Hereditary Neuroendocrine Tumors

Cancer Risk and Prevention Symposium
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Disclosures

Gwen Reiser has no financial disclosures

Dr. Whitney Goldner is the Vice-Chair of the NCCN Neuroendocrine and Adrenal Tumors Guideline Panel

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Objectives

1. Identify clinical features, natural history and inheritance patterns for inherited neuroendocrine tumors.

2. Assess evidence-based surveillance and management guidelines for patients with inherited neuroendocrine tumors.

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What classifies as an Endocrine Tumor?

Thyroid nodules/ Thyroid Cancer

Parathyroid masses/tumors (mostly benign)
- Primary hyperparathyroidism: adenoma or hyperplasia

Pituitary masses/tumors (mostly benign, minority cancer)
- Secretory or non secretory: prolactin, ACTH, TSH, gonadotropins

Adrenal masses/tumors (mostly benign, ACC: Adrenal Cortical Carcinoma)
- Usually secrete multiple hormones (cortisol, androgens, aldosterone)

Neuroendocrine tumors: NETs (benign or cancers)
- Gastroenteropancreatic (GI, Thymus, Pancreatic)
- Pheochromocytoma/Paraganglioma (secretory: metanephrines, normetanephrines; non-secretory)

Some of these present as part of an Endocrine Tumor Syndrome
- Important to screen for other components of the syndrome

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Conditions Associated with NET

Condition	Gene (s)	Neuroendocrine Neoplasia	Other Features
Multiple Endocrine Neoplasia Type 1 (MEN1)	*MEN1*	Parathyroid adenoma/hyperplasia Pancreatic or duodenal neuroendocrine tumors (Gastrinoma, Insulinoma, Glucagonoma, VIPoma/somatostatinoma) Pituitary adenomas Gastric carcinoids Bronchial/thymic carcinoids Adrenal adenomas	Facial angiofibromas Collagenomas Lipomas Meningiomas
Multiple Endocrine Neoplasia Type 2 (MEN2)	*RET*	Medullary thyroid carcinoma Pheochromocytoma Parathyroid adenoma/hyperplasia	Cutaneous lichens amyloidosis Hirschsprung disease Intestinal ganglioneuromas Mucosal neuromas Marfanoid habitus
Multiple Endocrine Neoplasia Type 4 (MEN4)	*CDKN1B*	Parathyroid adenoma/hyperplasia Pituitary adenomas Pancreatic or duodenal NET Papillary thyroid carcinoma	Meningioma Later onset than MEN1
Hereditary Paraganglioma and Pheochromocytoma	*SDHA, SDHB, SDHC, SDHD, SDHAF2, MAX, TMEM127*	Paraganglioma Pheochromocytoma	GIST Renal cell Carcinoma Paternal imprinting (SDHD)
vonHippel Lindau (VHL)	*VHL*	Pancreas RCC Paraganglioma/pheo	Hemangioblastoma (cerebellar/spinal) Retinal hemangioma
Tuberous Sclerosis (TS)	*TSC1, TSC2*	Pancreatic neuroendocrine tumors Paraganglioma/pheo Pituitary adenomas Parathyroid adenoma/hyperplasia	Renal angiomyolipoma and RCC Facial angiofibromas Ashleaf spot Shagreen patch
Neurofibromatosis Type 1 (NF1)	*NF1*	Pheochromocytoma Paraganglioma Pancreas NET	Neurofibromas Optic glioma Lisch nodules Café au lait macules Axillary/inguinal freckling Rhabdomyosarcoma GIST Breast GIST Nerve sheath Juvenile chronic myelomonocytic leukemia
Carney Complex	*PRKAR1A*	Thyroid	Blue nevi Myxomas Sertoli cell tumors Schwannomas
Familial Hyperparathyroidism	*AP2S1, CASR, CDC73, GNA11*	Parathyroid	Jaw tumor, renal cysts, Wilms tumor (CDC73)

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Genetic Testing Guidelines for NET

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Neuroendocrine and Adrenal Tumors

Genetics inMedicine | ACMG PRACTICE GUIDELINES

A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

Heather Hampel, MS, LGC[1], Robin L. Bennett, MS, LGC[2], Adam Buchanan, MS, MPH[3], Rachel Pearlman, MS, LGC[1], and Georgia L. Wiesner, MD[4]; for a Guideline Development Group of the American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and of the National Society of Genetic Counselors Practice Guidelines Committee

ENDOCRINE SOCIETY

Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline

Jacques W.M. Lenders [1], Quan-Yang Duh, Graeme Eisenhofer, Anne-Paule Gimenez-Roqueplo, Stefan K.G. Grebe, Mohammed Hassan Murad, Mitsuhide Naruse, Karel Pacak, William F. Young [2]

Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)

Rajesh V. Thakker ✉, Paul J. Newey, Gerard V. Walls, John Bilezikian, Henning Dralle, Peter R. Ebeling, Shlomo Melmed, Akihiro Sakurai, Francesco Tonelli, Maria Luisa Brandi ✉

The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 9, 1 September 2012, Pages 2990–3011, https://doi.org/10.1210/jc.2012-1230

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When To Think About Genetic Testing for NET Individuals with any of the following:

- Adrenocortical carcinoma
- Paraganglioma/ Pheochromocytoma
- Parathyroid adenoma or primary hyperparathyroidism before age 30 or multiple parathyroid adenomas
- Medullary thyroid carcinoma
- Two or more of the following:
  - Primary hyperparathyroidism
  - Duodenal/pancreatic neuroendocrine tumor
  - Pituitary adenoma
  - Foregut carcinoid (bronchial, thymic or gastric)
- Gastrinoma
- Duodenal/pancreatic NET

NCCN National Comprehensive Cancer Network® **NCCN Guidelines Version 1.2023 Neuroendocrine and Adrenal Tumors**

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Case 1

35 y/o male
Newly diagnosed Pancreas Neuroendocrine Tumor
History of kidney stones
Referred to Genetics

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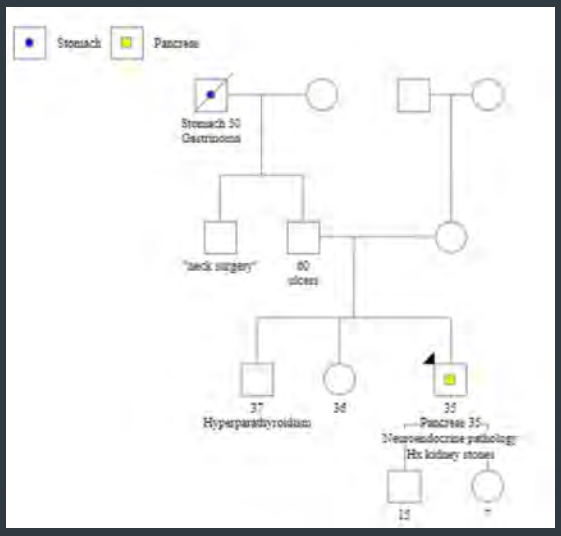
Case 1 Family History



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Genetic Test Results

MEN1+

RESULT: POSITIVE

MEN1	c.237del (p.Val80Trpfs*39)	heterozygous	PATHOGENIC

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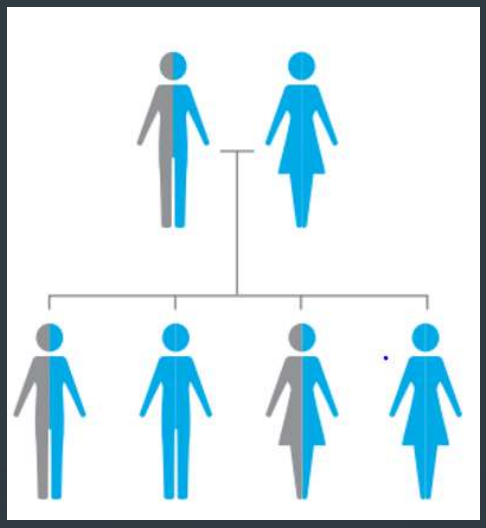
Inheritance of MEN1

Autosomal Dominant

1 in 2 (50%) chance

Variable expression

Reduced penetrance



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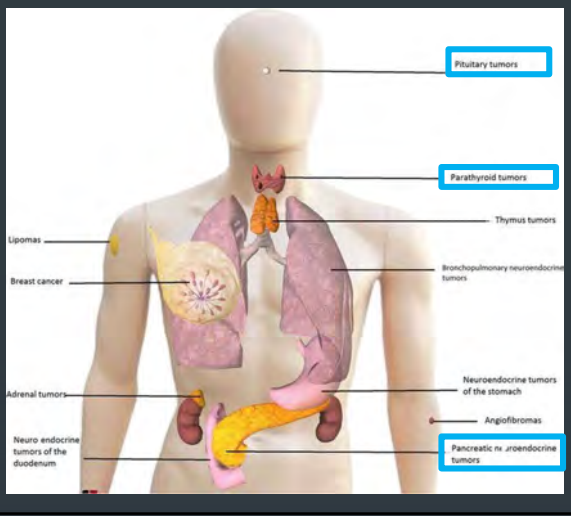
MEN1 Gene and Multiple Endocrine Neoplasia Type 1
Wermer syndrome
MEN1

Parathyroid tumors >95%

Pituitary tumors 30-40%

Pancreatic NETs 30-75%

Other:
Adrenal adenomas 27-36%
Angiofibromas
Collagenomas
Lipomas
Meningiomas



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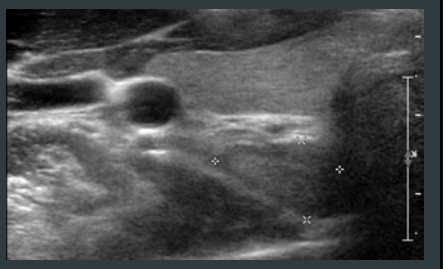
Parathyroid Tumors



- 4 gland hyperplasia

Workup for primary hyperparathyroidism

- Elevated serum calcium, high or inappropriately normal PTH, elevated urine calcium, (25OHD nl or low)
- Low BMD, kidney stones, ? Renal insufficiency
- Ultrasound or 4DCT best for showing masses
- Sestamibi by itself not very sensitive, fused with 4D CT the best

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Pituitary

Can be secreting or non secreting

- Prolactin
- IGF-1
- TSH (with Free T4)
- LH/FSH (with testosterone or estradiol (or evaluate for menses in women)
- Alpha subunits (often elevated in TSHoma, gonadotropinoma)
- ACTH (also with evaluation for hypercortisolemia)

Image with MRI sella with contrast

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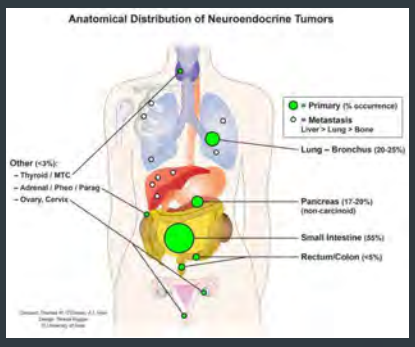
Neuroendocrine Tumors

GI Neuroendocrine tumors (GI-NET):
Pancreatic Neuroendocrine tumors (pNET)
Thymic Neuroendocrine tumors
Also called GEPNET(gastroenteropancreatic tumors)

- Gastric, duodenal, pancreatic, jejuno-ileal, colorectal
- Previously called carcinoid tumors



All NETs have the potential to secrete specific hormones into circulation

- Location is associated with hormone secreted
- Up to 80% of pNETs are non functional (non secreting)
  - Secretory: insulinomas, gastrinomas, glucagonomas, VIPomas, somatostatinomas
- Many GI-NETs can be associated with flushing, diarrhea, and wheezing (carcinoid syndrome)

The majority of pNET (77%) and intestinal NETs (91%) present with distant metastasis

- Liver, lymph nodes, peritoneum, mesentery
- Bone and lung less common

Metastasis can be associated with a desmoplastic reaction (fibrosis)

- May be related to hormones, tachykinins, TGFB

Pancreatic lesions in MEN1 more likely to be multicentric

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Hormonal secretions in functional PNETS

Hormone	Features	% of F-PNET	% Malignant	Additional Notes
Insulin	Recurrent hypoglycemia	40%	10%	
Glucagon	Diarrhea, glossitis, necrolytic migratory erythema, weight loss, hyperglycemia, blood clots	~5%	80%	
VIP	Diarrhea, hypokalemia, achlorhydria	<5%	80%	Also in colon, liver, adrenal tumors
ACTH	Cushingoid facies, weight gain, diabetes, hypertension	<1%	>80%	Co-existing ZE 35%, insulinoma 5%
GHRH	Acromegalic features, diabetes	<1%		Also in lung NETs, 75% have MEN1
PTHRP	Hypercalcemia	<1%		Also in multiple other cancers
Gastrin	Pain, Diarrhea (ZE Syndrome)	20%	>90%	Also in duodenum NETs, 25% have MEN1
Somatostatin	Diabetes, cholelithiasis, steatorrhea, weight loss	<5%	75%	Also in duodenum, jejunum, 50% have NF1
Serotonin	Flushing, diarrhea (Carcinoid syndrome)	<1%	>95%	8% with elevated urine 5HIAA without syndrome

ACTH: adrenocorticotrophic hormone; F-PNET: functional pancreatic neuroendocrine tumor; GHRH: growth hormone releasing hormone; 5HIAA: 5-hydroxyindoleacetic acid; MEN1: multiple endocrine neoplasia type 1; NF1: neurofibromatosis type 1; PTHRP: parathyroid hormone-related peptide; ZE: Zollinger Ellison; VIP: vasoactive intestinal polypeptide.

Data from Refs 14,30,32–34

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Case 2

Healthy 35 y/o female referred to Endocrine Clinic

Daughter found to have a thyroid nodule and biopsy showed medullary thyroid carcinoma

Thyroid nodule biopsy testing showed a RET mutation

Germline testing revealed a RET V804 mutation

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Are all genetic tests the same?

Germline mutation: mutation in your DNA that is in all your cells and you can pass on to your relatives

Somatic (tumor) mutation: mutations that can occur in your tumor, but may not be in your DNA.

**If you have a tumor mutation, then you should also have your germline DNA tested to see if this is something that your family can inherit

The genetics testing that is done on thyroid nodule biopsies is looking for somatic (tumor) mutations

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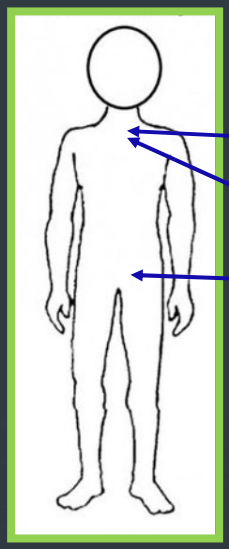
RET Gene and Multiple Endocrine Neoplasia Type 2

MEN2

(Sipple syndrome)



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Multiple Endocrine Neoplasia Type 2

RET gene

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Evaluation

- Always screen for Pheochromocytoma PRIOR to any invasive procedures or surgery!!
  - If they have a pheochromocytoma, this should be evaluated and treated first before other conditions
- Screen for hyperparathyroidism (same as with MEN1)
- Evaluate for medullary thyroid carcinoma

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Medullary Thyroid Carcinoma

Calcitonin producing tumor of the parafollicular C cells of the thyroid gland
Multifocal C cell hyperplasia is a precursor to cancer
Serum Calcitonin (basal or stimulated) are elevated

Diagnosis: Thyroid and neck ultrasound, FNA nodules

Prevention and cure: surgery before c cell hyperplasia progression to malignancy

Autosomal Dominant: RET mutation

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What if you have a RET mutation?

Table 4. Relationship of Common *RET* Mutations to Risk of Aggressive MTC in MEN2A and MEN2B, and to the Incidence of PHEO, HPTH, CLA, and HD in MEN2A

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]	*CLA*[d]	*HD*[d]
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

Germline mutation

THYROID
Volume 25, Number 6, 2015
© American Thyroid Association
DOI: 10.1089/thy.2014.0335

Wells et al. Revised ATA Medullary Thyroid Cancer Guidelines

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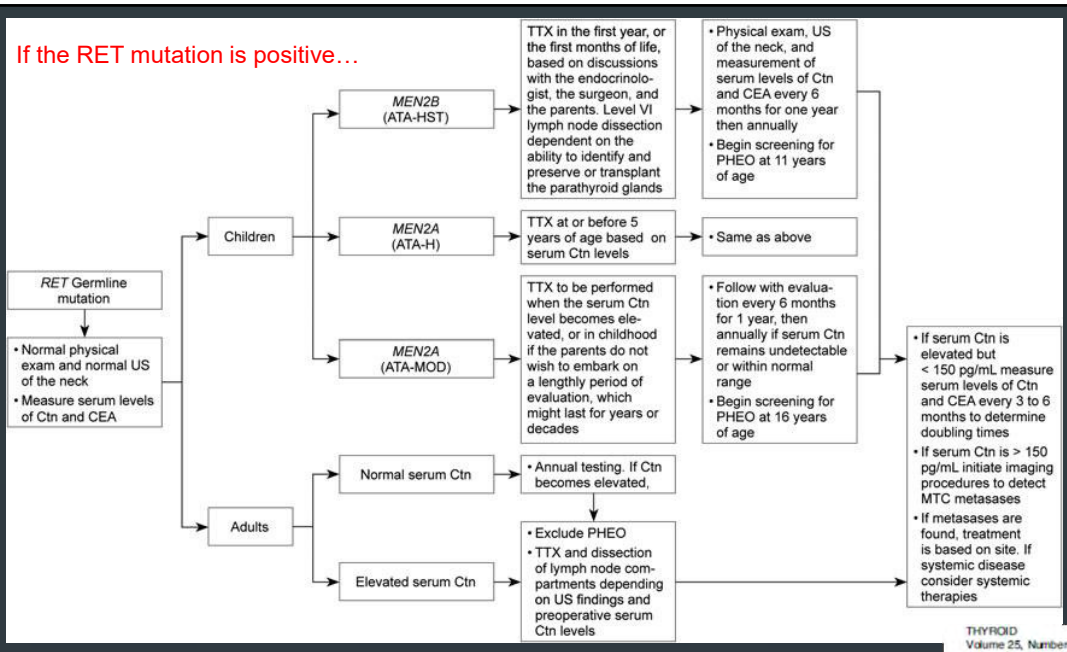
If the RET mutation is positive…



THYROID
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Case 3

38 y/o male referred to Hereditary Cancer Clinic

History of renal cell carcinoma (clear cell) at age 30

Paraganglioma identified at age 35

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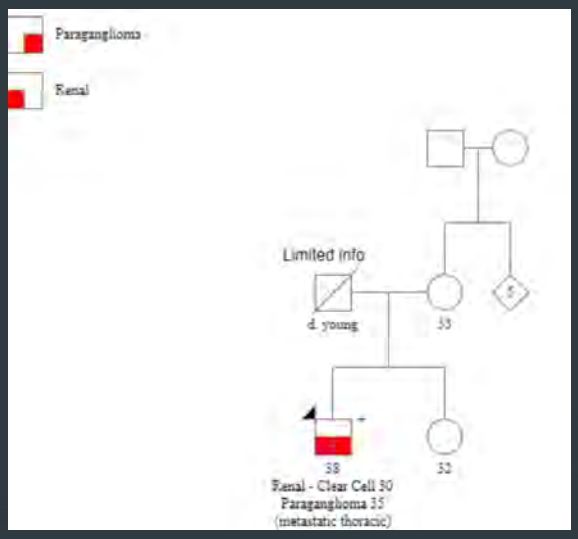
Case 3 Family History



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Hereditary Paraganglioma & Pheochromocytoma

4 nuclear genes encode Mitochondrial Complex II subunits

- *SDHA*
- *SDHB*
- *SDHC*
- *SDHD*
  - Function: catalyze conversion of succinate to fumarate in Krebs cycle and serves as complex II of electron transport chain
  - Impaired oxygen sensing lead to tumor development

SDHAF2
MAX
TMEM127

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Genetic Test Results

SDHB+

RESULTS		
SDHB	p.R90* Pathogenic Mutation:	Detected
SUMMARY		

POSITIVE: Pathogenic Mutation Detected

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Pheochromocytomas(Pheo) and Paragangliomas (PARA)

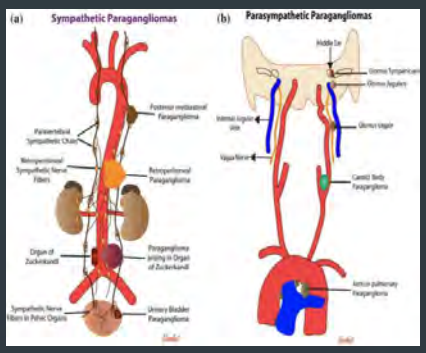
Tumors of the autonomic nervous system: 2-8 million persons affected

- Pheos (adrenal medulla), Paras (extra adrenal paraganglia)

40% arise in persons with a known germline genetic mutation

Metastatic disease: 15-25% of all pheos and paras

- 40% of metastatic pheos and paras have a known genetic mutation.
- 80% lymph nodes, 71% bone, 50% lungs
- Most are slow growing and 50-70% 5- year survival: chronic disease
- Some tumors can behave aggressively



NANETS guidelines. Pancreas journal.2021;50(

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Gene	Risk of Pheo/Para	Location	Risk of metastasis
NF1	1-13%	Pheo	12%
VHL	20%	Pheo	<5%
RET (MEN2)	50%	Pheo	<5%
SDHA	10%	Para, Pheo	12%
SDHB	25%	Para, HN, Pheo	25-50%
SDHC	Low	HN, Thoracic	<5%
SDHD	45%	HN, Para, Pheo	<5-8%
SDHAF2	Low	HN	Low
TMEM127	Low	Pheo, para less	<5%
MAX	Unknown	Pheo	unknown
FH	Low	Para	May be high

Genetic mutations

NANETS guidelines. Pancreasjournal.2021;50(1)

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Hereditary Paraganglioma Clinical Features

- Associated tumors:
  - GI Stromal Tumora
  - Renal Cell Carcinoma
- Symptoms:
  - HTN, sweating, headaches, palpitations, orthostatic hypotension, anxiety, nausea/vomiting
- Precipitants:
  - Glucocorticoids, MAO inhibitors, TCA, opiates, naloxone, glucagon, stimulants, chemotherapy, foods with tyramine

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THINGS TO AVOID PRIOR TO BIOCHEMICAL TESTING

Coffee
Tea
Bananas
Chocolate
Cocoa
Citrus fruits
Vanilla
Acute stress
Vigorous exercise
Caffeine

- Tylenol
- Levodopa, methyldopa
- Labetolol, carvedilol
- Tamsulosin
- Venlefaxine
- HCTZ
- Buspirone
- Lamotrigine
- Aribiprazole
- Stimulants (Ritalin, Adderall, Vivance)
- MAO inhibitors

Beware of false positive results

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Imaging

Pre-operative imaging

- CT or MRI of the area where the tumor is located (base of skull to pelvis)
- Functional imaging:
  - I-123 MIBG
  - PET/CT: higher sensitivity for metastatic Para
  - Ga68-DOTATATE PET/CT: best sensitivity for metastatic Para (should be done if considering PRRT)
  - FDG PET/CT; better than I-123 MIBG, not as sensitive as DOTATATE

Preparation for surgery:

- Alpha blockade, followed by beta blockade if tachycardic
- Fluid expansion, high salt diet

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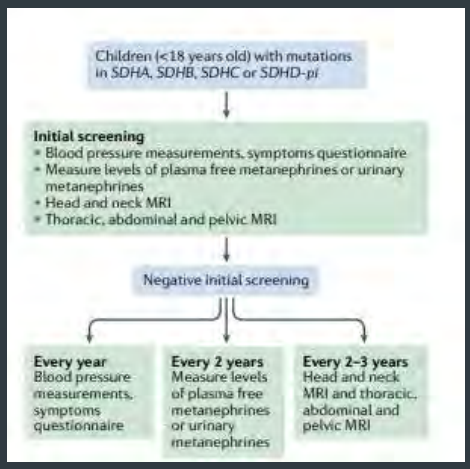
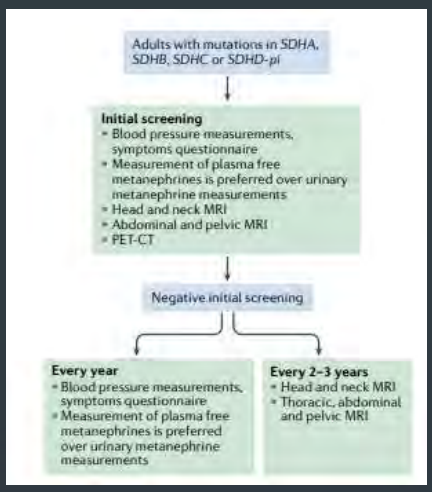
Hereditary Paraganglioma Screening



Nature Reviews, July 2021



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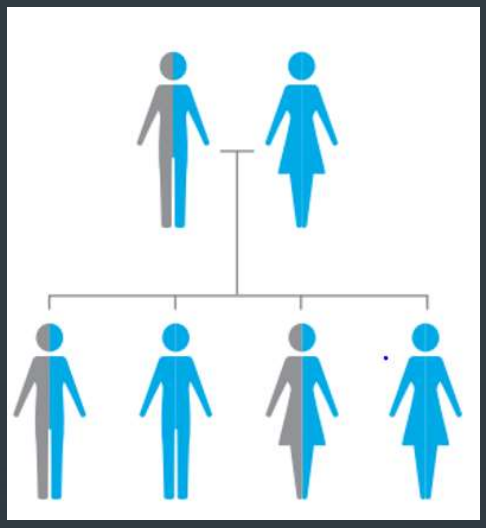
Inheritance of *SDHB*

Autosomal Dominant

1 in 2 (50%) chance

Variable expression

Reduced penetrance



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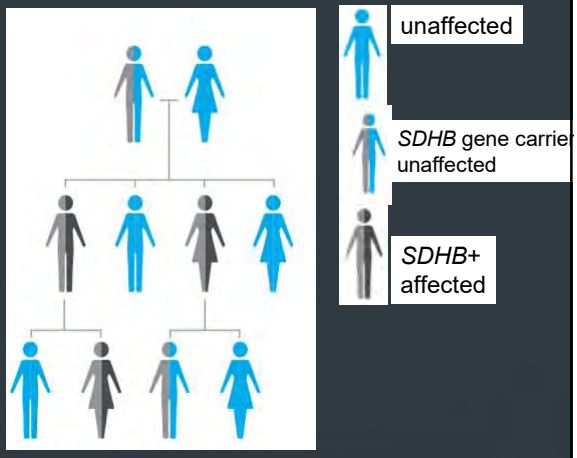
Inheritance of *SDHD*

Autosomal Dominant

1 in 2 (50%) chance to inherit gene

Paternal influence of expression



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Case 4

29 y/o female referred to Multidisciplinary Breast Clinic

Right breast intraductal carcinoma

History of childhood seizures

Macrocephaly

Multiple birthmarks and “bumps”

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Genetic Test Results

NF1+

RESULTS	
NF1	Pathogenic Mutation: p.R1748*
SUMMARY	

POSITIVE: Pathogenic Mutation Detected

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NF1 Gene and Neurofibromatosis Type1 Clinical Features

NF1
Diagnostic Criteria

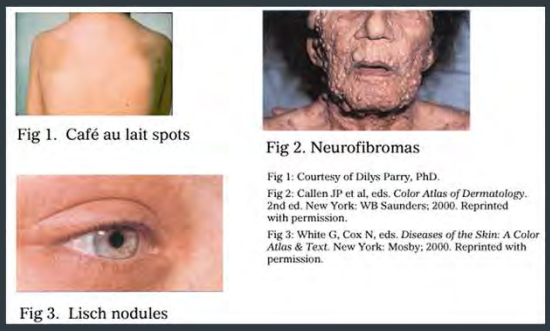

Fig 1. Café au lait spots

Fig 2. Neurofibromas

Fig 3. Lisch nodules

Fig 1: Courtesy of Dilys Parry, PhD.
Fig 2: Callen JP et al, eds. *Color Atlas of Dermatology*. 2nd ed. New York: WB Saunders; 2000. Reprinted with permission.
Fig 3: White G, Cox N, eds. *Diseases of the Skin: A Color Atlas & Text*. New York: Mosby; 2000. Reprinted with permission.

Must have at least 2 of the following:

- Six or more café au lait spots (prepubertal: >5 mm; postpubertal: >15 mm)
- Two or more neurofibromas of any type or ≥1 plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules (iris melanocytic hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
- First-degree relative with NF1

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Tumors/Cancer Associated with NF1
Lifetime Risk 60%

CNS tumors:

- Neurofibroma
- Astrocytoma
- Ependymoma
- Glioma (optic and non-optic)
- Primitive neuroectodermal tumor (PNET)

Malignant peripheral nerve sheath tumor **(8-19%)**
Carcinoid tumors
Paraganglioma and pheochromocytoma (**7%)**
Juvenile chronic myelomonocytic leukemia
Rhabdomyosarcoma
GIST (Gastrointestinal Stromal Tumor)
Breast cancer **(20-40%)** before age 50

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Neurofibromatosis Type1 Adult Management and Screening

ACMG PRACTICE GUIDELINE | Genetics inMedicine

Table 1 Assessment of adults with NF1

In addition to recommended age-and gender-specific screening and vaccinations, an annual general medical evaluation of the adult with NF1 should consider questions about:
Medical history
Signs and symptoms of 1) malignant peripheral nerve sheath tumor, 2) pheochromocytoma, 3) neuropathy, 4) depression, 5) chronic pain and pruritus, 6) fingertip pain
Bothersome/symptomatic cutaneous neurofibromas
Family planning/contraception (and referral for genetic counseling if needed)
Physical exam
Blood pressure
Clinical evaluation for scoliosis with Adam's forward bend test with referral if needed
Laboratory investigation
Consider in context of clinical presentation and age: serum vitamin D concentrations and supplementation
Imaging
Mammogram (women): start annually at age 30 years[a]
MRI breast with contrast (women): consider between ages 30 and 50 years[a]
Consider baseline MRI of known or suspected nonsuperficial plexiform neurofibromas
Consider in context of clinical presentation and age: dual energy X-ray absorptiometry

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