THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"75 year old female with bilateral adrenal nodules"

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Dr. Dojki does not have any relevant financial relationships with any commercial interests.

LEARNING OBJECTIVES:

1. Review clinical picture and diagnostic evaluation of Pheochromocytoma.
2. Discuss diagnostic challenges of Pheochromocytoma evaluation in patients with chronic kidney disease.
3. Discuss familial disorders with bilateral adrenal nodules and Pheochromocytoma.

Case Presentation:

- 75 year old female was referred to the hypertension clinic for evaluation for Pheochromocytoma.
- She has a long standing history of resistant hypertension on multiple medications.
- History of bilateral adrenal nodules since 2009.

HPI

- Initially presented to the surgery clinic in 2015 for evaluation of adrenal nodules (present since 2009 - no size of nodules or images available from then).
- Denies history of episodic hypertension, headaches, sweats or palpitations.
- No hormonal work up of bilateral adrenal nodules done since 2009.
- **CT Abdomen (08/2014)** performed at outside hospital for abdominal pain:
  - Bilateral Adrenal masses.
  - Right lesion is 3.6cm x 2.4 cm and has increased in size from 2011 scan (no measurements indicated).
  - Left lesion is 2.2 cm x 1.9 cm and is stable.

Pertinent History:

- **Past Medical History:**

  - Hypertension
  - Type 2 Diabetes Mellitus on insulin
  - CKD stage 4, GFR 23
  - Breast cancer
  - Anemia
  - Hyperlipidemia
  - CVA

- **PSHx:**

  - Complete Mastectomy
  - Total Abdominal Hysterectomy

- **Home medications:**

  - Amlodipine 10mg,
  - Lisinopril 10mg,
  - Metoprolol tartrate 25mg BID,
  - Lasix 40mg daily,
  - Hydralazine 25mg QID,
  - Insulin
  - Arimidex
  - FeSO4
  - Epogen
  - Simvastation

- Allergies: NKDA
- Social Hx: Does not smoke, use alcohol or illicit drugs. Retired
- Physical Exam:
  BP 161/77; 145/68
  Pulse 80; 82
  Temp 96.5F
  weight 76kg
  Height 5 ft 4 inches

Component	Latest Ref Rng	7/13/2015
Glucose, Ser/Plasma	60 - 109 mg/dL	88
Sodium	134 - 149 mmol/L	142
Potassium, Ser/Plasma	3.5 - 5.0 mmol/L	5.0
Chloride	95 - 108 mmol/L	106
Carbon Dioxide	23 - 30 mmol/L	**19 (L)**
Anion Gap	6 - 15 mmol/L	**17 (H)**
BUN	7 - 20 mg/dL	**45 (H)**
Creatinine	0.5 - 1.4 mg/dL	**2.1 (H)**
GFR Estimate (Calc)	>59 mL/min/BSA	**23 (L)**
Calcium	8.4 - 10.2 mg/dL	9.8
Norepinephrine	pg/mL	600
Epinephrine, Plasma	pg/mL	**193 (H)**
Dopamine	pg/mL	**31 (H)**
Normetanephrine	<0.90 nmol/L	**1.5 (H)**
Metanephrine	<0.50 nmol/L	**2.8 (H)**
Aldosterone	<=21 ng/dL	5.6
ACTH	<52 pg/mL	33.5
Renin		3.1

Norepi: 700-750 pg/ml (supine)
Epi: <111 pg/mL (supine)
Dopamine <30 pg/mL

24 hr urinary free cortisol: 2.1mcg (Reference range: 2.5-45mcg/24hrs)

FDG-PET scan 08/31/2015

- No significantly FDG avid lesion to definitely suggest tumor.
- Bilateral adrenal masses are only slightly FDG avid.
- While this may indicate a benign etiology, non FDG avid tumor account be entirely excluded.

→ Since PET scan with uptake in both adrenals, referred to hypertension specialist for evaluation.

- Elevated plasma fractionated metanephrines concerning for functional adrenal pheochromocytoma; however these levels are more likely to be elevated in the setting of CKD.
- PET scan was performed, however CT/MRI more sensitive for evaluating pheochromocytoma.
- Repeat imaging: Plan for MRI Abdomen & pelvis (CT with contrast not done due to CKD)
- Repeat plasma metanephrines: 11/25/2016
  Plasma Free normetanephrines: 1.3 nmol/L (<0.90)
  Plasma Free metanephrines: 3.6nmol/L (<0.50)

MRI abdomen 11/14/2016:

- Abdominal exam limited due to lack of IV contrast due to CKD.
- Bilateral adrenal gland nodules are noted, restricting diffusion.
- The right lateral nodule measures approximately 3.8 x 2.0 cm (previously 3.6cm x 2.4 cm in 2014). The lesion is multi-septated with fluid fluid levels.
- The left adrenal gland nodules measures 3.0 x 2.2 cm (previously 2.2 cm x 1.9 cm in 2014) and demonstrates drop in signal on out of phase images consistent with microscopic fat (fat containing adenoma).
- FINAL IMPRESSION: Indeterminate multi-septated right adrenal gland nodule with fluid fluid levels

03/07/2017: Hypertension clinic

- Exam: BP 138/60, pulse 85, weight 66kg, Ht 5 ft 4 inches
  BMI 25.
  Exam: unremarkable

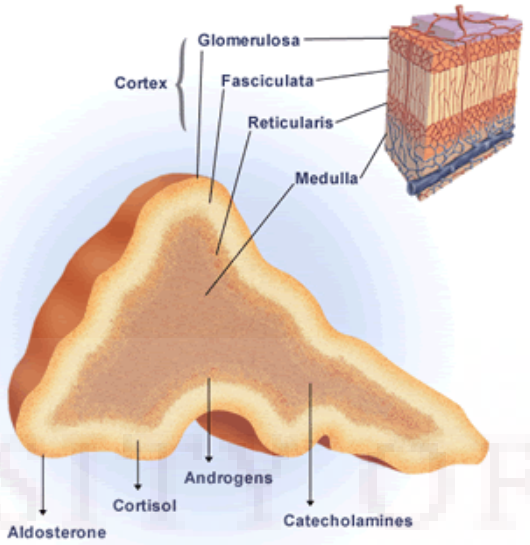
- Anti-hypertensive regimen changed:
  - Stopped hydralazine and metoprolol
  - Stopped lisinopril
  - continued amlodipine 10mg daily
  - started clonidine patch 0.1mg weekly.
  - stopped lasix and substituted with torsemide 10mg daily.
  - low potassium diet given CKD stage 4

Component	Latest Ref Rng	3/7/2017	11/14/2016	9/26/2016	7/13/2015
Glucose, Ser/Plasma	60 - 109 mg/dL				88
Sodium	134 - 149 mmol/L				142
Potassium, Ser/Plasma	3.5 - 5.0 mmol/L				5.0
Chloride	95 - 108 mmol/L				106
Carbon Dioxide	23 - 30 mmol/L				**19 (L)**
Anion Gap	6 - 15 mmol/L				**17 (H)**
BUN	7 - 20 mg/dL				**45 (H)**
Creatinine	0.5 - 1.4 mg/dL				**2.1 (H)**
GFR Estimate (Calc)	>59 mL/min/BSA				**23 (L)**
Calcium	8.4 - 10.2 mg/dL				9.8
Norepinephrine	pg/mL				600
Epinephrine, Plasma	pg/mL				**193 (H)**
Dopamine	pg/mL				**31 (H)**
Urine Albumin, Random	mg/dL	5.6			
Urine Creatinine, Random	mg/dL	68.83			
Urine Albumin/Creatinine	<30 ug/mg	**81.4 (H)**			
Normetanephrine	<0.90 nmol/L	**1.1 (H)**			**1.5 (H)**
Metanephrine	<0.50 nmol/L	**3.4 (H)**			**2.8 (H)**
Creatinine (POC)	0.5 - 1.4 mg/dL		**2.31 (H)**	**2.45 (H)**	
GFR estimated (POC)	>59 mL/min/BSA		**21 (L)**	**19 (L)**	
Aldosterone	<=21 ng/dL				5.6
ACTH	<52 pg/mL				33.5
Renin					3.1

MIBG (I-123) scan 04/05/2017

- Abnormal activity within both adrenal nodules, which is suspicious and may represent pheochromocytoma.
- Surgical consultation with Dr Angelos placed.

PHEOCHROMOCYTOMA:



- In 1912, a pathologist named Pick coined the term pheochromocytoma — after the Greek words phaios, meaning dark or dusky, and chroma, meaning color—to describe the chromaffin reaction seen in adrenomedullary tumors.
- Catecholamine secreting tumors that arise from chromaffin cells of the adrenal medulla.
- Rare neoplasms, occurring in less than 0.2% of patients with hypertension.
- Estimated annual incidence is between 2 and 8 cases per 1 million in the general population [1] (Likely to be an underestimate as 50% of pheochromocytomas were diagnosed at autopsy[2].
- Although may occur at any age, most common in the fourth to fifth decade and are equally common in men and women

[1] Beard CM, Sheps SG, Kurland LT, et al. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1983; 58:802.
[2]Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc 1981; 56:354.

- Abdomen: 95 %
  - 85 - 90 % intraadrenal (pheochromocytoma),
  - 5 - 10 % are multiple.

- Approximately 10 - 15 % of catecholamine-secreting tumors are extraadrenal and are referred to as catecholamine-secreting paragangliomas.
- 10 % of all catecholamine-secreting tumors are malignant - local invasion into surrounding tissues and organs (eg, kidney, liver) or distant metastases, which may occur as long as 20 years after resection - long-term follow-up is indicated in all patients.
- Most catecholamine-secreting tumors are sporadic (Dx on basis of symptoms or an incidentally on imaging.
- 30 % of patients have the disease as part of a familial disorder (more likely to be bilateral adrenal pheochromocytomas or paragangliomas) and present at a younger age.

Clinical presentation:

- Classic triad — The classic triad of symptoms in patients with a pheochromocytoma consists of episodic headache, sweating, and tachycardia [1]

1. Sustained or paroxysmal hypertension is the most common sign of pheochromocytoma, but approximately 5 -15 % of patients present with normal blood pressure. The frequency of normotension is higher in patients with adrenal incidentaloma or in those undergoing periodic screening for familial pheochromocytoma.

2. Headache, which may be mild or severe and variable in duration, occurs in up to 90% of symptomatic patients.

3. Generalized sweating occurs in up to 60 - 70 %of symptomatic patients.

- About 50% have paroxysmal hypertension; most of the rest have either primary hypertension or normal blood pressure.

- Most patients with pheochromocytoma do not have the three classic symptoms [2]

[1] Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. Medicine (Baltimore) 1991; 70:46.
[2] Baguet JP, Hammer L, Mazzuco TL, et al. Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients. Eur J Endocrinol 2004; 150:681.

Less common symptoms and signs

- forceful palpitations,
- tremors,
- pallor,
- dyspnea,
- generalized weakness,
- panic attack-type symptoms (particularly in pheos that produce epinephrine)
- Orthostatic hypotension
- visual blurring,
- papilledema,
- weight loss,
- increased erythrocyte sedimentation rate,
- insulin resistance, hyperglycemia,
- leukocytosis,
- psychiatric disorders,
- secondary erythrocytosis (rare) due to overproduction of erythropoietin
- Cardiomyopathy (rare) attributed to catecholamine excess that is similar to stress-induced (takotsubo) cardiomyopathy. Patients may present with pulmonary edema and may deteriorate with initiation of beta-adrenergic blockade.
- Paroxysmal elevations in blood pressure – during diagnostic procedures (eg, colonoscopy), induction of anesthesia, surgery, with certain foods or beverages containing tyramine, or with certain drugs (such as metoclopramide or monoamine oxidase inhibitors [MAOIs])

Asymptomatic patients!

- Widespread use of imaging, an increasing number of pheochromocytoma patients have no symptoms and are diagnosed in the course of investigation of an adrenal incidentaloma or have one of the genetic forms of the disease.
- Study showed 19 of 33 patients (57.6%) with adrenal pheochromocytoma diagnosed from 1995 to 2002 were asymptomatic, and their adrenal tumors were discovered incidentally on imaging done for other reasons [1]

[1] Motta-Ramirez GA, Remer EM, Herts BR, et al. Comparison of CT findings in symptomatic and incidentally discovered pheochromocytomas. AJR Am J Roentgenol 2005; 185:684.

Diagnostic Evaluation:

- Urinary and plasma fractionated metanephrines and catecholamines
- If there is a low index of suspicion, suggest checking 24-hour urinary fractionated catecholamines and metanephrines; if there is a high index of suspicion, suggest checking plasma fractionated metanephrines.
- 24-hour urine fractionated metanephrines and catecholamines; (Se = 98 %, Sp = 98 %).
- Although measurement of plasma fractionated metanephrines has a sensitivity of 96 to 100 %, the specificity is poor at 85 to 89 %.
- Biochemical confirmation of the diagnosis should be followed by radiological evaluation to locate the tumor

- Low risk for pheochromocytoma — 24-hour urinary fractionated catecholamines and metanephrines should be the first test

- Resistant hypertension
- Hyperadrenergic spells (eg, self-limited episodes of non-exertional palpitations, diaphoresis, headache, tremor, or pallor)
- An incidentally discovered adrenal mass that does not have imaging characteristics consistent with pheochromocytoma

- High risk for pheochromocytoma — Measuring plasma fractionated metanephrines is a first-line.

- A family history of pheochromocytoma
- A genetic syndrome that predisposes to pheochromocytoma (eg, VHL MEN2)
- A past history of resected pheochromocytoma
- An incidentally discovered adrenal mass that has imaging characteristics consistent with pheochromocytoma

Medications that may increase measured levels of catecholamines and metanephrines

Tricyclic antidepressants
Levodopa
Drugs containing adrenergic receptor agonists (eg, decongestants)
Amphetamines
Buspirone and most psychoactive agents
Prochlorperazine
Reserpine
Withdrawal from clonidine and other drugs
Ethanol

- Drugs known to give false-positive results in catecholamine testing include: labetalol, sotalol, benzodiazepines, methyldopa.
- Physical stress and obstructive sleep apnea also cause false-positive results.

-Most laboratories now measure fractionated catecholamines (dopamine, norepinephrine, and epinephrine) and fractionated metanephrines (metanephrine and normetanephrine) by high-performance liquid chromatography (HPLC) with electrochemical detection or tandem mass spectroscopy (MS/MS).
-These techniques have overcome the problems with fluorometric analysis (eg, false positive results caused by alpha-methyldopa, labetalol, or sotalol, and false negative results caused by imaging contrast agents).

CT and MRI:

- Sporadic pheochromocytoma – computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is usually performed first.
  (Either test is a reasonable first test as both detect almost all sporadic tumors because most are 3 cm or larger in diameter.
- In sporadic pheochromocytoma, both CT and MRI are quite sensitive (98 to 100 %) but are only about 70% specific because of the higher prevalence of adrenal "incidentalomas".
- The choice between CT and MRI depends upon:

- CT: exposure to radiation but no risk of exacerbation of hypertension if current radiographic contrast agents are given.
  - CT with low-osmolar contrast is safe for patients with pheochromocytoma even without alpha or beta blocker pretreatment[1].
  - After intravenous (IV) low-osmolar contrast administration for CT scan, there was a significant increase in diastolic blood pressure but no increase in plasma catecholamine levels or episodes of hypertensive crises.

- MRI: there is neither radiation nor dye.
  - This more expensive test can distinguish pheochromocytoma from other adrenal masses; on T2-weighted images, pheochromocytomas appear hyperintense and other adrenal tumors isointense, as compared with the liver.
  - However, MRI lacks the superior spatial resolution of CT.

Baid SK, Lai EW, Wesley RA, et al. Brief communication: radiographic contrast infusion and catecholamine release in patients with pheochromocytoma. Ann Intern Med 2009; 150:27.

Imaging phenotype of pheochromocytoma:

- high Hounsfield unit density on non-contrast CT scan (>20HU)
- Increased mass vascularity
- marked enhancement with intravenous [IV] contrast medium on CT with delayed contrast washout [<50 percent at 10 minutes]
- high signal intensity on T2-weighted MRI,
- cystic and hemorrhagic changes,
- bilaterality,
- or larger size [eg, >4 cm])

MIBG

- If abdominal and pelvic CT or MRI is negative in the presence of clinical and biochemical evidence of pheochromocytoma, one ought first to reconsider the diagnosis.
- If it is still considered likely, then iodine-123 (123-I) metaiodobenzylguanidine (MIBG) scintigraphy may be done. An MIBG scan can detect tumors not detected by CT or MRI, or multiple tumors when CT or MRI is positive.
- MIBG is a compound resembling norepinephrine that is taken up by adrenergic tissue.
- MIBG scintigraphy is indicated in patients with large (eg, >10 cm) adrenal pheochromocytomas (increased risk of malignancy) or paraganglioma (increased risk of multiple tumors and malignancy)
- Surgery is never indicated based on MIBG findings alone; MIBG findings should always be corroborated by findings on computed imaging.
- Normal adrenal glands take up MIBG, and the uptake may be asymmetric.
- MIBG is less sensitive in smaller adrenal lesions such that tumors <2.5 cm are likely to be negative.

FDG-PET:

- Fludeoxyglucose-positron emission tomography (FDG-PET) is more sensitive than 123-I MIBG and CT/MRI for detection of metastatic disease.

- Prospective study of 216 patients with suspected pheochromocytoma/paraganglioma – looking at the utility of integrated FDG-PET/CT imaging as compared with 123-I MIBG and conventional cross-sectional imaging with CT or MRI [1]
  - 60 of whom had non-metastatic pheochromocytoma/paraganglioma,
  - 95 of whom had metastatic pheochromocytoma/paraganglioma, and
  - 61 of whom did not have pheochromocytoma/paraganglioma.

- For the primary tumor, the sensitivity of PET/CT for non-metastatic tumors was similar to that of 123-I MIBG but less than that of CT/MRI (77, 75, and 96 percent, respectively).

- Among the patients who had paraganglioma/pheochromocytoma ruled out, specificity was comparable (90, 92, and 90 percent, respectively).

- When the analysis was limited to 26 paragangliomas of the head and neck, PET/CT was more sensitive than 123-I MIBG (85 versus 52 percent).

[1]Timmers HJ, Chen CC, Carrasquillo JA, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. J Natl Cancer Inst 2012; 104:700.

Learning Objectives:

- Discuss diagnostic challenges of Pheochromocytoma evaluation in patients with chronic kidney disease.

Pheochromocytoma and chronic kidney disease:

- The usual screening test involving a 24-hour urinary collection for metanephrines and catecholamines is useless in anuric/oliguric patients.
- Clouding the issue is the fact that many patients with ESRD are hypertensive due to their renal disease.
- Although measurement of serum catecholamine concentrations would seem logical, patients undergoing long-term HD have increased levels compared with the controls.
- Furthermore, no definitive reference ranges for serum catecholamine concentrations have been established for patients receiving long-term HD [1].

[1] Stumvoll M, Radjaipour M, Seif F. Diagnostic considerations in pheochromocytoma and chronic hemodialysis: case report and review of the literature. Am J Nephrol. 1995;15:147-151.

Am J Nephrol 1995;15:147–151
(DOI:10.1159/000168820)

Diagnostic Considerations in Pheochromocytoma and Chronic Hemodialysis: Case Report and Review of the Literature

Stumvoll M.[a] · Radjaipour M.[b] · Seif F.[b]

Author affiliations

[a]University of Rochester Medical School, Division of Endocrinology and Metabolism, Rochester, N.Y., USA; [b]Medizinische Universitätsklinik, Abteilung fiir Endokrinologie, Tubingen, Deutschland

- Evaluated the literature comparing catecholamine levels in hypertensive controls and in hypertensive patients receiving long-term HD. The authors found:
- norepinephrine concentration was consistently elevated in the long-term HD group, but never more than 3-fold.
- The dopamine level was increased approximately 2-fold in the long-term HD group.
- Epinephrine, however, was not significantly different in the 2 groups.
- Looking at pheochromocytoma in patients receiving long-term HD, this same review noted epinephrine and norepinephrine concentrations to be at least 3.3-fold higher than normal values in 4 of 7 and 5 of 7 case reports, respectively.
- We conclude that plasma epinephrine elevations can be evaluated in the conventional manner, and norepinephrine concentrations beyond a 3-fold elevation should raise the suspicion of a pathological catechol excess syndrome.

Endocr Pract. 2014 Feb;20(2):139-44. doi: 10.4158/EP13251.OR.

Plasma free metanephrine and normetanephrine levels are increased in patients with chronic kidney disease.

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- OBJECTIVE: to assess plasma free metanephrine (MN) and normetanephrine (NMN) in chronic kidney disease patients (CKD) with or without dialysis.
- METHODS: In this prospective observational study we performed enzyme-linked immunosorbent assays (ELISAs) to evaluate plasma free MN and NMN in 48 CKD patients (15 with stage 3-5 CKD without dialysis, 26 on hemodialysis [HD], and 7 continuous ambulatory peritoneal dialysis [CAPD]), 30 patients with histologically proven pheochromocytoma, and 43 hypertensive patients.
- Adrenal masses were ruled out by abdominal computed tomography (CT) scans in all CKD and control hypertensive patients.

RESULTS:

- - All 3 CKD groups (HD, CAPD, and CKD without dialysis) had significantly higher plasma free MN and NMN levels than the control hypertensive group (P<.0055).
  - HD and CAPD patients had significantly lower plasma free NMN (P<.0055), but free MN levels were not significantly different than those observed in pheochromocytoma patients.
  - In patients with HD, CAPD, and CKD without dialysis, plasma free MN and NMN were higher than manufacturer's upper limits of normal in 57.7% and 28.5%, 13.3% and 61.5%, and 85.7% and 26.6%, respectively.
  - Regression models showed that the number of dialysis years was significantly correlated with plasma free MN (r = 0.615, P<.001) but not free NMN.

- CONCLUSION: Plasma free MN and NMN levels are frequently elevated in CKD patients, particularly in those on dialysis.
  - Plasma free MN levels significantly overlap with the range in pheochromocytoma patients and correlate with the number of years on dialysis.

- Discuss familial disorders with bilateral adrenal nodules and Pheochromocytoma.

Genetic testing should be considered if a patient has one or more of the following:

- Paraganglioma
- Bilateral adrenal pheochromocytoma
- Unilateral adrenal pheochromocytoma and a family history of pheochromocytoma/paraganglioma
- Unilateral adrenal pheochromocytoma onset at a young age (eg, <45 years), or
- Other clinical findings suggestive of one of the syndromic disorders

Gene	Loci	Protein function	Syndrome	Clinical manifestations or associated TU	Inheritance	Primary location	Malignacy rate
RET	10q11.2	Transmembrane tyrosine kinase	MEN2A	MTC, Hyperparathyroidism, cutaneous lichen amyloidosis	AD	PCC (single ou bilateral)	<5%
			MEN2B	MTC, mucosal neuromas, marfanoid habitus			
VHL	3p25–26	Ubiquitin ligase 3E activity	VHL	Hemangioblastomas, clear-cell renal cell carcinomas; endolymphatic sac tumors, cystadenomas; pancreatic islet cell tumor	AD	PCC (>bilateral)	<5%
NF1	17q11.2	GTPase	NF1	Café au lait macules, neurofibromas, iris Linch nodules, optic nerve gliomas, dysplasia of the long bones, astrocytomas, soft tissue sarcomas, CML, childhood learning disabilities, seizures	AD	PCC (>single)	12%
SDHD	11q23.1	Complex II anchoring subunit	PGL1	Papillary thyroid cancer; GIST	AD; PI	HNPGL/MPGL	<5%
SDHAF2	11q13.1	Cofactor for complex II	PGL2	GIST	AD; PI	HNPGL/MPGL	Low
SDHC	1q23.3	Complex II-anchoring subunit	PGL3	GIST	AD	HNPGL > SPCC = TAPGL = MPGL	Low
SDHB	1p36.1	Complex II catalytic subunit	PGL4	Renal cell carcinomas; GIST, thyroid tumors, neuroblastomas	AD	TAPGL > HNPGL = SPGL = MPGL < SPCC	30–70%
SDHA	5p15	Complex II catalytic subunit			AD	TAPGL/HNPGL	Low
TMEM127	2q11.2	Transmembrane protein			AD	SPCC > BPCC > TAPGL = HNPGL = MPGL	Low
MAX	14q23–3	BHL HLZ transcription factor			ADPI	SPCC = BPCC > TAPGL	10%

AD, autosomal dominant; PI, paternal inheritance; TAPGL, thoracic or abdominal PGL; HNPGL, head and neck PGL; SPCC/PGL, single PCC/PGL; BPC/PGL, bilateral PCC/PGL; MPGL, multiplal PGL.

Familial pheochromocytoma Tx:

- For patients with multiple endocrine neoplasia type 2 (MEN2) (which is a diffuse medullary disease) with evidence of bilateral disease >2 cm in diameter on imaging, we suggest consideration of complete bilateral adrenalectomy because of the risk of recurrent pheochromocytoma.
- For most patients with von Hippel-Lindau (VHL) (which is a less diffuse medullary disease) with evidence of bilateral disease on imaging, we suggest cortical-sparing bilateral adrenalectomy. Because of the risk of recurrent disease in these patients, we recommend long-term biochemical monitoring.
- For patients with a high malignancy rate in the kindred, we suggest not performing cortical-sparing adrenalectomy.
- In patients with MEN2 or VHL with unilateral pheochromocytoma, we suggest unilateral adrenalectomy. These patients then need annual biochemical testing indefinitely for evidence of contralateral pheochromocytoma.

Thank you!