Genetics of Paragangliomas and Pheochromocytomas

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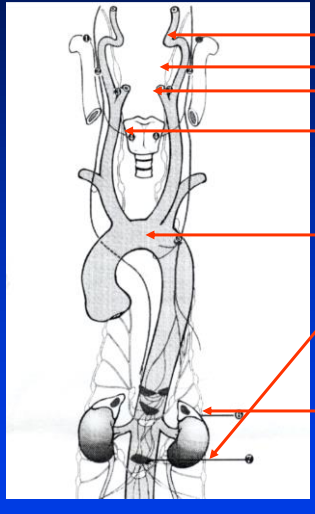
Pheochromocytoma and paraganglioma (PPGLs)

Paraganglions associated with parasympathetic system

10% metastatic dissemination

Paraganglions associated with sympathetic system



jugular
vagal
carotid
tracheal

Head and neck Paraganglioma (usually non secreting)

aortic

Zuckerland

Paraganglioma (Extra-adrenal pheochromocytoma)

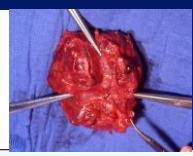
adrenal

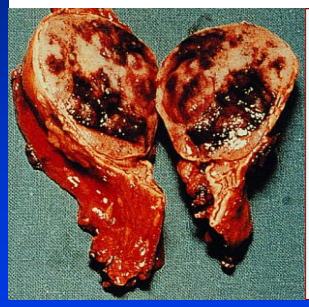
Pheochromocytoma (secreting catecholamines)

Adapted from Defraigne et al, *Rev Med Liège* 1997; 52:485-497

Pheochromocytoma

- Rare endocrine tumour
- Annual incidence: 2-8/Million
- 0.1-0.6 % of hypertensive patients
- 5% of incidentaloma





Suggestive signs/ symptoms:

Recent, labile, refractory hypertension

Paradoxical blood pressure response

(chir, anesth, beta-blockers)

Adrenal mass

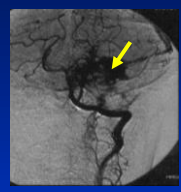
Family history of pheochromocytoma

Lenders et al., *Lancet* 2005; 366: 665-675

Head and neck paraganglioma

(1/30 000)

- Neural crest tumors
- Main localizations
  - carotid bifurcation
  - jugular foramen
  - middle ear



- Usually benign, non secreting
- Local complications and intracranial extension
- High-risk surgery in advanced forms
- Familial (30 %)

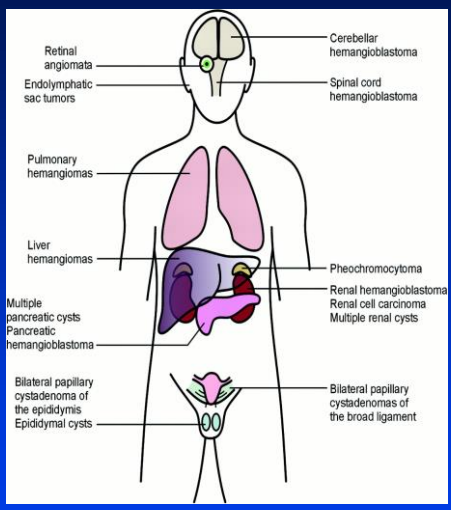
Genes associated with syndromic forms of phaeochromocytoma

Gene	Chromosome	Mutations*	Malignancy *
VHL	3p25-26	2-11 %	5 %
RET	10q11.2	< 5 %	3 %
NF1	17q11.2	Unknown	11%

*in apparently sporadic phaeochromocytoma

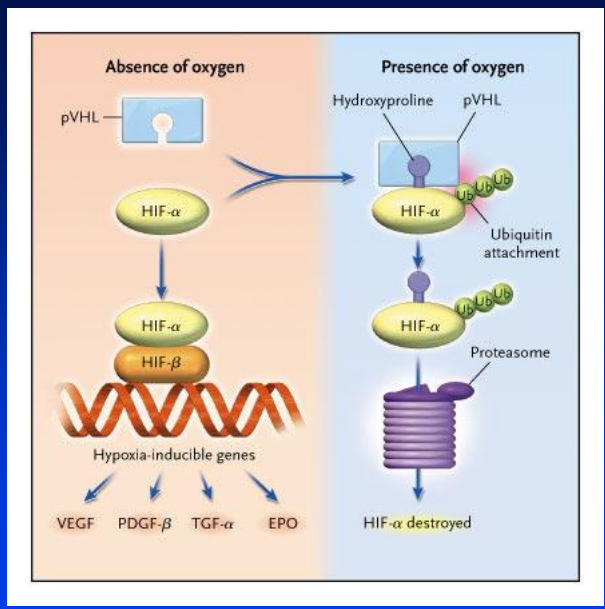
Lenders et al., *Lancet* 2005; 366: 665-675

von Hippel-Lindau (*VHL*)



DISEASE PHENOTYPE	TUMOUR RISK PHE	HAB	RCC
1	LOW	HIGH	HIGH
1			
1			
1			
1			
1			
1			
2A	HIGH	HIGH	LOW
2A			
2B	HIGH	HIGH	HIGH
2B			
2C	YES	NO	NO
2C			
2C			

Friedrich Ca *et al*. *Hum. Mol. Genet*. 2001 10: 763-767.
Clifford SC *et al*. *Hum. Mol. Genet*. 2001 10: 1029-1038.



George DJ, Kaelin WG Jr. *N Engl J Med*. 2003; 349:419-421

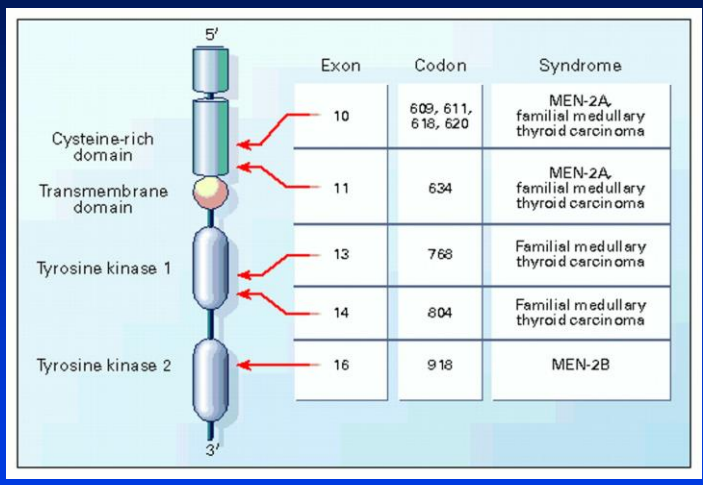
Multiple endocrine neoplasia type 2

A: Medullary thyroid carcinoma
Phaeochromocytoma
Hyperparathyroidism
Cutaneous lichen amyloidosis
FMTC: Familial medullary thyroid carcinoma only

B: Medullary thyroid carcinoma
Phaeochromocytoma
Multiple neuromas
Marfanoid habitus

Lenders et al., *Lancet* 2005; 366: 665-675

Mutations of the RET Proto-Oncogene Associated with MEN-2.



Eng, C. N Engl J Med 1996;335:943-951

The NEW ENGLAND JOURNAL of MEDICINE

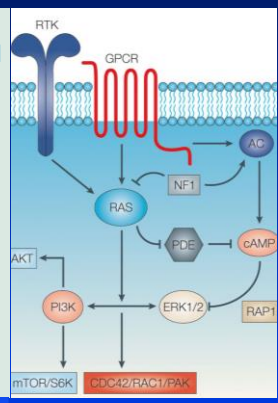
Neurofibromatosis type 1: < 1% pheochromocytoma

NIH diagnostic criteria (2 or more)

- Six or more café-au-lait macules (>0·5 cm at largest diameter in a prepubertal child or >1·5 cm in post-pubertal individuals)
- Axillary freckling or freckling in inguinal regions
- Two or more neurofibromas of any type or one or more plexiform neurofibromas
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion (sphenoid wing dysplasia, long-bone dysplasia)
- An optic pathway glioma
- A first-degree relative with neurofibromatosis type 1 diagnosed by the above criteria

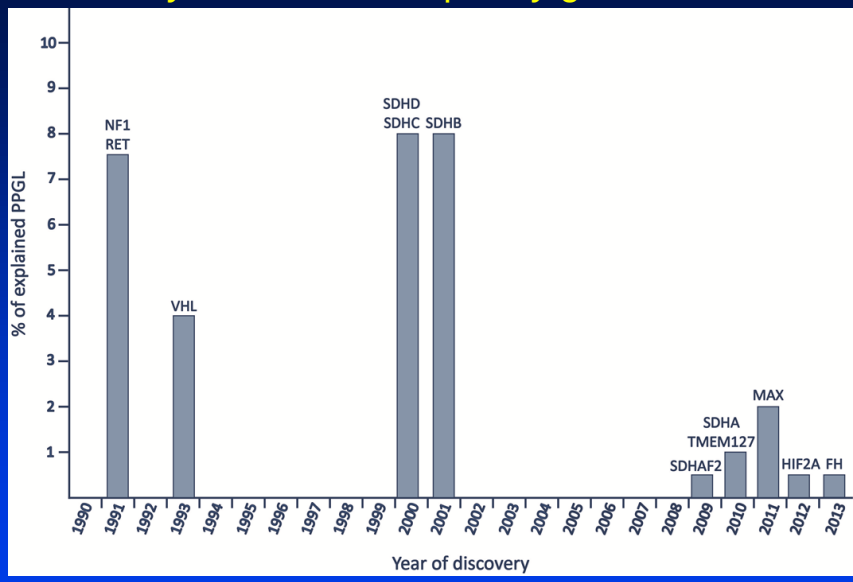
Hirbe and Gutmann
Lancet Neurol. 2014;13: 834-43

NF 1
- 57 exons
- 350 kb
- > 300 mutations



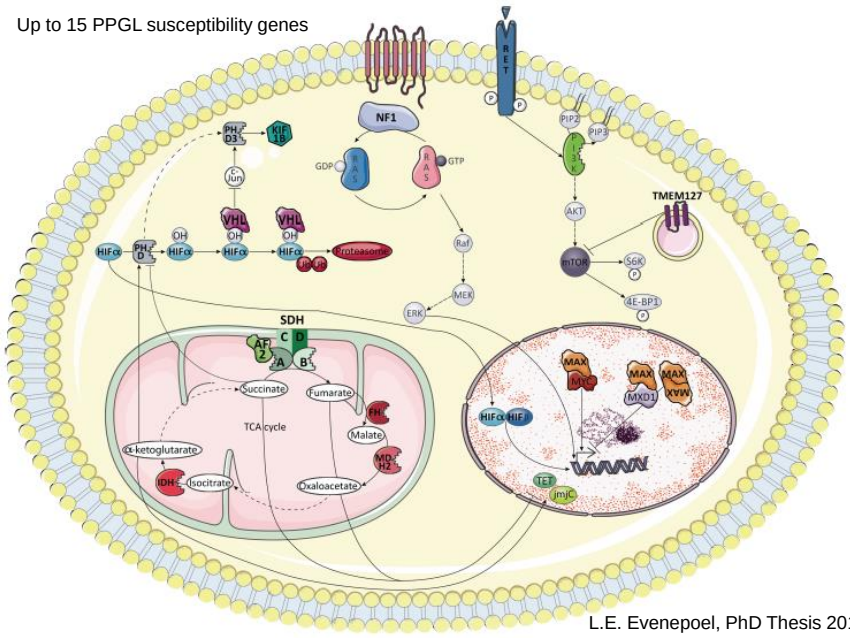
Rubin and Gutmann
Nature Reviews Cancer 2005: 5, 557-564

Discovery of PPGL susceptibilty genes: timeline



L. Evenepoel and A. Persu
Adapted from Favier et al. *Nature Reviews Endocrinology* 2015; 11, 101–111

Up to 15 PPGL susceptibility genes

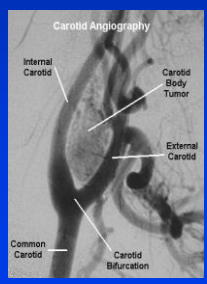


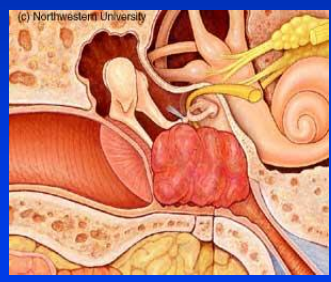
L.E. Evenepoel, PhD Thesis 2018

Mutations in *SDHD*, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma

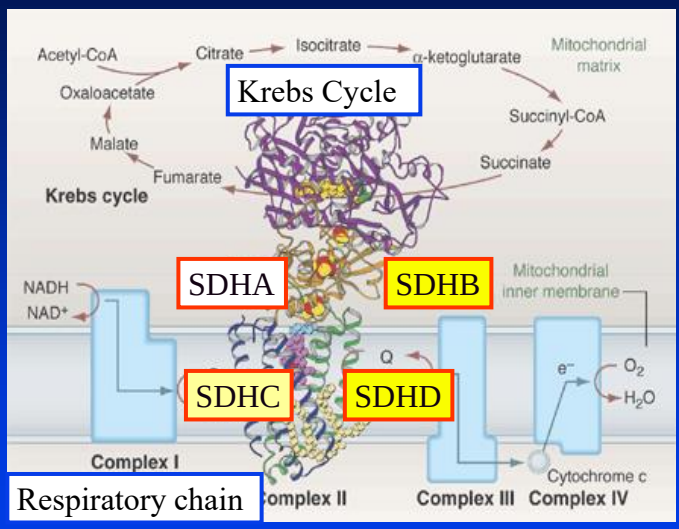
Bora E. Baysal,[1]* Robert E. Ferrell,[2] Joan E. Willett-Brozick,[1] Elizabeth C. Lawrence,[2] David Myssiorek,[5] Anne Bosch,[6] Andel van der Mey,[7] Peter E. M. Taschner,[6] Wendy S. Rubinstein,[3] Eugene N. Myers,[4] Charles W. Richard III,[9] Cees J. Cornelisse,[8] Peter Devilee,[6] B. Devlin[1]

4 FEBRUARY 2000 VOL 287 SCIENCE www.sciencemag.org



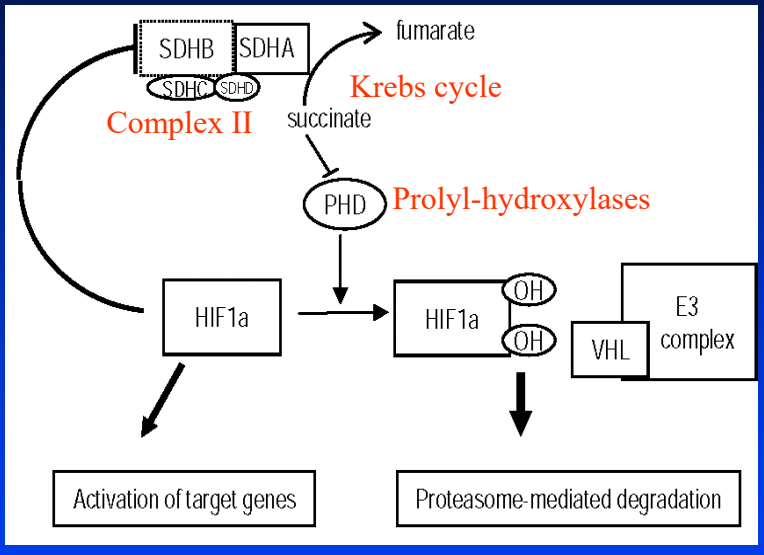


SDHx subunits



L. Hederstedt. *Science*. 2003;299:671-2

Link pheochromocytoma and *SDH* genes?



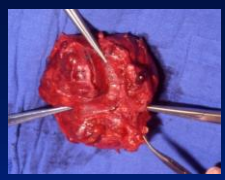
Dahia PLM et al.. *PloS Genet*.2005; 1: e8

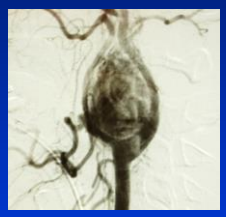
PPGLs: main/ classical susceptibility genes

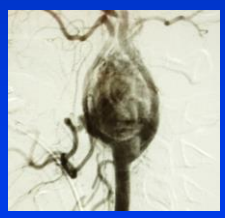
Genes	Mutations	Malignancy	Inheritance
VHL	7 %	Low	AD
RET	6 %	Low	AD
NF1	3%	Low	AD
SDHB	10 %	High	AD
SDHD	9 %	Low	AD + MI

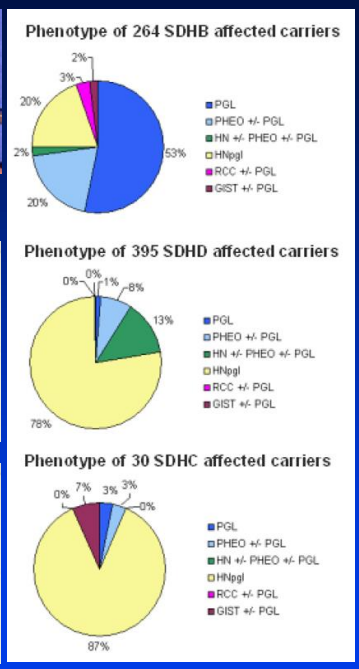
AD: autosomal dominant; MI: maternal imprinting

Adapted from:
Pacak K *et al. Nat Clin Pract Endocrinol Metab* 2007; **3:** 92–102
Favier et al. *Nature Reviews Endocrinology* 2015; 11, 101–111.



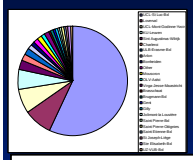




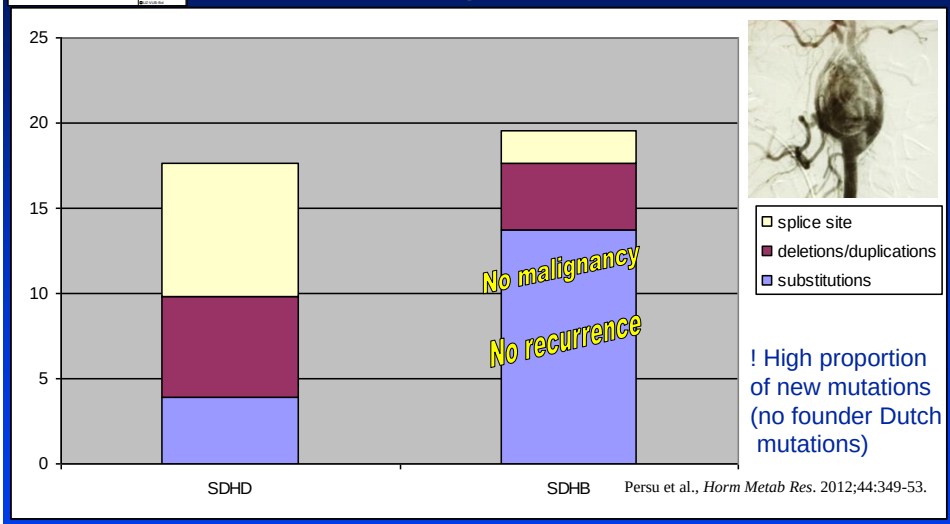


SDHB mutations:
More frequent
in thoraco-abdominal
paraganglioma
Increased risk of recurrence
and malignancy.

Modified from
Pasini and Stratakis
JIM 2009; 266: 19-42



Genetic profile of sporadic head and neck paragangliomas in Belgium



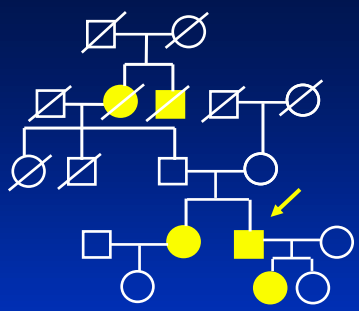
! High proportion
of new mutations
(no founder Dutch
mutations)

Persu et al., *Horm Metab Res*. 2012;44:349-53.

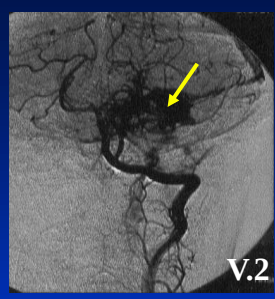
Parental imprinting

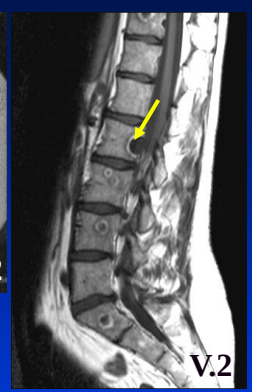
Selective inactivation of one parental allele of a gene (usually by methylation)

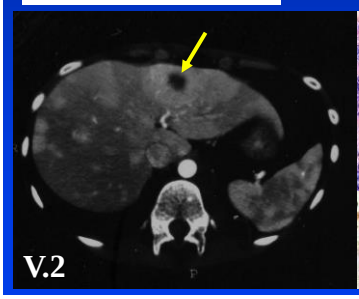
SDHD deletion: dominant inheritance + maternal imprinting

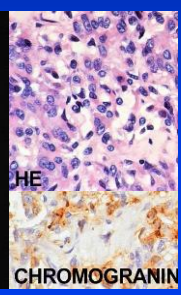


Lemaire et al., JIM 1999; 246: 113-6

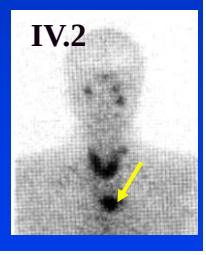








Multiple Rare Localizations

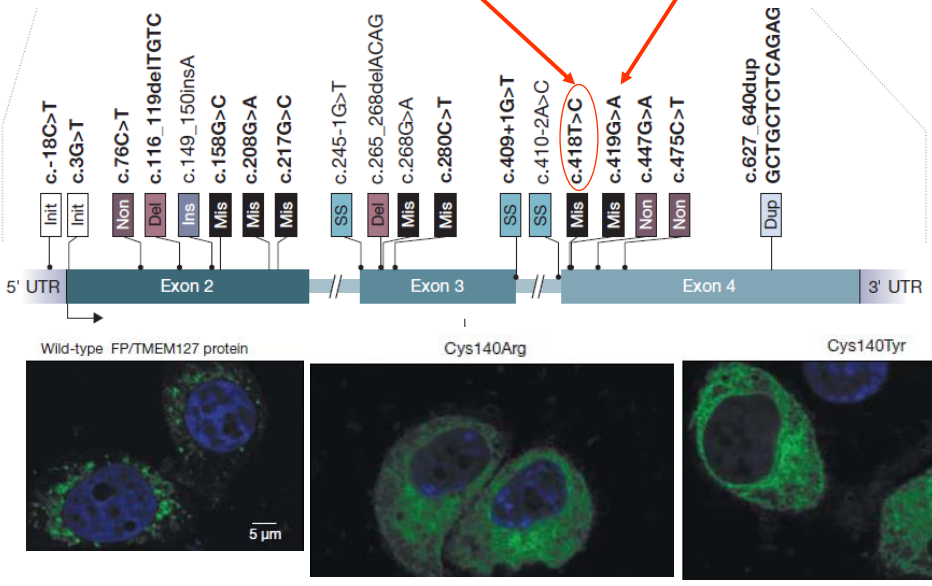


TMEM 127

Yao L, …Vikkula M,…Persu A,…Dahia PL. *JAMA*. 2010; 304:2611-9.

47 yo Belgian female with benign unilateral adrenal pheochromocytoma

Diffuse bone metastasis



PPGLs: susceptibility genes and associated phenotype

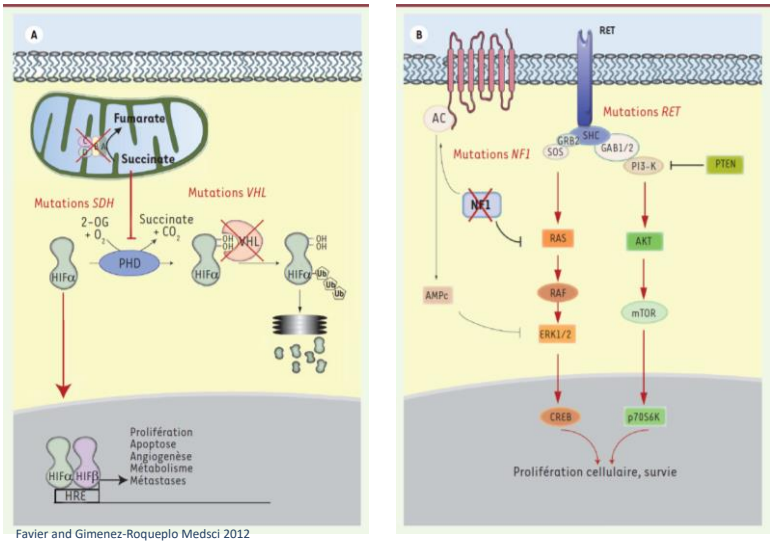
Genes	Predominant tumour site	Tumour number (multiple versus single)	Family history (relative frequency)	Malignancy risk	Related conditions
NF1	Pheochromocytoma > paraganglioma	Single	High	Moderate	Neurofibromas, MPNSTs and gliomas
RET	Pheochromocytoma	Multiple	High	Low	MTC, hyperparathyroidism and marfanoid habitus
VHL	Pheochromocytoma > paraganglioma	Multiple	High	Low	RCCs and CNS hemangioblastomas
SDHA	Paraganglioma	Single	Low	?*	GISTs
SDHB	Paraganglioma > pheochromocytoma	Multiple	Low	High	GISTs and RCCs
SDHC	Paraganglioma	Multiple	Low	Low	GISTs
SDHD	Paraganglioma > pheochromocytoma	Multiple	High	Low	GISTs and pituitary adenomas
SDHAF2	Paraganglioma	Multiple	High	?	None reported
TMEM127	Pheochromocytoma	Single	Moderate to low	Low	None reported.* RCC recently described, although not in association with pheochromocytoma.
MAX	Pheochromocytoma > paraganglioma	Single	Moderate to low	Low	None reported
HIF2	Paraganglioma > pheochromocytoma	Multiple	?	?	Polycythemia and somatostatinomas
KIF1B	Pheochromocytoma?	?	?	?	Neuroblastoma?
PHD2	Paraganglioma?	?	?	?	Polycythemia
HRAS	Pheochromocytoma?	Single	?	?	None reported; gene mutated in multiple cancers‡
FH	Pheochromocytoma?	?	?	?	Uterine leiomyoma

Patricia L. M. Dahia. Nature Reviews Cancer 14, 108–119 (2014)

Future: microarray profiling

Cluster 1 → pseudohypoxia pathway

Cluster 2 → MAPK pathway



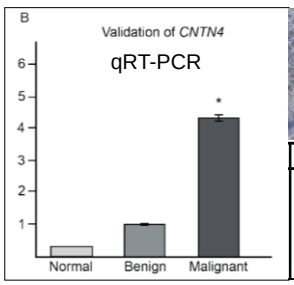
Favier and Gimenez-Roqueplo Medsci 2012

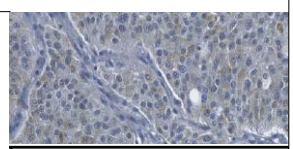
Expression of Contactin 4 is associated with malignant behavior in pheochromocytomas and paragangliomas.

L. Evenepoel,…,M. Vikkula,…, W. N.M. Dinjens, Alexandre Persu* and Esther Korpershoek*

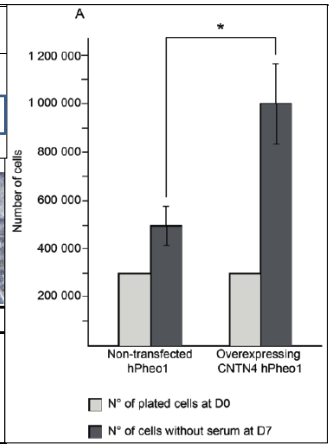
J Clin Endocrinol Metab. 2018;103: 46-55.

Gene	mRNA expression array	
	FDR	FC
CNTN4 (Contactin 4)	0.001	4.62

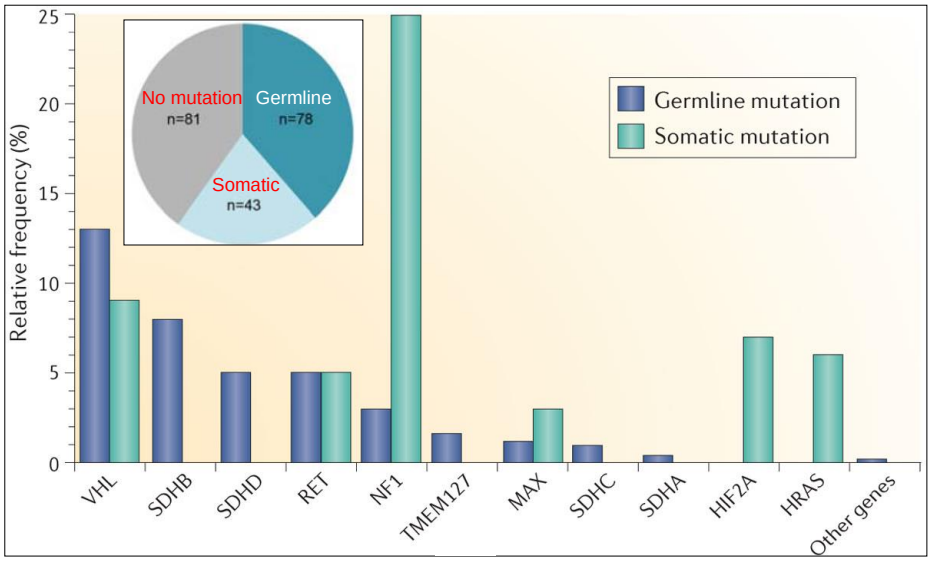




TMA
p=0.002 (81 benign and 13 malignant) positive: 58% of malignant *vs.* 17% of benign

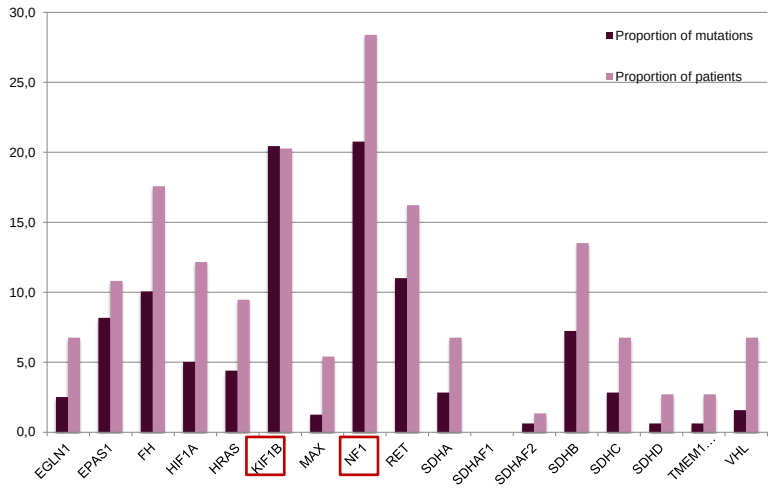


Frequency of germline and somatic mutations in PPGLs



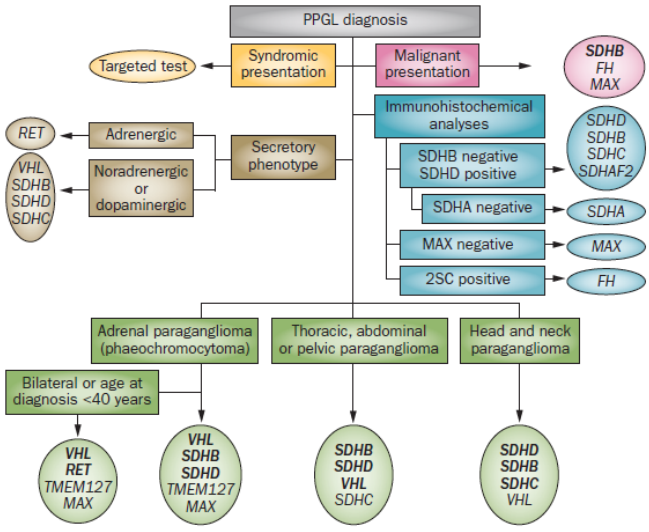
Burnichon et al., *HMG* 2012; 21: 5397-5405
Dahia P. *Nat Rev Cancer*. 2014:108-19.

54% of somatic mutations in a Belgium series of PPGLs



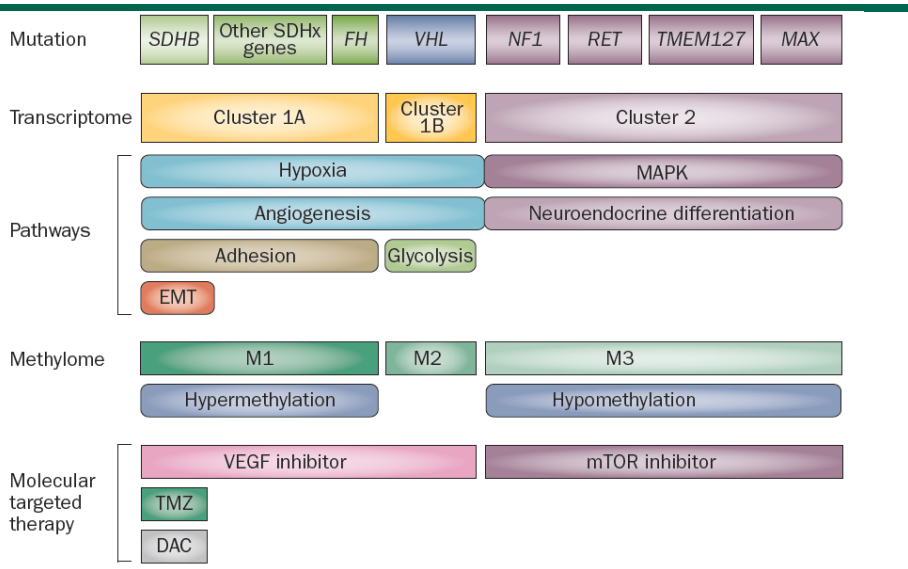
Evenepoel L, Helaers R, Vroonen L, Aydin S, Hamoir M, Maiter D, Vikkula M, Persu A.
Endocr Relat Cancer. 2017 Aug;24(8):L57-L61.

Genetic screening algorithm



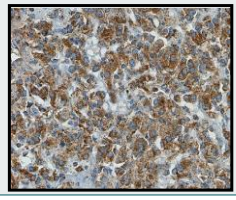
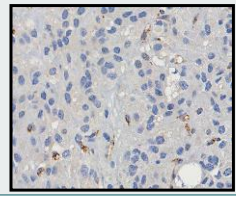
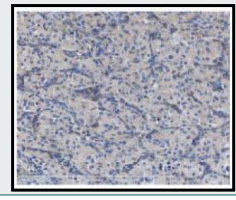
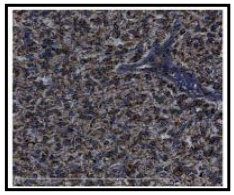
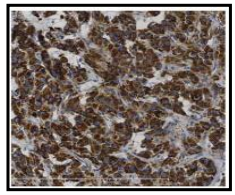
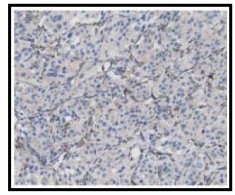
Favier, Amar and Gimenez-Roqueplo, Nat Rev Endocrinol 2014

From integrated genomics to targeted therapies



Favier, Amar and Gimenez-Roqueplo, Nat Rev Endocrinol 2014

Immunohistochemistry (IHC)

	Wild –type	SDHB, D or C mutation	SDHA mutation
SDHB IHC			
SDHA IHC			

Nederveen F. et al. *Lancet Oncol*. 2009;10(8):764-71
Korpershoek E.et al. *J Clin Endocrin Metab*. 2011;96(9):1472-6

A new way to do genetics: *SDHx* immunohistochemistry

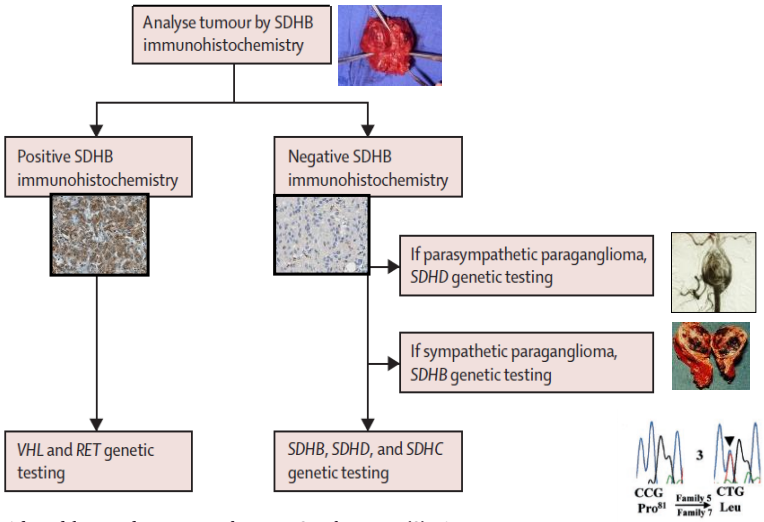
	Number of tumours	SDHB immunohistochemistry negative	SDHB immunohistochemistry positive	Sensitivity (95% CI)	Specificity (95% CI)
Retrospective					
SDH-related					
SDHB	34	34	0	100% (90–100)	..
SDHC	4	4	0	100% (40–100)	..
SDHD	38	38	0	100% (91–100)	..
Non-SDH related					
RET	12	0	12	..	100% (74–100)
VHL	24	0	24	..	100% (86–100)
NF1	29	0	29	..	100% (88–100)
Sporadic	34	3	31	..	91% (76–98)
Prospective					
SDH-related	26	26	0	100% (87–100)	..
Non-SDH related	19	3	16	..	84% (60–97)

Table 2: SDHB immunohistochemistry test results according to subgroups within SDH-related and non-SDH-related tumours

Nederveen F. et al.; Lancet Oncol. 2009;10:764-71.

Further validated in Papathomas TG, Oudijk L, Persu A, …. Vikkula M, … de Krijger RR. *Mod Pathol*. 2015 Jun;28(6):807-21.

Screening strategy based on IHC?
(limited to operated PPGLs)



Adapted from Nederveen F. et al. *Lancet Oncol.* 2009;10(8):764-71

Genetic screening of PPGLs: a pragmatic approach

Syndromic presentation: oriented genetic screening
(MEN II> RET; von Hippel-Lindau> VHL)

All other PPGLs:
Screening of SDHD, SDHB, SDHC and VHL
- Exon sequencing
- MLPA (search for deletions ~ 10% of cases)

Screening of other susceptibility genes in « negative » cases, especially if early, familial, bilateral, recurrent or metastatic PPGL.

In operated patients, SDHx by immuno-histochemistry if available.

Since 2018 at the CUSL: Next Generation Sequencing
(exhaustive panel including all known susceptibility genes).

Adapted from J Vlayen (KCE), M Bex (UZ Leuven), B Bravenboer (UZ Brussel), K Claes (UZ Gent), B Lapauw (UZ Gent), A Persu (Cliniques universitaires Saint-Luc), K Poppe (CHU Saint-Pierre), U Ullman (Institut de Pathologie de Gosselies), T Van Maerken (UZ Gent), L Vroonen (Université de Liège), Be Poppe (UZ Gent). Oncogenetic testing for persons with hereditary endocrine cancer syndromes (http://kce.fgov.be/fr/publication/report/tests-oncog%C3%A9n%C3%A9tiques-pour-personnes-ayant-une-pr%C3%A9disposition-h%C3%A9r%C3%A9ditaire-aux-canc).