30-year-old woman with large adrenal mass

Kerim B. Kaylan, Adult Endocrinology Fellow

Endorama, 5/9/24

To earn credit for today's activity text code:

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I do not have any relevant financial relationships with any commercial interests.

Learning objectives

1. Review the initial presentation and diagnostic approach to adrenal masses.
2. Discuss genetic syndromes to consider in the evaluation of adrenal masses.

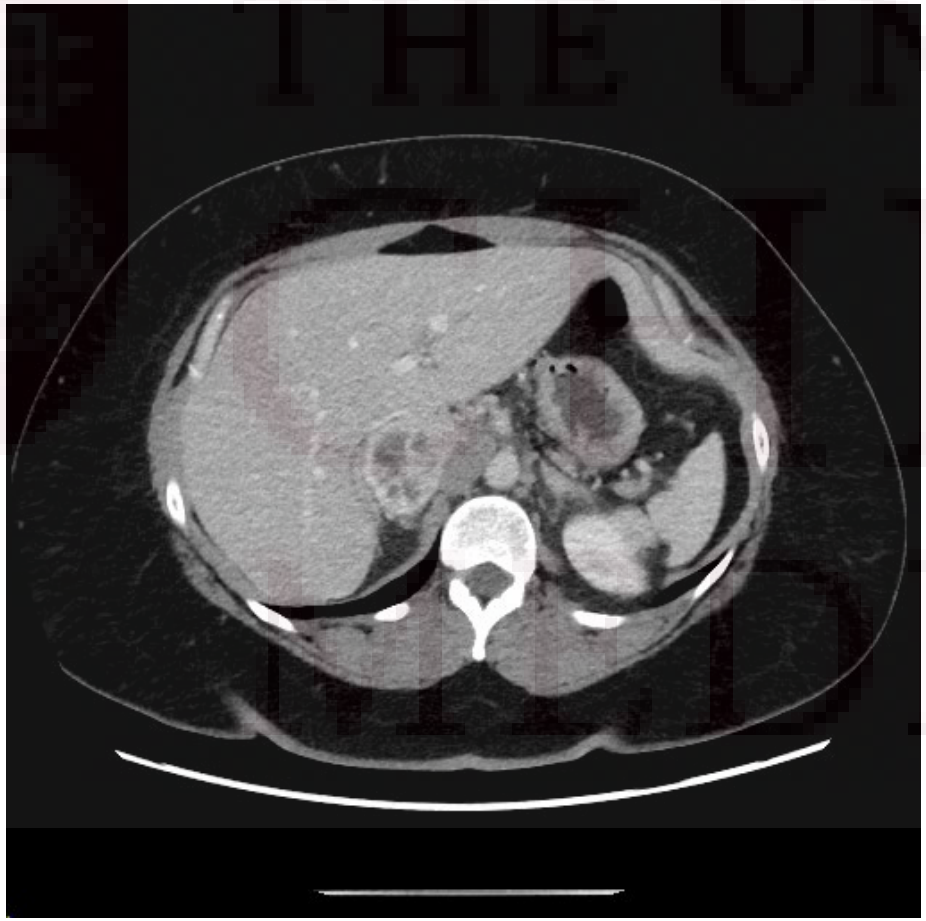
Initial presentation

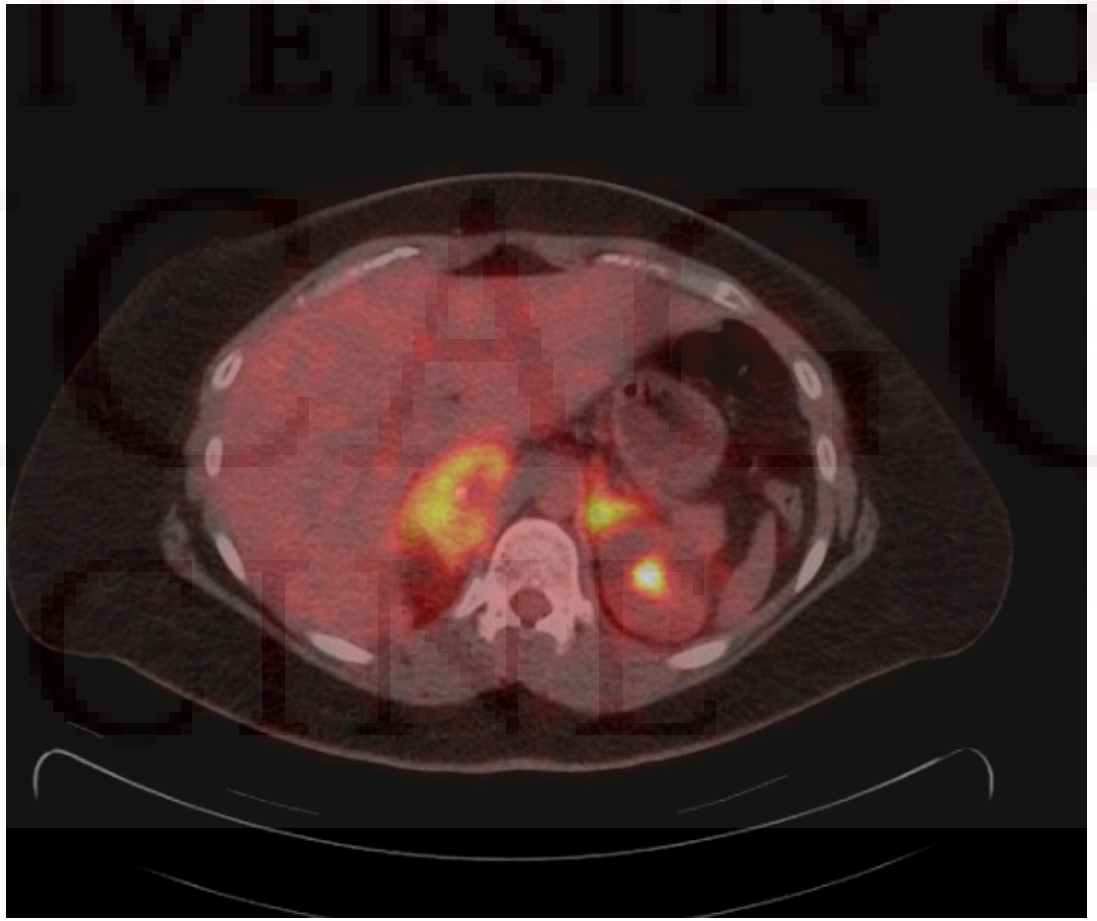
- 30-year-old woman presenting with one week of umbilical pain and drainage for which she went to an outside ER
- CT abdomen/pelvis showed a **soft tissue lesion which was necrotic appearing the expected location of the right adrenal gland measuring 5.8 cm in largest diameter** with mass effect on the IVC
- There was also **necrotic peripancreatic lymphadenopathy** but no significant umbilical findings
- Other than the umbilical symptoms, which resolved on follow up, she has had some **weight loss** and **palpitations** as well as **excess sweatiness**. She was on two BP medications recently prescribed by another doctor

Initial presentation, continued

- She subsequently had an FDG PET/CT which showed a **hypermetabolic right adrenal mass** with associated adenopathy the region of the pancreas as well as a solitary hypermetabolic superior left tracheal lymph node
- MRI of the adrenal gland showed **large heterogenous right adrenal mass** with areas of calcification and suspected central necrosis measuring **6.3 cm in largest diameter**; the left adrenal gland was noted to be unremarkable
- She was referred to an endocrinologist and urologist, and an EUS of the pancreatic nodes was planned. Hormonal work-up was performed

Imaging: CT and PET/CT





Relevant history

PMH

T2D, IBS, pseudotumor cerebri, anemia, asthma, fibromyalgia, Raynaud's disease, migraine without aura, HTN, HLD, ADHD, anxiety

PSH

Pilonodal cyst drainage, foot surgery for "bony tumor," right shoulder surgery for dislocation

Allergies

Formaldehyde, detemir, glargine, regular insulin, shellfish, bee venom, norethindrone-estradiol

Family

No history of parathyroid disease, hypercalcemia, thyroid cancer, pituitary tumors, adrenal masses

Social

Monthly drinker, social

Never smoker, no other drugs

Medications

Albuterol

Amlodipine-benazepril 10-20 mg daily

Cymbalta

Ozempic 0.25 weekly

Rizatriptan PRN

Vyvanse

Physical exam

BP 134/82 | **Pulse 110** | Temp 97.1 °F (36.2 °C) | Ht 1.66 m (5' 5.5") | Wt 88.5 kg (195 lb) | BMI 31.96 kg/m²

GENERAL: well-dressed and groomed
EYES: sclera anicteric
HEENT: normocephalic
NECK: supple; no cervical or supraclavicular lymphadenopathy
RESPIRATORY: clear to auscultation
CARDIOVASCULAR: regular rate
ABDOMEN: soft, **mild TTP RUQ**, nondistended, no masses
MUSCULOSKELETAL: no pain on palpation of vertebral column
EXTREMITIES: no cyanosis, clubbing or edema
NEUROLOGIC: alert and oriented x3; affect appropriate, no gross neurologic deficit
SKIN: no rashes, no petechiae or purpura

Labs and diagnostics

- BMP: Na 145 / K 4.4 / Cl 102 / CO2 27 / BUN 13 / Cr 0.90 / **Glu 188**
- LFT: **Prot 9.1** / Alb 4.3 / Bili 1.2 / Alk phos 98 / AST 28 / ALT 39
- CBC: Hgb 14.6 / WBC 8.9 / **Plt 566**
- **Ca 11.5** (previous calcium elevated going back 15 years)
- SPEP with immunofixation with non-specific increase in beta fraction but no monoclonal gammopathy
- Iron 103 / TIBC 455 / TSAT 23 / **ferritin 217**
- LDH 188

Labs and diagnostics, continued

- Metanephrines, plasma
  - **Normetanephrine 928 pg/ml (0-210.1)**
  - Metanephrines 14.3 (0-88)
- Catecholamines, plasma
  - **Norepinephrine 4475 pg/ml (0-874)**
  - Epinephrine 19 pg/ml (0-62)
  - Dopamine <30 pg/ml (0-48)
- **Renin 9.7 ng/ml/hr (0.167-5.38)**
- Aldosterone 5.6 ng/dl (0-30)
- ARR 0.58 (<30)
- DHEAS 175.8 (45-270)

Results of EUS with biopsy

A. Peripancreatic lymph node

[…] **benign lymph node** […]

B. Periportal lymph node

[…] **metastatic tumor cells consistent with metastatic pheochromocytoma** [□]

C. Right adrenal gland

[□] **Multiple fragments of pheochromocytoma** […]

In addition to referral to an endocrine surgeon, what additional steps would you like to pursue?

Factors that interfere with biochemical testing

Stimulation of exogenous catecholamines	Exogenous catecholamines	Drugs that alter catecholamine metabolism	Drugs that interfere with biochemical assays
• Emotional and physical stress (surgery, trauma) • Drug withdrawal (alcohol, clonidine) • Drugs (vasodilators, caffeine, nicotine, theophylline, ephedrine, amphetamines) • Hypoglycemia • Obstructive sleep apnea • Myocardial ischemia • Stroke	• Bronchodilators • Appetite suppressants • Decongestants	• β-Blockers • Phenoxybenzamine • Tricyclic antidepressants • Levodopa • Theophylline • MAO inhibitors	• Labetalol, sotalol • Acetaminophen • Clofibrate • Quinidine

Lenders et al. *The Journal of Clinical Endocrinology & Metabolism* 99, no. 6 (June 1, 2014): 1915–42

Table 2. Medications That Are Implicated in Adverse Reactions in Patients with Pheochromocytoma and That Can Precipitate a Crisis

Class of Drugs	Examples
Dopamine D2 receptor antagonists (including some antiemetic agents and antipsychotics)	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
β-Adrenergic receptor blockers[a]	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Opioid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Amitriptyline, imipramine,
Serotonin reuptake inhibitors (rarely reported)	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids	Dexamethasone, prednisone, hydrocortisone, betamethasone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

[a] Although most case reports on β-adrenergic receptor blockers pertain to nonselective blockers, selective β_1-blockers may also precipitate a crisis because at higher doses they may lose β_1-selectivity.

Lenders et al. *The Journal of Clinical Endocrinology & Metabolism* 99, no. 6 (June 1, 2014): 1915–42

Should this patient get genetic testing, and is there a specific genetic mutation or syndrome you might be more concerned about?

Genetics of pheochromocytoma

- Endocrine Society guidelines recommend that **all patients** with pheochromocytoma or paraganglioma (PPGL) should be engaged in shared decision-making for genetic testing
- At least **1/3 of patients with PPGLs have disease causing germline mutations**, and at least 14 different susceptibility genes have been reported (per last guidelines, more are under investigation)
- The highest frequencies of germline mutations are for ***SDHB*** (10.3%), ***SDHD*** (8.9%), ***VHL*** (7.3%), ***RET*** (6.3%), and ***NF1*** (3.3%)
- Mutations in ***SDHB*** lead to **metastatic disease in 40% or more of affected patients**
- Establishing hereditary syndromes in the proband may result in **earlier diagnosis and treatment** in relatives

Germline mutations in PPGL patients

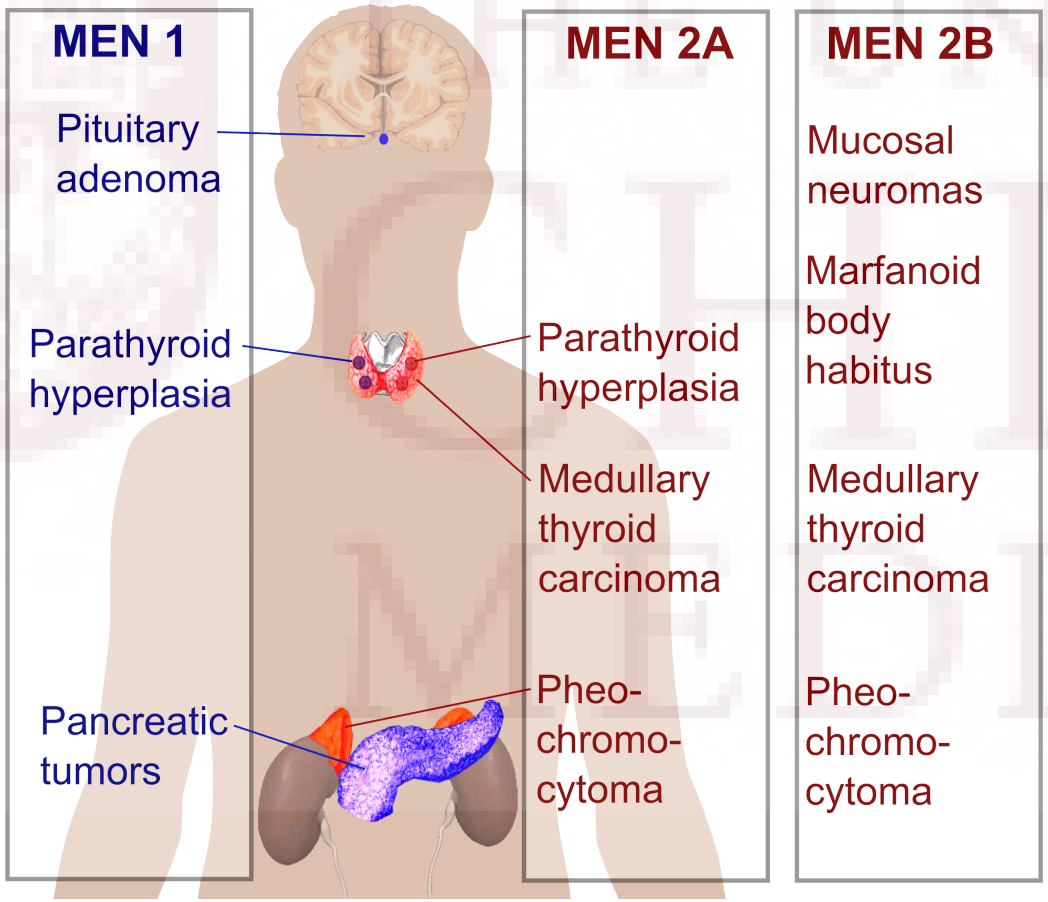
Table 8. Detected Germline Mutations in All PPGL Patients

First Author, Year (Ref.)	No. of Cases	Mutations											
		SDHB	*SDHD*	*SDHC*	*VHL*	*RET*	*NF1*	*SDHA*	*SDHAF2*	*TMEM127*	MAX	n	%
Lefebvre, 2012 (170)	269	21	12	6	ND	ND	ND	ND	0	5	ND	44	16.3
Amar, 2005 (165); Burnichon, 2009 (166)	721	99	131	16	25	16	13	ND	ND	ND	ND	30	41.6
Mannelli, 2009 (162)	501	24	47	4	48	27	11	ND	ND	ND	ND	16	32.1
Cascón, 2009 (163)	237	25	11	1	20	36	ND	ND	ND	ND	ND	93	39.2
Jafri, 2012 (167)	501	121	44	ND	19	ND	ND	ND	ND	ND	ND	18	36.7
Erlic, 2009 (168)	1149	73	28	2	120	80	43	ND	ND	ND	ND	34	30.1
Korpershoek, 2011 (169)	316	16	26	2	19	26	21	5	5	2	ND	12	38.6
Total n	3694	379	299	31	251	185	88	5	5	7		12	33.8
Mutation rate		10.3	8.9	1.0 (31/3193)	7.3 (251/3425)	6.3 (185/2924)	3.3 (88/2687)						

ND, not determined.

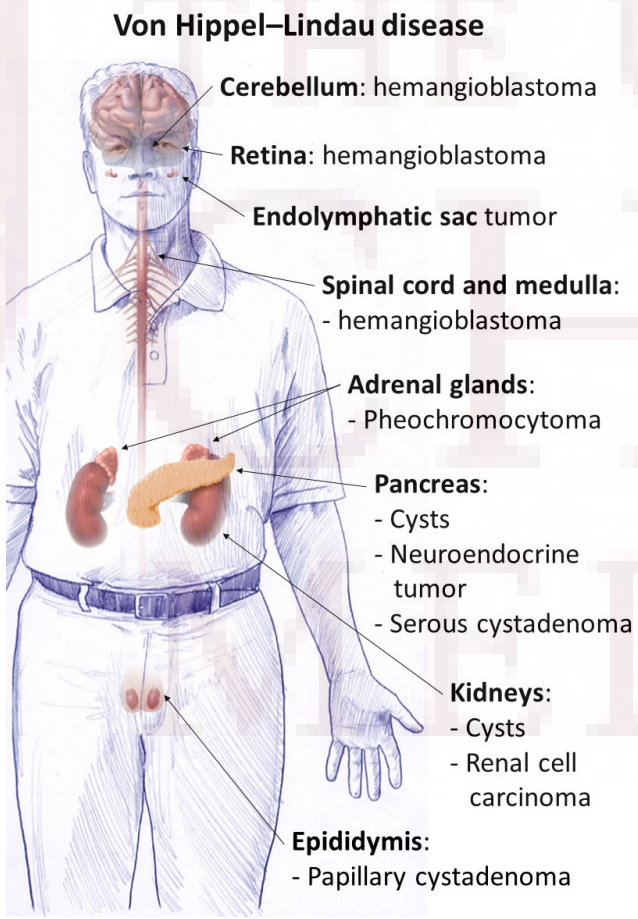
Lenders et al. *The Journal of Clinical Endocrinology & Metabolism* 99, no. 6 (June 1, 2014): 1915–42

MEN2A, MEN2B (*RET* gene)



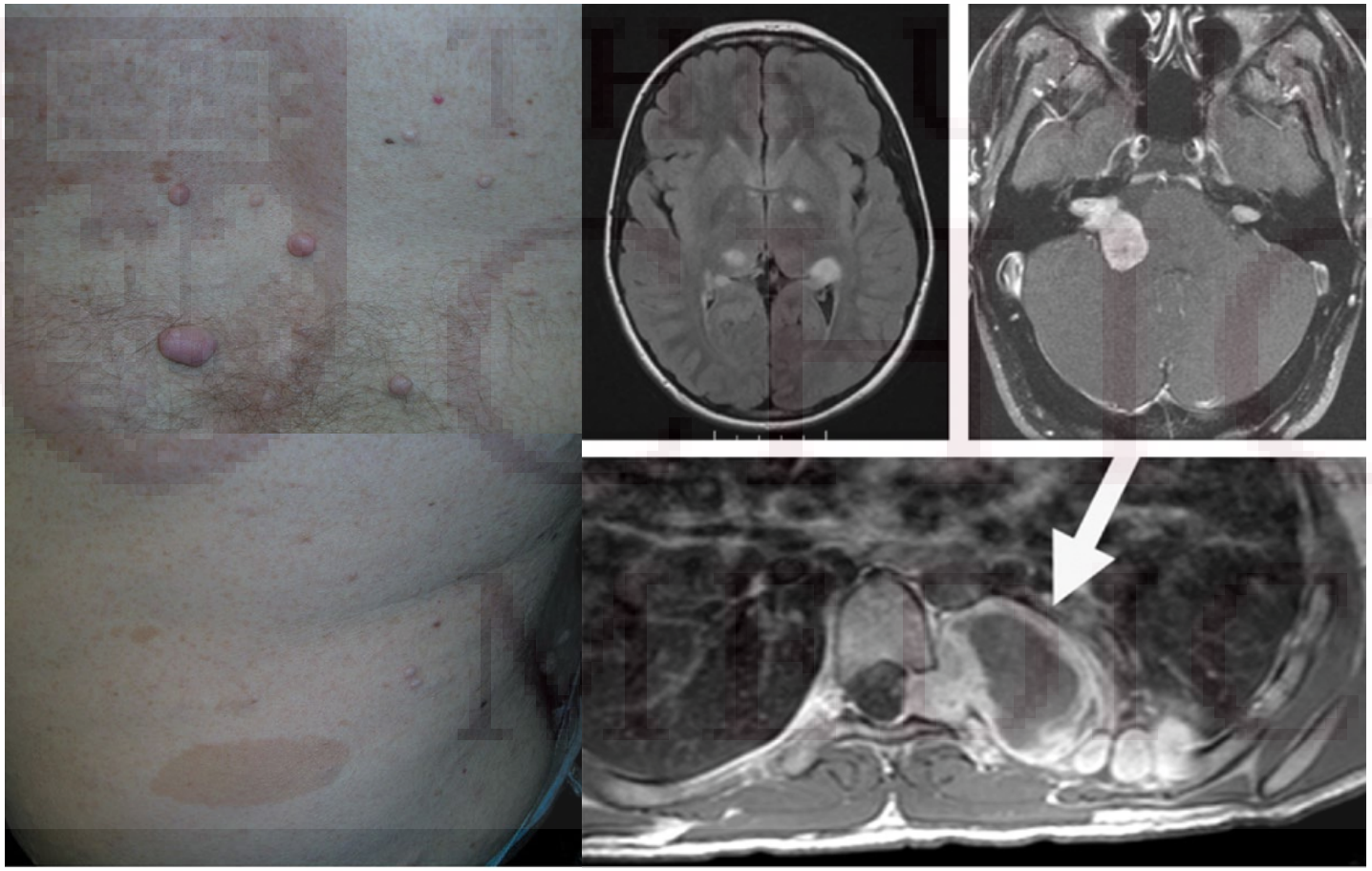
- Pheochromocytoma is found in ~50% of MEN2A and MEN2B patients
- Usually benign, bilateral, confined to adrenal glands, and presenting earlier in life
- May present as hypertensive crisis during surgery for MTC during childhood

Von Hippel-Lindau (*VHL* gene)



- Pheochromocytoma is found in 10–20% of vHL patients
- Can be unilateral or bilateral, and rarely is there extra-adrenal or head/neck paraganglioma
- Mean age of diagnosis of pheochromocytoma is 30 years, 5% will have metastatic disease

Neurofibromatosis, type 1 (*NF1* gene)



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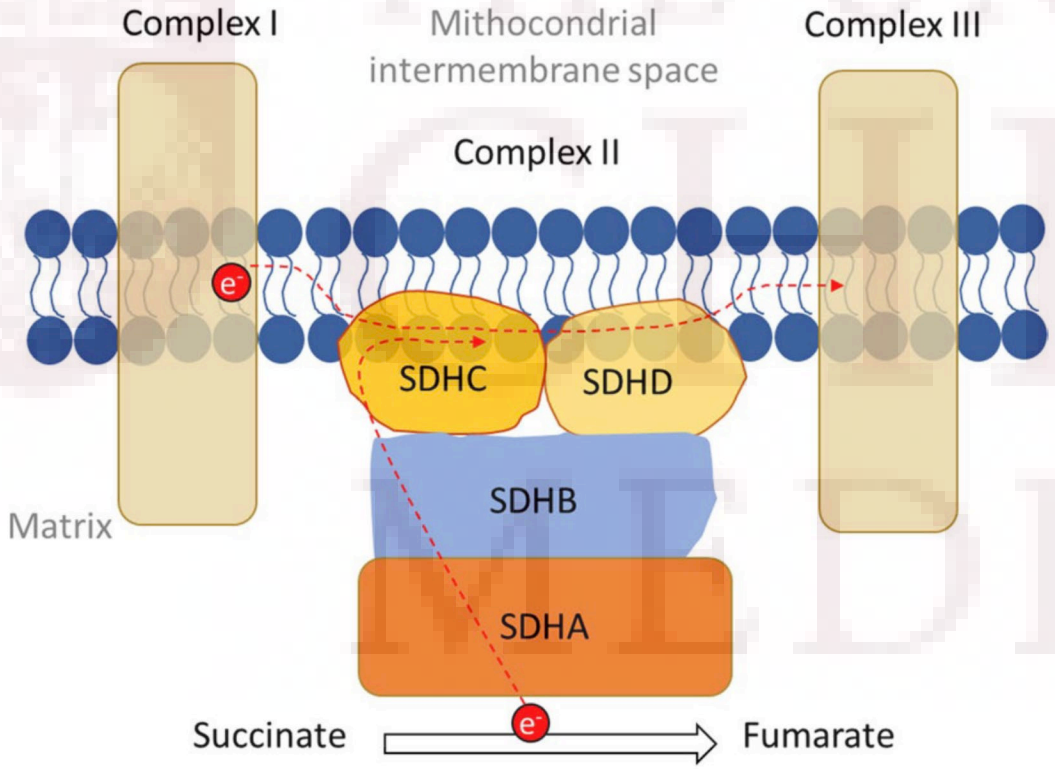
Source: A.H. Ropper, M.A. Samuels, J.P. Klein, Sashank Prasad Adams and Victor's Principles of Neurology, 12th Edition Copyright © 2023 by McGraw-Hill Education. All rights reserved.

- Pheochromocytoma is found in ~5% of NF1 patients and are not in the diagnostic criteria
- Can be unilateral or bilateral, and 12% of those diagnosed are metastatic
- All of those with NF1 and hypertension should be screened

SDHx (A, B, C, D, AF2) syndromes



- Pheochromocytoma or paragangliomas plus GIST, RCC, or pituitary adenomas
- Pheochromocytoma is found in:
  - 25-50% of *SDHB* patients, of which 40% are metastatic
  - 10-24% of *SDHD* patients
  - 1-9% of *SDHC* patients
- SDH deficiency causes:
  - Mitochondrial failure (increased glycolysis, anaerobic metabolism)
  - Excess ROS
  - Excess succinate (HIF activation, epigenetic changes, macrophage polarization)

Takács-Vellai et al. Cancer Metastasis Rev. 2021 Dec 1;40(4):1177–201.

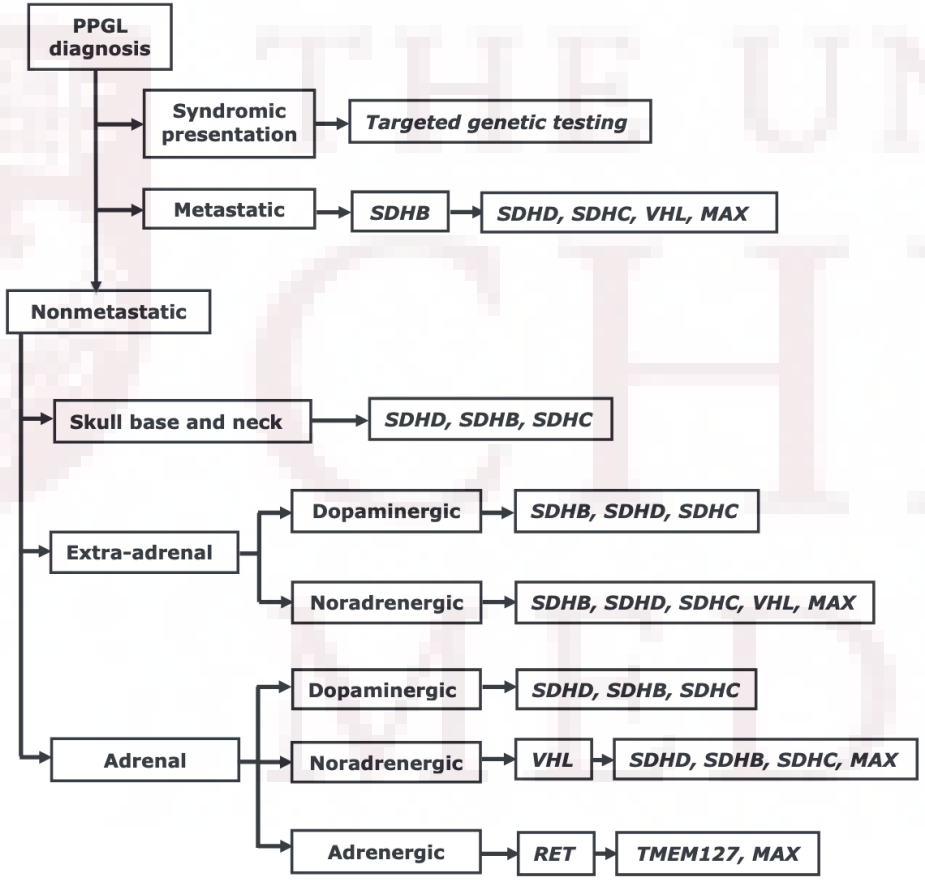
Summary of syndromic PPGL etiologies

Gene	Features or syndrome	Metastasis risk	Location	Biochemical profile
RET	MEN2A, MEN2B	Low	Adrenal, possibly bilateral	Adrenergic
VHL	Von Hippel-Lindau	High	Adrenal, possibly bilateral; extra-adrenal	Noradrenergic
NF1	Neurofibromatosis, type 1	Moderate	Adrenal	
SDHB	RCC, GIST, pituitary adenomas	Highest	SBHN; adrenal, extra-adrenal	Dopaminergic, noradrenergic, adrenergic
SDHD	RCC, GIST, pituitary adenomas	Low-moderate	SBHN-multifocal; adrenal, extra-adrenal	Dopaminergic, noradrenergic, adrenergic
SDHC	RCC, GIST, pituitary adenomas	Low-moderate	SBHN; adrenal, extra-adrenal (thoracic)	Dopaminergic, noradrenergic, adrenergic

Fishbein L. Hematol Oncol Clin North Am 2016;30(1):135–150.

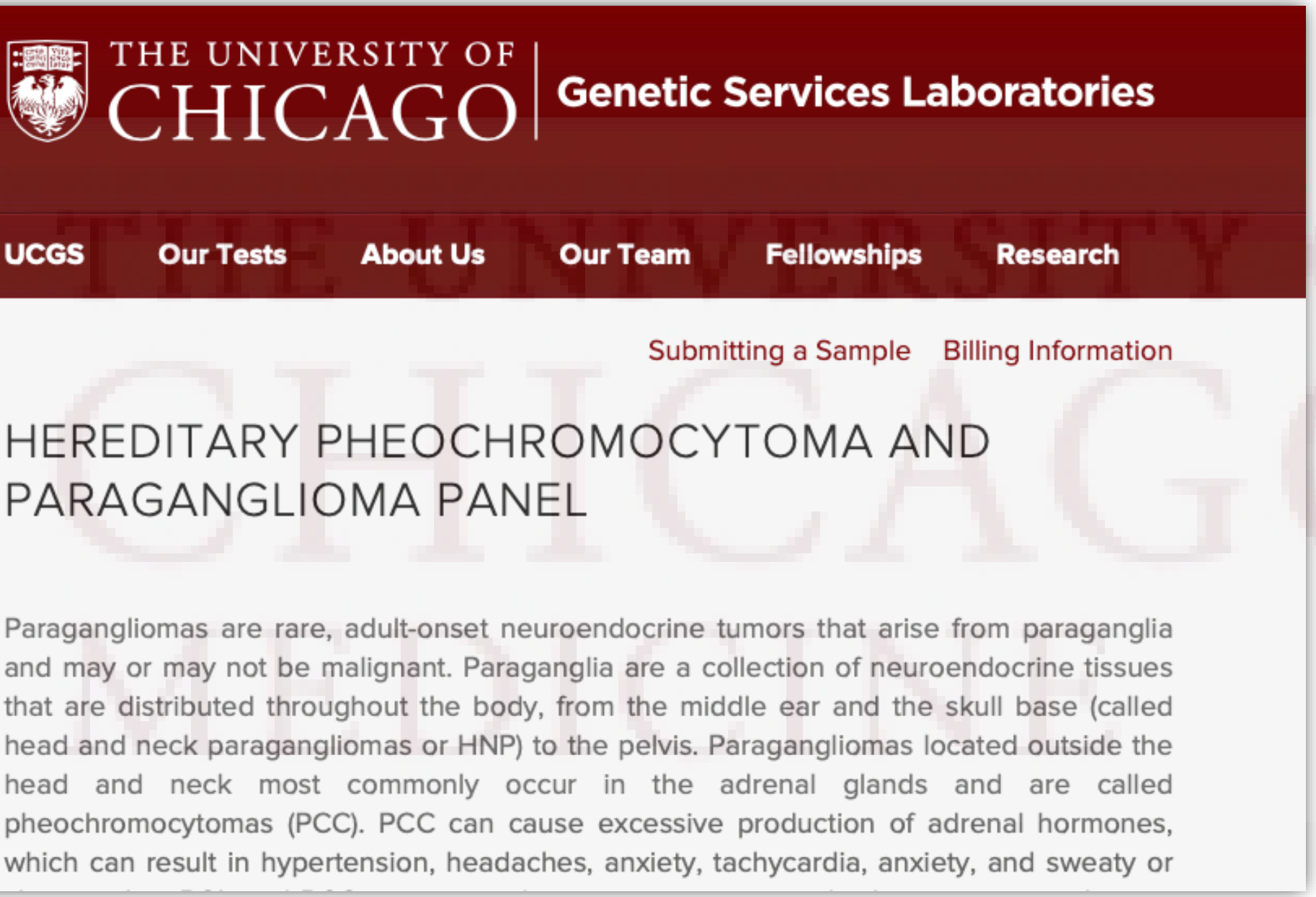
Which genes should we test for our patient and why?

Which genes to test



1. Syndromic versus metastatic?
2. Location of tumor?
3. Noradrenergic, adrenergic, or dopaminergic?

Lenders et al. *The Journal of Clinical Endocrinology & Metabolism* 99, no. 6 (June 1, 2014): 1915–42. https://doi.org/10.1210/jc.2014-1498.



https://dnatesting.uchicago.edu/tests/hereditary-pheochromocytoma-and-paraganglioma-panel

EXPERT CONSENSUS DOCUMENT

Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas

The NGS in PPGL (NGSnPPGL) Study Group, Rodrigo A. Toledo[1,2], Nelly Burnichon[3,4], Alberto Cascon[5], Diana E. Benn[6], Jean-Pierre Bayley[7], Jenny Welander[8], Carli M. Tops[9],

susceptibility genes implicated in the diagnosis of inherited PPGLs, next-generation sequencing (NGS) technology is ideally suited for carrying out genetic screening of these individuals. This Consensus Statement, formulated by a study group comprised of experts in the field, proposes specific recommendations for the use of diagnostic NGS in hereditary PPGLs. In brief, the study group recommends target gene panels for screening of germ line DNA, technical adaptations to address different modes of disease transmission, orthogonal validation of NGS findings, standardized classification of variant pathogenicity and uniform reporting of the findings. The

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Toledo et al. *Nature Reviews Endocrinology* 13, no. 4 (April 2017): 233–47

Back to our patient...

Peri-operative course

- Her prior BP medications (amlodipine-benazepril) were stopped and she was **started on alpha blockade** (both doxazosin and later phenoxybenzamine due to intolerance)
- Intraoperatively her adrenal vein was ligated and **adrenal mass and gland were removed** in addition to hepatoduodenal LN. IVC was noted to be plump with mild ascites and firm liver
- She received 4 L of fluids and 1.5 L 5% albumin perioperatively and went to **SICU for pressors and continued aggressive fluid management** for hypotension
- **ACTH stim with peak cortisol 17.2 and baseline cortisol 3.0 and ACTH 3.5 (early afternoon)**, started on hydrocortisone subsequently without improvement in hemodynamics or symptoms and subsequently trialed off while admitted and discharged without steroids

Follow-up and genetics counseling

- Pathology showed 1/3 LN positive, otherwise consistent with pheochromocytoma
- Recovering well at post-surgical follow-up with plan for plasma metanephrines (<0.20), Dotatate PET (pending), CT (stable)
- Seen in Genetics with unremarkable family history, pathogenic variant c.242C>T (p.Pro81Leu) identified in *VHL* gene
- Seen in Cancer Genetics/Preventative Oncology by Dr. Canham for start of formal surveillance

Lifetime risk of vHL-associated tumors

Table 2. Lifetime risks of VHL-associated tumors

Tumor[a]	Risk	Youngest/mean age of diagnosis (years)
CNS hemangioblastoma	60%–80%	9/30
Cerebellar	44%–72%	9/31
Brainstem	10%–25%	12/32
Spinal	13%–50%	8/33
Retinal angioma/hemangioblastoma	25%–60%	0/25
Renal	25%–75%	12/39
Cyst	42%	12/37
RCC[b]	17%–70%	13/44
PHEO[c]	10%–25%	2/27
ELST[d]	10%–15%	6/22
Pancreatic	35%–75%	5/36
Cyst	21%	5/33
NET[e]	10%–17%	16/35
Papillary cystadenoma		
Epididymis	25%–60%	17/24
Broad ligament[f]	10%	16/unknown (16–46)

- Most vHL-related tumors are benign but due to mass effect or post-surgical complications can have significant morbidity
- Mortality most associated with RCC, pancreatic NET, and CNS hemangioblastoma

Rednam et al. *Clinical Cancer Research* 23, no. 12 (June 14, 2017): e68–75.

Long-term monitoring for vHL

Proposed vHL tumor surveillance regimen with an emphasis on the pediatric age range

Tumor	Recommended surveillance	Age to begin	Interval
Retinal HB	Eye exam including retina[a]	Birth	Annual
PHEO	Blood pressure at all medical visits[b]	2 years	
	PFM[c,d,e,f] or 24-h urine fractionated metanephrines[g]	2 years	Annual
ELST	Audiogram	5 years	Biennial
CNS HB	MRI brain with and without contrast[h]	8 years	Biennial[i]
	MRI spine with contrast		
RCC	MRI abdomen[j]	10 years	Annual
Pancreatic NET	MRI abdomen	10 years	Annual

Rednam et al. *Clinical Cancer Research* 23, no. 12 (June 14, 2017): e68–75.

Prognosis

- Hypertension-free survival in patients without recurrence of pheochromocytoma was 74% at 5 years and 45% at 10 years
- Patients with malignant tumors have a 5-year survival of <85% (79% for pheochromocytoma and 89% for paraganglioma), 10-year overall survival of 73%, and 15-year overall survival of 65%
- Risk factors for rapid disease progression: male sex (OR 2.75), older age (OR 1.04/year), synchronous metastasis (OR 11.63), larger tumor size (OR 1.14/cm), elevated dopamine (OR 3.93)

Plouin et al. Hypertension. 1997 May;29(5):1133–9.
Hamidi et al. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3296–305.

What about her calcium and renin!?

Renin and norepinephrine

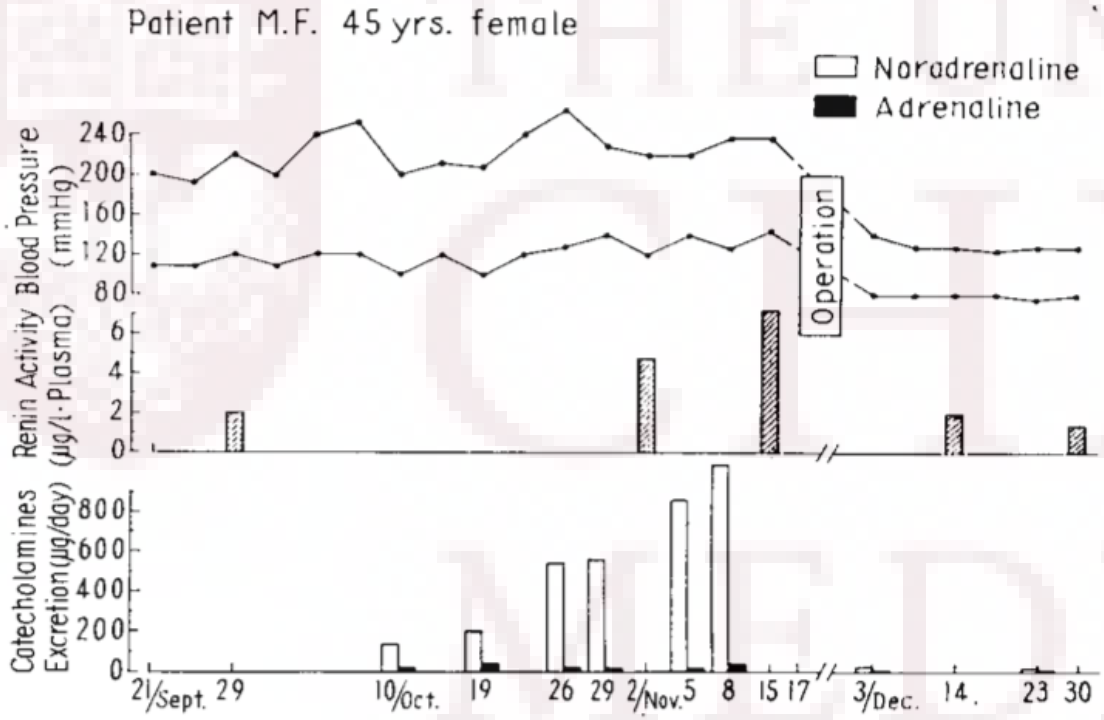


Fig. 1. Changes in blood pressure, urinary excretion of catecholamines and plasma renin activity in a patient (case 1) with pheochromocytoma.

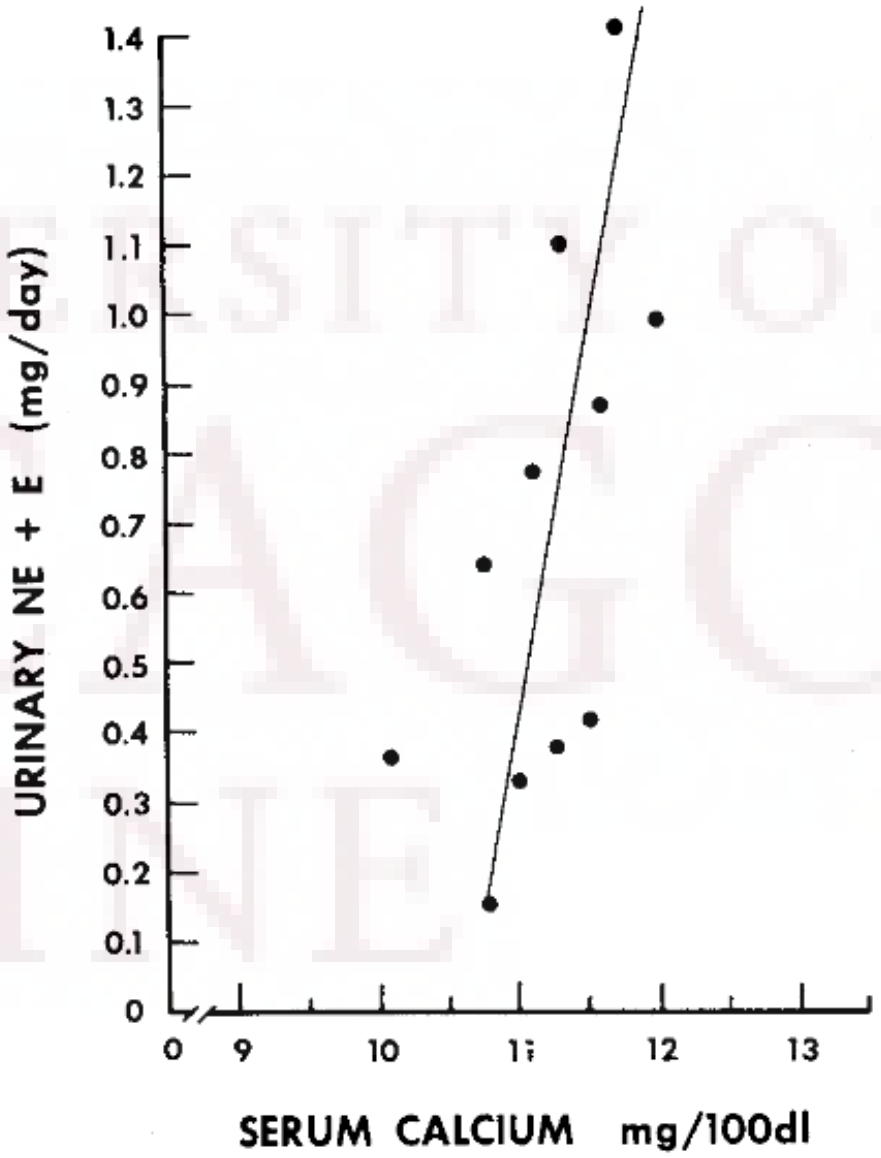
- Catecholamines can stimulate renin release from the JG cells of the kidney via β-adrenoreceptor activation
- Some case reports suggest this is the case for patients with pheochromocytoma, though we have limited data

Maebashi et al. Jpn Circ J. 1968;32(10):1427–32.

Calcium labs on follow-up

- Ca 9.8 / Alb 4.2 / PTH 18 / Phos 2.9
- 25-OH vitamin D 31
- PTHrp <0.4
- Vitamin A 79.7 (32.5-78)
- SPEP normal
- No prior PTH levels available

- Some prior case reports of PTHrp-mediate hypercalcemia…



Atuk et al. *Medicine* 58, no. 3 (May 1979): 209.

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Questions?