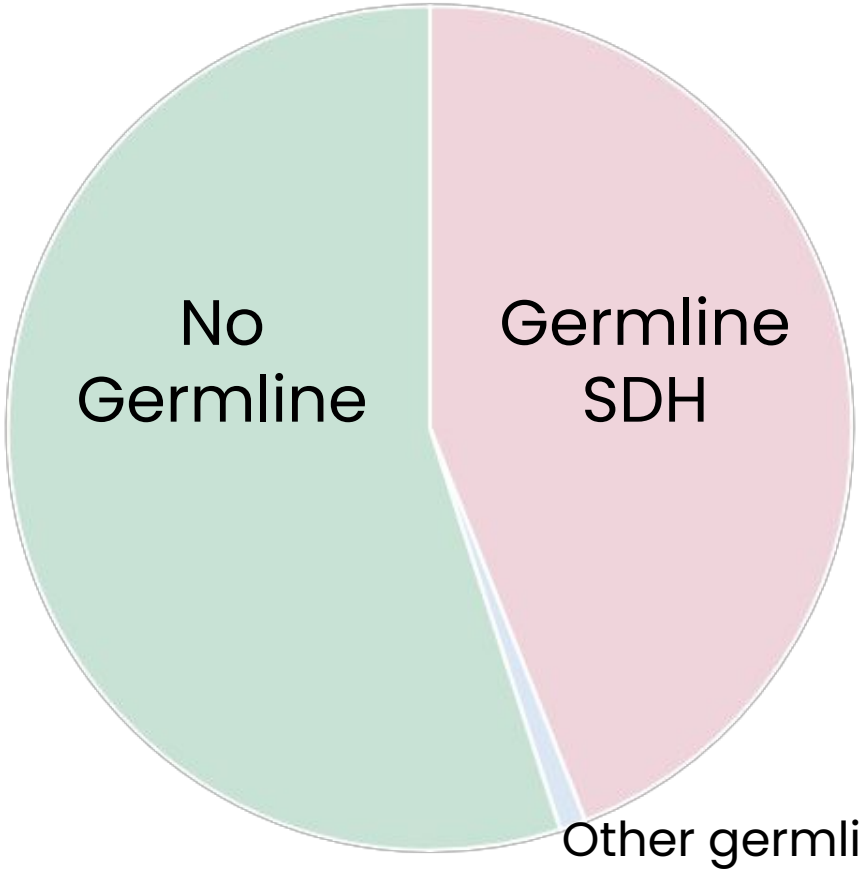
^{68}Ga-DOTA-TATE
^{18}F-DOPA
^{18}F-FDG

Cell receptor/transporter
= Structure on the outside of cancer cells

WHY?
- Multifocal
- Metastasis suspected
- PRRT as therapy considered
- Germline *SDHx* mutation

PRRT = Peptide receptor radionuclide therapy

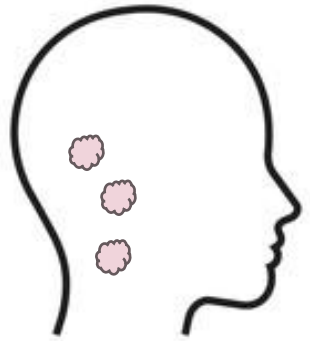
GENETIC BACKGROUND



Succinate dehydrogenase
A
B
C
D
AF2

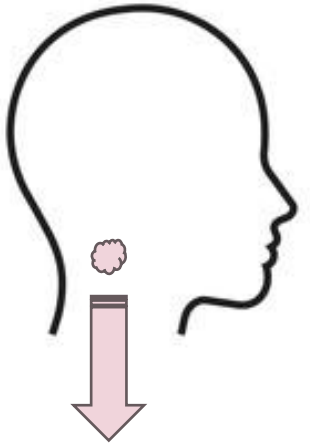
GENETIC TESTING is important!

SDHD



Most common
Multifocal HN-PGLs

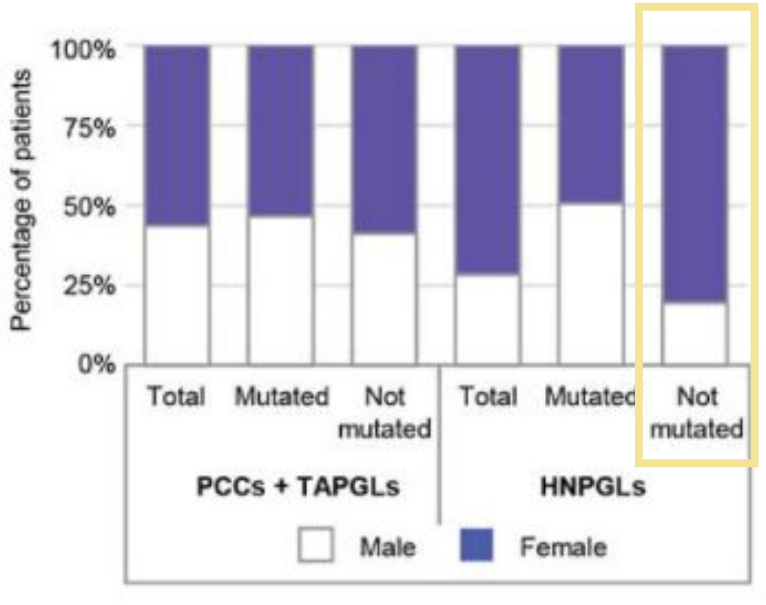
SDHB



Spreading

GENETIC BACKGROUND

HN-PGL without germline predisposition



Mellid et al.. https://doi.org/10.1016/j.gendis.2025.101705

SDHx-like HN-PGLs

- Previously undetected alterations in *SDHx* genes
- SDHB immunohistochemistry positive

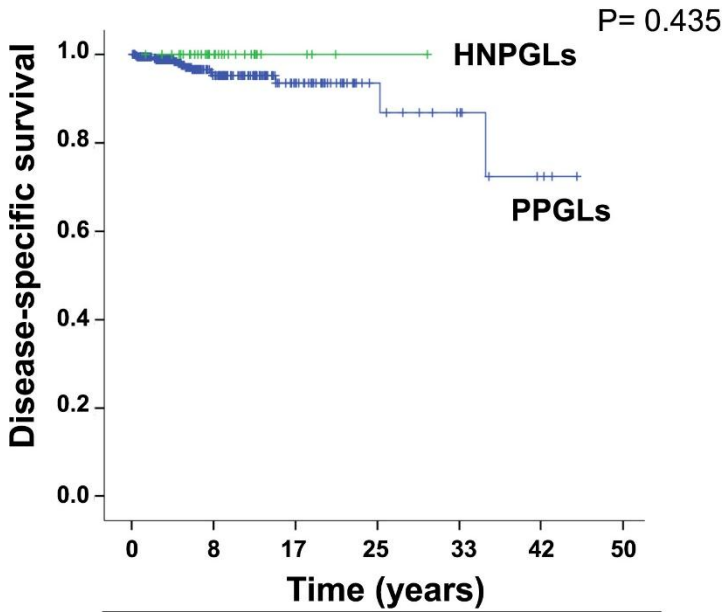
DNMT3A-like HN-PGLs

- Related to chromatin remodelling
- *STAG2* mutations (X chromosome)

Women more often suffer from HN-PGL unrelated to hereditary mutations

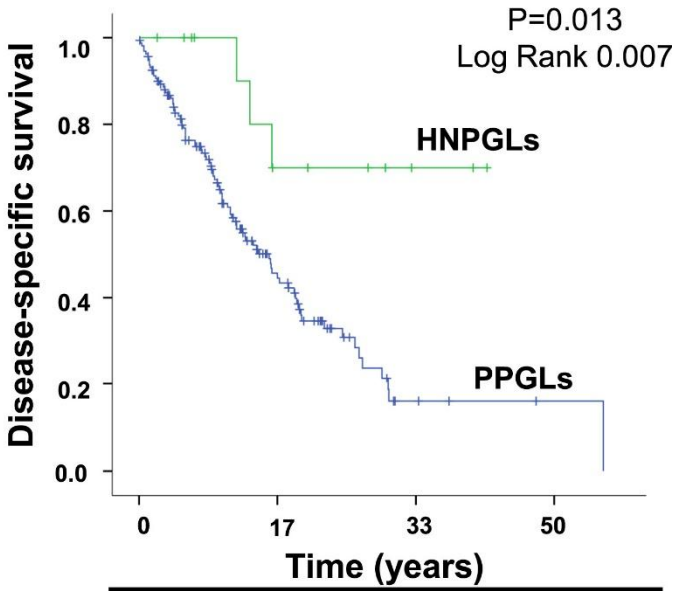
BETTER PROGNOSIS FOR PATIENTS WITH HN-PGL

Patients without metastatic disease



Survival	HNPGLs	PPGLs
5-year	100%	96.8%
20-year	100%	93.7%

Patients with metastatic disease



Survival	HNPGLs	PPGLs
5-year	100%	84.7%
20-year	84.2%	57.3%

Pamporaki et al. DOI: 10.1016/j.ejca.2022.03.032

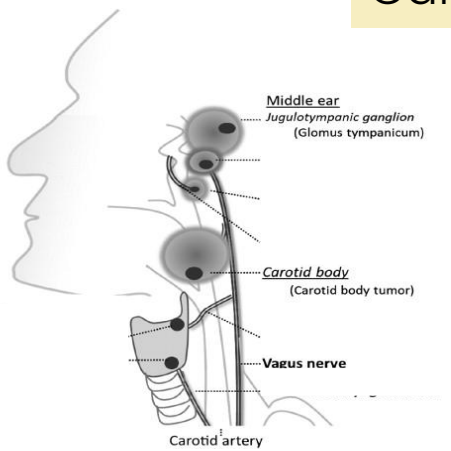
PREDICTORS OF METASTASIS (SPREADING)

Factors analysed:

- Man/woman
- Age when first tumor occurs
- Plasma biochemistry positive
- Tumor size
- Tumor location

Patients without germline PV

Carotid body location



9% of patients with spreading

Patients with germline SDHx PV

Large tumor size

Age (<42y)

SDHB PV

14% of patients with spreading

Richter et al. DOI: 10.1093/ejendo/lvae113

MANAGEMENT RECOMMENDATIONS

Before surgery

- Clinical investigation: previous history of HN-PGL or PPGL
- Imaging of head and neck region
- Plasma biochemistry (Normetanephrine, Methoxytyramine)
  - When Normetanephrine high: consider use of Alpha-blocker (e.g. Phenoxybenzamine) before surgery to prevent complications during surgery

MANAGEMENT RECOMMENDATIONS

Before surgery

- Germline genetic testing for PPGL genes

No germline PV

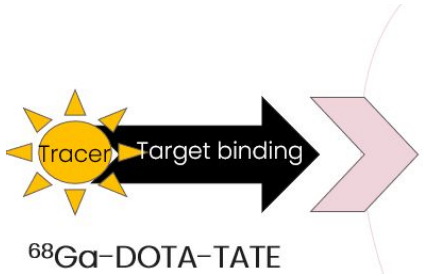
+ low likelihood of multiple tumours and spreading
+ not carotid body location

PET/CT not routinely required

"Active observation" can be considered

SDHx germline PV

PET/CT to identify other tumors or spreading



- Management by multi-disciplinary team -
Surgery, PRRT, external beam radiotherapy

MANAGEMENT RECOMMENDATIONS - TREATMENT

1. Surgery is generally the preferred treatment. Potential for cure.

2. Especially patients with germline SDHx should be treated early when tumors are still small.

Note: New targeted therapy available for inoperable or metastatic PPGLs: Belzutifan (Welireg).

MANAGEMENT RECOMMENDATIONS – FOLLOW-UP

No germline PV

- Duration: ~15 years
- Flexible intervals:
  - Clinical investigation
  - MRI of head/neck
  - Plasma biochemistry only if initial tumor was positive
- "Active observation" PET/CT

Regrowth of original HN-PGL or new HN-PGL (40%),
but **no other PPGL** occur.
Spreading can occur.

SDHx germline PV

- Duration: life-long

Interval	
1 year	• Clinical investigation • Plasma biochemistry • Ultrasound of neck
2-3 years	MRI of head/neck, abdomen-pelvis or PET/CT

Catch new tumours (74%) early to prevent spreading!
Not only HN-PGL can occur, also **other PPGL (14%)**!

Richter et al. DOI: 10.1093/ejendo/lvae113

FUTURE DIRECTIONS

- Improvements in prognosis – AI
  - predicting the likelihood of spreading
  - better informed decisions on active observation versus surgery

- New targeted therapies, e.g. directed towards pathways active in SDHx-related tumors

THANK YOU FOR LISTENING.