Current Cardiology Reports (2019) 21: 104
https://doi.org/10.1007/s11886-019-1184-y

HYPERTENSION (DS GELLER AND DL COHEN, SECTION EDITORS)

Pheochromocytoma/Paraganglioma: Is This a Genetic Disorder?

Lauren Fishbein [1]

Published online: 31 July 2019

Abstract

Pheochromocytomas and paragangliomas (PCC/PGL) are neuroendocrine tumors of the adrenal medulla and extra-adrenal ganglia which often over-secrete catecholamines leading to cardiovascular morbidity and even mortality. These unique tumors have the highest heritability of all solid tumor types with up to 35–40% of patients with PCC/PGL having a germline predisposition.

Purpose of Review To review the germline susceptibility genes and clinical syndromes associated with PCC/PGL.

Recent Findings There are over 12 PCC/PGL susceptibility genes identified in a wide range of pathways. Each gene is associated with a clinical syndrome with varying penetrance for both primary and metastatic PCC/PGL and often includes increased risk for additional tumors besides PCC/PGL.

Summary Patients with sporadic or hereditary PCC/PGL should be monitored for life given the risk of multiple primary tumors, recurrence, and metastatic disease. All patients with PCC/PGL should be referred for consideration for clinical genetic testing given the high heritability of disease.

Keywords Pheochromocytoma · Paraganglioma · Genetics · Hereditary · Metastatic pheochromocytoma

Introduction

Pheochromocytomas and paragangliomas are tumors of the adrenal medulla and extra-adrenal paraganglia, respectively. The incidence of pheochromocytoma/paraganglioma is 2–8 per million and they account for at least 0.2–0.6% of all patients with hypertension [1]. The perioperative mortality previously was quite high due to secretion of catecholamines from these tumors leading to hemodynamic instability, but with the use of perioperative alpha blockade and improvements in anesthesia, the morbidity and mortality rates are as low as 0–2% around surgical resection [2]. Nevertheless, consequences from undiagnosed tumors can be grave and include uncontrolled hypertension, stroke, cardiomyopathy, and even death. Particularly vulnerable populations for missed diagnosis include younger patients with hypertension, patients with resistant hypertension, patients with acute dilated cardiomyopathy and Takotsubo cardiomyopathy, and patients with adrenal incidentalomas.

A unique feature of pheochromocytomas and paragangliomas is that up to 35–40% are associated with a hereditary predisposition due to germline pathogenic variants in over 12 susceptibility genes [3, 4]. Knowing if a patient carries a pathogenic variant in a susceptibility gene is important as it alters the surveillance and screening needed for the patient based on the associated tumor syndrome, and it affects the clinical care of the relatives who may be asymptomatic carriers. Given this, it is imperative that all providers involved in the multi-disciplinary care of patients with pheochromocytomas and paragangliomas are aware of the genetic disorders associated with these unique tumors. This review focuses on the germline susceptibility genes that predispose to development of pheochromocytomas and paragangliomas and discusses the clinical syndromes and surveillance recommendations associated with alterations in each gene.

Screening and Diagnosis

Screening for pheochromocytoma and paraganglioma (PCC/PGL) should be initiated for any individual with new onset

This article is part of the Topical Collection on *Hypertension*

✉ Lauren Fishbein
lauren.fishbein@ucdenver.edu

[1] Department of Medicine, Division of Endocrinology, Metabolism and Diabetes, Division of Biomedical Informatics and Personalized Medicine, University of Colorado School of Medicine, 12801 E. 17th Ave, MS 8106, Aurora, CO 80045, USA

difficult to control hypertension, especially for children and young adults. In addition, any patient with an adrenal incidentaloma should be screened for pheochromocytoma whether hypertensive or not [5, 6]. The hypertension associated with PCC/PGL can be sustained, episodic or orthostatic. The classic triad of symptoms includes headaches, palpitations, and diaphoresis, but this triad is not seen in many patients [7]. Other symptoms can include anxiety, tachycardia, syncope, nausea, abdominal pain, new onset hyperglycemia, or worsening diabetes mellitus and some patients are asymptomatic [8–10]. Symptoms from head and neck PGL often are secondary to mass effect rather than catecholamine secretion as most are derived from parasympathetic ganglia and are usually non-secreting. For this reason, many head and neck PGL are found incidentally but symptoms can include tinnitus, neck pain, and dysphagia. Some PCC/PGL located outside the head and neck region also can be non-secreting, associated with minimal symptoms and found incidentally. Nevertheless, the majority of PCC/PGL are secreting and providers must suspect PCC/PGL in order to make the diagnosis. Once suspected, the mainstay of diagnosis for the secreting tumors is biochemical testing with plasma free metanephrines or 24 h urine fractionated metanephrines and catecholamines [11•]. With newer technologies, the plasma and urine tests have nearly equal sensitivity and specificity [11•, 12]. In an ideal setting, patients should be supine for 30 min prior to plasma collection for accurate measurement. There are many medications and substances which can lead to false positive elevations of catecholamines and metanephrines and these should be avoided if possible. Some of these include tricyclics, alpha blockers, MAOIs, sympathomimetics, cocaine, and even acetaminophen, depending on the laboratory assay run [11•]. Positive results from biochemical testing should be followed up with cross sectional imaging using CT or MRI to localize the tumor. Surgical removal after perioperative alpha blockade is the mainstay of treatment.

Genetics

Previously, PCC/PGLs were thought to be connected with genetic syndromes only 10% of the time, based on the association with the classic cancer predisposition syndromes of neurofibromatosis type 1, von Hippel-Lindau syndrome, and multiple endocrine neoplasia type 2. In the last two decades, however, the field of genetics of PCC/PGL has exploded. There are now over 12 genes predisposing to PCC/PGL and they account for 35–40% of all cases [3, 4, 13] (see Table 1 and Fig. 1). Large-scale genomic studies have shown that another about 30% have tumor specific somatic driver mutations, in the same predisposition genes and in additional genes [14, 15, 16•, 17]. Taken together, we now know the driving event for tumorigenesis in about 60–70% of cases.

Germline Genetics

Because up to 40% of PCC/PGL are associated with inherited susceptibility gene pathogenic variants, expert guidelines recommend that all patients with PCC/PGL be considered for clinical genetic testing [11•, 18]. Clinical genetic testing most often is performed now using targeted sequencing of panels of genes rather than using a one gene at a time approach. Screening and surveillance guidelines differ based on the germline mutation status (see Table 2). At minimum, all patients who have had PCC/PGL (sporadic or hereditary) should be monitoring for life with annual biochemical testing with plasma free metanephrines or 24 h urine fractionated metanephrines/catecholamines. If a person carries a pathogenic variant in a susceptibility gene, additional screening tests may be recommended based on the genetic condition and other possible associated tumors. In addition, the proband's blood relatives should be offered cascade genetic testing specific for the known pathogenic variant. Any family member who tests positive should be screened appropriately. The PCC/PGL susceptibility genes and associated clinical syndromes are discussed below.

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is a common autosomal dominant condition affecting about 1 in 3000 individuals and caused by pathogenic variants in the *NF1* gene located on chromosome 17 [19]. The *NF1* gene encodes the protein neurofibromin, which inactivates RAS to regulate the MAP kinase pathway for cellular proliferation [20]. When neurofibromin is mutated and inactivated, there is uncontrolled cell proliferation, leading to tumorigenesis.

NF1 usually is diagnosed by history and physical exam before any clinical genetic testing is performed. The clinical criteria for diagnosis includes patients having two or more of the following: six or more café-au-lait spots of certain size based on pubertal status, Lisch nodules which are benign iris hamartomas, two or more cutaneous neurofibromas, one or more plexiform neurofibroma, axillary or inguinal freckling, optic glioma, sphenoid dysplasia, or thinning of the long bones, and a first degree relative with NF1 [19]. Pheochromocytomas are associated with NF1, although not part of the diagnostic criteria. It is reported that 3–5% of patients with NF1 will develop PCC/PGL [19, 21, 22]; however, this number actually may be higher. A study of 48 patients with NF1 evaluated in a hypertension clinic found that 15% had PCC [22], and an autopsy study of patients with NF1 suggested up to 13% of patients have PCC/PGL [23]. Almost all PCC/PGL associated with NF1 will be intra-adrenal pheochromocytomas and they can be bilateral. The median age of diagnosis of PCC in patients with NF1 is

Table 1 Susceptibility genes and syndromes

Gene	Syndrome	% PCC/PGL associated with germline pathogenic variant	Clinical features	Biochemical profile
NF1	Neurofibromatosis type 1	3%	Café-au-lait spots Neurofibromas (cutaneous or plexiform) Lisch nodules Axillary/inguinal freckling Optic gliomas Skeletal dysplasia Pheochromocytomas (not part of diagnostic criteria)	Adrenergic predominance
VHL	von Hippel-Lindau disease	6%	CNS and retinal hemangioblastomas Clear cell renal cell carcinoma Pancreatic neuroendocrine tumors Pheochromocytomas Renal and pancreatic cysts Endolymphatic sac tumors Epididymal cysts	Noradrenergic
MEN2	Multiple endocrine neoplasia type 2	7%	MEN2A: Medullary thyroid cancer Hyperparathyroidism Pheochromocytomas MEN2B: Medullary thyroid cancer Pheochromocytomas Marfanoid habitus Mucosal and cutaneous neuromas Gastrointestinal ganglioneuromas	Adrenergic predominance
SDHx genes	Hereditary paraganglioma-pheochromocytoma syndrome	*SDHB* 10% *SDHD* 9% *SDHC* 1% *SDHA* < 1% *SDHAF2* < 0.1%	Pheochromocytomas and paragangliomas And in *SDHB*, *SDHD*, *SDHC*: Clear cell renal cell carcinomas Gastrointestinal stromal tumors And in *SDHA:* Gastrointestinal stromal tumors	Noradrenergic Possibly dopaminergic Possibly non-secreting
TMEM127	Hereditary pheochromocytoma and paraganglioma	< 1%	Pheochromocytomas Possibly paragangliomas and renal cell carcinomas	Adrenergic predominance
MAX	Hereditary pheochromocytoma and paraganglioma	< 1%	Pheochromocytomas and paragangliomas	Adrenergic predominance
EPAS1	Polycythemia paraganglioma syndrome	< 1%	Polycythemia Rare pheochromocytomas and paragangliomas Rare somatostatinomas	Noradrenergic
FH	Hereditary leiomyomatosis and renal cell cancer syndrome	< 1%	Cutaneous and uterine leiomyomas Type 2 papillary renal cell carcinomas Rare pheochromocytomas and paragangliomas	Noradrenergic
MDH2	Hereditary pheochromocytoma and paraganglioma	< 1%	Pheochromocytomas and paragangliomas	Noradrenergic

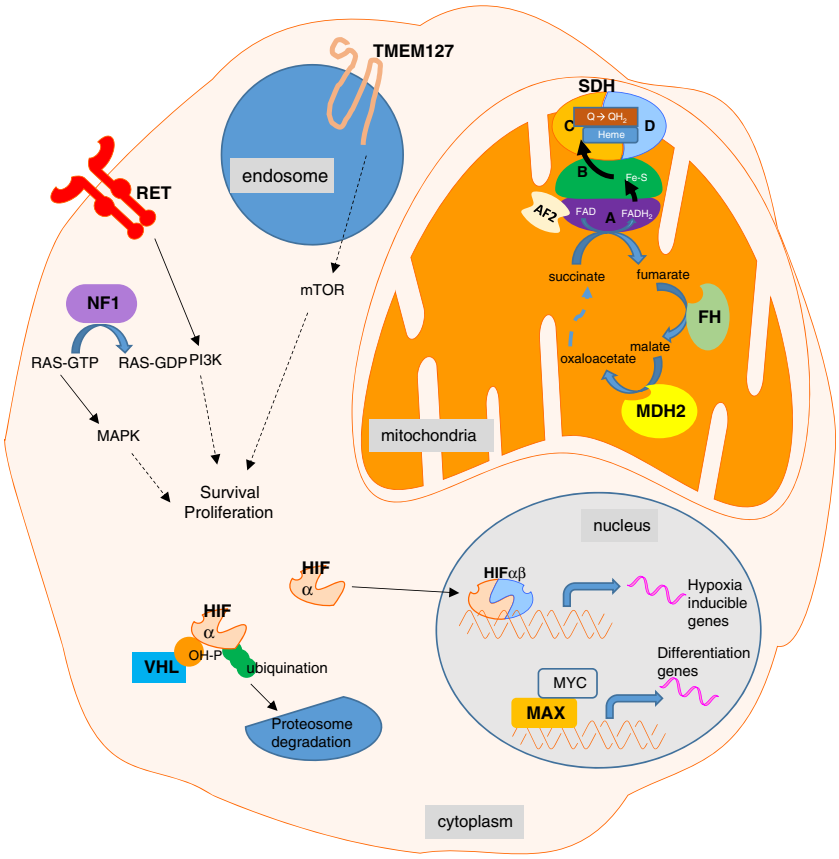

Fig. 1 Schematic of the roles in the cell for the protein products from the pheochromocytoma and paraganglioma susceptibility genes.

41 years old [21]. The risk of malignancy in NF1 associated PCC is high, up to 12% [19, 21, 24]. Most NF1 associated pheochromocytomas will have epinephrine/metanephrine secretion [25].

The most recent guidelines from the American College of Medical Genetics and Genomics (ACMG) suggest that patients with NF1 be screened for PCC/PGL if hypertensive and over the age of 30 or pregnant [19]. These guidelines do not suggest screening asymptomatic patients with NF1 for pheochromocytoma. However, other experts suggest that all patients with NF1 have biochemical testing for PCC/PGL at least every 3 years based on one study of 41 patients with NF1 and PCC/PGL [21]. This study found that only 7.3% of PCC/PGL in patients with NF1 were discovered by case detection and 31% were found incidentally [21]. These data suggest screening should occur in all patients with NF1; however, of course, this study is limited by the small sample size.

Table 2 Screening recommendations for pathogenic variant carriers

Gene	Screening Recommendations
NF1	Biochemical testing[§] in hypertensive patients over age 30 or pregnant
VHL and *RET*	Annual biochemical testing[§]
SDHx genes, *TMEM127* and *MAX*	Annual biochemical testing[§*]
	Biennial full body imaging from neck to pelvis with MRI or CT
EPAS1, FH and *MDH2*	Unknown, likely:
	Annual biochemical testing[§]
	Biennial full body imaging from neck to pelvis with MRI or CT

[§] Biochemical testing means plasma free metanephrines or 24hr urine fractionated metanephrines and catecholamines.

*Because of the potential for dopaminergic secretion of PCC/PGL, screening for *SDHx* carriers may include both plasma metanephrines and catecholamines.

Biennial time interval is the current recommendation which may change with further research.

von Hippel-Lindau Syndrome

von Hippel-Lindau (vHL) syndrome is an autosomal dominant cancer predisposition syndrome which affects 1 in 36,000 individuals and is caused by inactivating pathogenic variants in the *VHL* gene on chromosome 3 [26]. The VHL protein regulates hypoxia inducible factor alpha (HIFα). In the presence of oxygen, VHL protein binds HIFα and ubiquitinates it for proteosomal degradation [27]. In the presence of hypoxia or if VHL is mutated, this interaction cannot occur, and HIFα moves into the nucleus to act as a transcription factor activating genes involved in angiogenesis, thereby promoting tumorigenesis.

vHL syndrome is characterized by hemangioblastomas of the central nervous system, clear cell renal cell carcinoma and renal cysts, pancreatic neuroendocrine tumors and pancreatic cysts, endolymphatic sac tumors and epididymal cysts as well as pheochromocytomas [26, 28]. About 20% of patients with vHL will develop intra-adrenal pheochromocytoma [29] with rare reports of extra-adrenal paraganglioma [30, 31]. The vHL-associated pheochromocytomas can be unilateral or bilateral, and the mean age at diagnosis is 30 years old. Metastatic disease is rare, occurring in about 5% of patients [32]. Biochemical testing shows a norepinephrine/normetanephrine predominance [25], thought to occur because of silencing, by promoter hypermethylation, of the enzyme PNMT which converts norepinephrine to epinephrine in the adrenal medulla.

There are genotype-phenotype correlations with the pathogenic variants of *VHL*. Certain *VHL* pathogenic variants are more highly associated with PCC, usually missense mutations on the surface of the protein [33]. On the other hand, patients with *VHL* pathogenic variants that are truncating or exonic deletions have a lower penetrance for developing PCC and a higher penetrance for renal cell cancer [33]. Nevertheless, all patients with vHL, regardless of the exact variant, are recommended to be screened for PCC/PGL annually with plasma metanephrines beginning at age 5 [26, 28].

Multiple Endocrine Neoplasia Type 2

Multiple endocrine neoplasia type 2 (MEN2) is another autosomal dominant syndrome which affects 1 in 30,000 individuals and caused by pathogenic variants which activate the protoconcogene *RET*, located on chromosome 10 [34]. The RET protein is a tyrosine kinase receptor on the cell membrane which, when activated by ligand binding or by mutations, sends signals through the PI3 kinase pathway to stimulate cell growth and survival.

There are two subtypes of MEN2: MEN2A, and MEN2B [35]. Over 90% of patients with germline activating *RET* pathogenic variants will have MEN2A, characterized by risk for medullary thyroid cancer, hyperparathyroidism, and pheochromocytoma. Patients with only medullary thyroid cancer (familial medullary thyroid cancer) were considered a third subtype in the past but now are thought to be part of MEN2A, just with low penetrance for hyperparathyroidism and pheochromocytoma. Ten percent of patients with *RET* activating pathogenic variants will develop MEN2B, characterized by medullary thyroid cancer and pheochromocytoma but no risk of hyperparathyroidism. These patients with MEN2B also develop mucosal and cutaneous neuromas especially on the lips and eyelids, gastrointestinal ganglioneuromas and a marfanoid habitus. In patients with MEN2, diagnosis of PCC occurs after or with the diagnosis of medullary thyroid cancer in 85% of cases, but it can occur before the diagnosis of medullary thyroid cancer in about 15% of cases [36]. About 50% of patients with MEN2 will develop pheochromocytoma and at least 50% of those patients will have bilateral disease [35, 36]. Paragangliomas are rare. The mean age for developing PCC/PGL in MEN2 is between ages 30 and 40 [35]. The risk of metastatic pheochromocytoma for patients with MEN2 is low at less than 5%. Most MEN2-associated pheochromocytomas will have epinephrine/metanephrine secretion [25].

Guidelines recommend annual biochemical testing with plasma free metanephrines for pheochromocytoma screening in patients with MEN2 starting at different ages depending on the *RET* codon mutated given varying genotype-phenotype correlations. Those individuals with the higher risk mutations for PCC/PGL in codons 634, 918, and 883 are screened earlier beginning at age 11, and those with all other mutations considered moderate risk can start screening later, at age 16 [35].

Hereditary Paraganglioma-Pheochromocytoma Syndrome

After the discovery of the classic cancer predisposition syndromes described above, there were still patients who clearly had hereditary cases of PCC/PGL without having clinical features of NF1, vHL or MEN2. Ultimately, the majority of these cases were found to have hereditary paraganglioma-pheochromocytoma syndrome caused by pathogenic variants in the *Succinate Dehydrogenase Subunit (SDH)* genes, *SDHA*, *SDHB*, *SDHC*, *SDHD,* and the co-factor, *SDHAF2*. The succinate dehydrogenase complex is complex II of the mitochondrial respiratory chain and also functions as an enzyme converting succinate to fumarate in the Kreb's cycle. When the complex is disrupted by loss-of-function pathogenic variants, high levels of succinate accumulate and competitively inhibit 2-oxoglutarate-dependant dioxygenases, such as histone and DNA

demethylases, as well as HIF prolyl-hydroxlases, because of the structural similarity between succinate and 2-oxyglutarate (also called α-ketoglutarate) [37, 38].

The clinical syndrome associated with pathogenic variants in each *SDHx* gene is described below. *SDHx*-associated PCC/PGL have a norepinephrine/normetanephrine predominant profile [25], thought to be secondary to hypermethylation of the *PNMT* gene promoter, silencing expression of the gene, similar to *VHL*-associated tumors. Guidelines by the American Association of Cancer Researchers (AACR) recommend that asymptomatic carriers of pathogenic variants in *SDHx* genes have at least annual biochemical testing with plasma free metanephrines or 24 h urine fractionated metanephrines and catecholamines to detect secreting PCC/PGL and biennial full body imaging from neck to pelvis with CT or MRI to detect non-secreting PCC/PGL and other associated tumor types as will be described below [39•]. Each gene when disrupted is associated with different penetrance of disease, although one limitation is that many studies are based on under 50–100 cases for some of the genes. Hopefully with time and larger databases, more precise information about genotype/phenotype correlations and penetrance will be determined and used to help guide screening recommendations.

SDHA

Heterozygous pathogenic variants in *SDHA* lead to hereditary paraganglioma-pheochromocytoma syndrome [40]. *SDHA* is located on chromosome 5 and has several pseudogenes on chromosome 5 and 3, making variant testing more challenging [41]. Most commercial panel tests will sequence the gene with confidence but do not assess for deletions or duplications given this challenge. *SDHA* pathogenic variants are associated with gastrointestinal stromal tumors most frequently but also lead to PCC/PGL [40, 42–44]. *SDHA* pathogenic variants account for less than 1% of all PCC/PGL and the penetrance is quite low at 10% by age 70 for non-index *SDHA* carriers [43]. However, of those patients who develop PCC/PGL, there is a high rate of metastatic disease at 12% [42]. *SDHA* pathogenic carriers can develop PCC/PGL at any location in the body, including head and neck PGLs, and the median age at diagnosis is 43 years old [42, 43]. Homozygous mutations in *SDHA* lead to Leigh's syndrome which is an early onset neurodegenerative disorder often with an associated cardiomyopathy [45].

SDHB

Heterozygous pathogenic variants in *SDHB*, on chromosome 1, lead to hereditary paraganglioma-pheochromocytoma syndrome [46]. Up to 10% of all patients with PCC/PGL will have pathogenic variants in *SDHB*. *SDHB* pathogenic variant carriers usually have single extra-adrenal PGL; however, they can develop multiple primary tumors in any location (adrenal, head and neck, thoracic or extra-adrenal). The median age at diagnosis of PCC/PGL is 32 years [47]. The penetrance of *SDHB* pathogenic variants for PCC/PGL is about 25% by age 60 [48•, 49, 50]. Once a tumor forms, the risk of metastatic disease is high around 23–25% [48•, 51, 52]. *SDHB* pathogenic variants also increase risk for a patient developing clear cell renal cell carcinoma with about a 4–5% risk by age 60, and an increased risk as well for gastrointestinal stromal tumors [48•].

SDHD

Heterozygous pathogenic variants in *SDHD* also lead to hereditary paraganglioma-pheochromocytoma syndrome [53]. *SDHD* gene is located on chromosome 11, and pathogenic variants in the gene are associated with almost exclusively paternal transmission of disease with rare exception [54–56]. The paternal transmission can make recognizing familial inheritance difficult as the disease may seem to "skip" generations. Patients with *SDHD* pathogenic variants have perhaps the highest penetrance of all *SDHx* genes with a 43% risk of developing PCC/PGL by age 60 [48•] and *SDHD* pathogenic variants account for about 9% of all PCC/PGL. Patients also are at risk for gastrointestinal stromal tumors and clear cell renal cell carcinoma, although with less risk than *SDHB* pathogenic variant carriers [48•, 57]. The most common presentation is that of multiple head and neck PGLs, although primary tumors can develop in any location and many patients have multiple primary tumors throughout the lifetime [48•, 50, 57]. The median age of PCC/PGL diagnosis with *SDHD* pathogenic variants is 33 years [47]. The risk of metastatic disease is low at less than 5% [48•, 52].

SDHC

The *SDHC* gene is located on chromosome 1 and heterozygous pathogenic variants lead to hereditary paraganglioma-pheochromocytoma syndrome [58]. Less than 1% of patients with PCC/PGL have pathogenic variants in this gene making it difficult to assess penetrance given the small number of patients. One study suggests the penetrance is 25% by age 60 [48•]; however, this study is limited by the small sample size and bias given high number of probands (only 43 *SDHC* pathogenic variant carriers, over half of which ($N = 26$) were probands). The estimated penetrance from this study is higher than most experts believe, as allegorically there is usually only one affected family member. Most patients develop a single head and neck PGL (over 80%). PGLs in the thoracic compartment are the next most common location (10%) [59]. The mean age at PCC/PGL diagnosis is 38 years old and there is a very low risk of metastatic disease [47, 59].

SDHAF2

SDHAF2 is a co-factor for the succinate dehydrogenase complex and pathogenic variants in the gene located on chromosome 11 have been reported in a few families with head and neck PGLs, often multiple and bilateral [42, 60, 61]. *SDHAF2* pathogenic variants account for less than 0.1% of PCC/PGL [42]. Interestingly, expression of disease in *SDHAF2* pathogenic variant carriers shows paternal transmission, similar to *SDHD*. There is limited data given the small number of patients with *SDHAF2* pathogenic variants but the malignancy rate is believed to be negligible.

Other Genes Associated with Hereditary Pheochromocytoma and Paraganglioma

Several additional susceptibility genes have been identified which together contribute to about 2% of cases of PCC/PGL. For example, loss-of-function germline pathogenic variants in *TMEM127* (*Transmembrane Protein 127*) increase risk of PCC/PGL and clear cell renal cell carcinoma [62–64]. TMEM127 is a transmembrane protein on the early endosome thought to play a role in the mTOR pathway. Germline pathogenic variants causing loss-of-function in the transcription factor *MAX* (*Myc-associated Protein X*) also increase risk for PCC/PGL [65, 66]. These patients often have PCC which can be multifocal within a single adrenal gland or develop bilateral PCC [65, 66]. The number of cases are limited and there are conflicting reports of increased risk of malignancy in *MAX*-associated PCC/PGL [42, 65, 66]. Somatic mosaic gain-of-function variants in *EPAS1*, encoding HIF2α, lead to increased risk of PCC/PGL with or without polycythemia and somatostatinomas [67–71].

Two additional Kreb's cycle genes are implicated as PCC/PGL susceptibility genes. *Fumarate Hydratase*, *FH*, coverts fumarate to malate. *FH* loss-of-function pathogenic variants lead to hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) [72]. Germline pathogenic variants in *FH* have been found in a few families with PCC/PGL [73, 74]. Interestingly, all reported cases have been in patients without features of HLRCC syndrome and the mutations are in different regions of the gene. *Malate Dehydrogenase*, *MDH2,* coverts malate to oxaloacetate. A few families have been reported with heterozygous loss-of-function pathogenic variants in this gene and PCC/PGL [75, 76].

Through genomic approaches, more genes are being identified which have germline variants in patients with either hereditary or multiple primary PCC/PGL, including *SCL25A11* [77], *GOT2* [78], *DNMT3A* [79], and *DLST* [80]. These genes potentially may be additional low penetrant susceptibility genes for PCC/PGL, but further studies are needed to prove causality.

Conclusions

In conclusion, pheochromocytomas and paragangliomas are the most commonly inherited solid tumor type with up to 35–40% of patients having a known susceptibility gene pathogenic variant. Therefore, all patients with PCC/PGL should be referred for genetic counseling and testing, even in patients without a recognized familial inheritance. Knowing the germline susceptibility will allow for improved surveillance and screening for the patients and their family members. Even patients with sporadic PCC/PGL (patients with no identified susceptibility gene) should be monitored for life with at least annual biochemical testing to screen for recurrence or metastatic disease, which can have a long latency period, even 20-40 years after primary tumor diagnosis. As more PCC/PGL susceptibility gene pathogenic variant carriers are identified and larger databases and studies are completed, screening recommendations may change over time. Finally, patients with sporadic disease but phenotypes suspicious for hereditary disease (i.e., familial cases, multiple primary tumors, metastatic disease, young age, etc.) should be considered for referral back to medical genetics every 5 years or so to be re-evaluated as newly confirmed PCC/PGL susceptibility genes may be identified.

Funding Information LF is supported by the American Cancer Society Mentored Research Scholar Grant MRSG-15-063-01-TBG.

Compliance with Ethical Standards

Conflict of Interest Lauren Fishbein declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lloyd RVOR, Kloppel G, Rosai J. WHO classification of tumours: pathology and genetics of tumours of endocrine organs. 4th ed. Lyon: IARC; 2017.
2. Bruynzeel H, Feelders RA, Groenland TH, van den Meiracker AH, van Eijck CH, Lange JF, et al. Risk factors for hemodynamic

instability during surgery for pheochromocytoma. J Clin Endocrinol Metab. 2010;95(2):678–85. https://doi.org/10.1210/jc.2009-1051.
3. Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. Nat Rev Endocrinol. 2015;11(2):101–11. https://doi.org/10.1038/nrendo.2014.188.
4. Fishbein L, Merrill S, Fraker DL, Cohen DL, Nathanson KL. Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing. Ann Surg Oncol. 2013;20(5):1444–50. https://doi.org/10.1245/s10434-013-2942-5.
5. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European network for the study of adrenal tumors. Eur J Endocrinol. 2016;175(2):G1–G34. https://doi.org/10.1530/EJE-16-0467.
6. Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, et al. The American Association of Clinical Endocrinologists and American Association of endocrine surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009;15(Suppl 1):1–20. https://doi.org/10.4158/EP.15.S1.1.
7. Cohen DL, Fraker D, Townsend RR. Lack of symptoms in patients with histologic evidence of pheochromocytoma: a diagnostic challenge. Ann N Y Acad Sci. 2006;1073:47–51. https://doi.org/10.1196/annals.1353.005.
8. Kopetschke R, Slisko M, Kilisli A, Tuschy U, Wallaschofski H, Fassnacht M, et al. Frequent incidental discovery of phaeochromocytoma: data from a German cohort of 201 phaeochromocytoma. Eur J Endocrinol. 2009;161(2):355–61. https://doi.org/10.1530/EJE-09-0384.
9. Mannelli M, Ianni L, Cilotti A, Conti A. Pheochromocytoma in Italy: a multicentric retrospective study. Eur J Endocrinol. 1999;141(6):619–24.
10. Wachtel H, Cerullo I, Bartlett EK, Roses RE, Cohen DL, Kelz RR, et al. Clinicopathologic characteristics of incidentally identified pheochromocytoma. Ann Surg Oncol. 2015;22(1):132–8. https://doi.org/10.1245/s10434-014-3933-x.
11.• Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–42. https://doi.org/10.1210/jc.2014-1498. **The Endocrine Society guidelines for the evaluation and treatment of pheochromocytomas and paragangliomas.**
12. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287(11):1427–34.
13. Mannelli M, Castellano M, Schiavi F, Filetti S, Giacche M, Mori L, et al. Clinically guided genetic screening in a large cohort of italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. J Clin Endocrinol Metab. 2009;94(5):1541–7. https://doi.org/10.1210/jc.2008-2419.
14. Burnichon N, Vescovo L, Amar L, Libe R, de Reynies A, Venisse A, et al. Integrative genomic analysis reveals somatic mutations in pheochromocytoma and paraganglioma. Hum Mol Genet. 2011;20(20):3974–85. https://doi.org/10.1093/hmg/ddr324.
15. Castro-Vega LJ, Letouze E, Burnichon N, Buffet A, Disderot PH, Khalifa E, et al. Multi-omics analysis defines core genomic alterations in pheochromocytomas and paragangliomas. Nat Commun. 2015;6:6044. https://doi.org/10.1038/ncomms7044.
16.• Fishbein L, Leshchiner I, Walter V, Danilova L, Robertson AG, Johnson AR, et al. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. Cancer Cell. 2017;31(2):181–93. https://doi.org/10.1016/j.ccell.2017.01.001. **The Cancer Genome Atlas (TCGA) paper on germline and somatic genetics of pheochromocytoma and paraganglioma using integrated genomic sequencing.**
17. Flynn A, Benn D, Clifton-Bligh R, Robinson B, Trainer AH, James P, et al. The genomic landscape of phaeochromocytoma. J Pathol. 2015;236(1):78–89. https://doi.org/10.1002/path.4503.
18. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. 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. Genet Med. 2015;17(1):70–87. https://doi.org/10.1038/gim.2014.147.
19. Stewart DR, Korf BR, Nathanson KL, Stevenson DA, Yohay K. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(7):671–82. https://doi.org/10.1038/gim.2018.28.
20. Yap YS, McPherson JR, Ong CK, Rozen SG, Teh BT, Lee AS, et al. The NF1 gene revisited - from bench to bedside. Oncotarget. 2014;5(15):5873–92. https://doi.org/10.18632/oncotarget.2194.
21. Gruber LM, Erickson D, Babovic-Vuksanovic D, Thompson GB, Young WF Jr, Bancos I. Pheochromocytoma and paraganglioma in patients with neurofibromatosis type 1. Clin Endocrinol. 2016;86:141–9. https://doi.org/10.1111/cen.13163.
22. Zinnamosca L, Petramala L, Cotesta D, Marinelli C, Schina M, Cianci R, et al. Neurofibromatosis type 1 (NF1) and pheochromocytoma: prevalence, clinical and cardiovascular aspects. Arch Dermatol Res. 2011;303(5):317–25. https://doi.org/10.1007/s00403-010-1090-z.
23. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. von Recklinghausen's disease and pheochromocytomas. J Urol. 1999;162(5):1582–6.
24. Bausch B, Borozdin W, Neumann HP. Clinical and genetic characteristics of patients with neurofibromatosis type 1 and pheochromocytoma. N Engl J Med. 2006;354(25):2729–31. https://doi.org/10.1056/NEJMc066006.
25. Eisenhofer G, Lenders JW, Timmers H, Mannelli M, Grebe SK, Hofbauer LC, et al. Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. Clin Chem. 2011;57(3):411–20. https://doi.org/10.1373/clinchem.2010.153320.
26. Binderup ML, Bisgaard ML, Harbud V, Moller HU, Gimsing S, Friis-Hansen L, et al. Von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. 3rd edition. Dan Med J. 2013;60(12):B4763.
27. Min JH, Yang H, Ivan M, Gertler F, Kaelin WG Jr, Pavletich NP. Structure of an HIF-1alpha -pVHL complex: hydroxyproline recognition in signaling. Science. 2002;296(5574):1886–9. https://doi.org/10.1126/science.1073440.
28. VHL Alliance. The VHL handbook. 5th ed. Boston (MA): VHL Alliance. 2015.
29. Delman KA, Shapiro SE, Jonasch EW, Lee JE, Curley SA, Evans DB, et al. Abdominal visceral lesions in von Hippel-Lindau disease: incidence and clinical behavior of pancreatic and adrenal lesions at a single center. World J Surg. 2006;30(5):665–9. https://doi.org/10.1007/s00268-005-0359-4.
30. Boedeker CC, Erlic Z, Richard S, Kontny U, Gimenez-Roqueplo AP, Cascon A, et al. Head and neck paragangliomas in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. J Clin Endocrinol Metab. 2009;94(6):1938–44. https://doi.org/10.1210/jc.2009-0354.
31. Gaal J, van Nederveen FH, Erlic Z, Korpershoek E, Oldenburg R, Boedeker CC, et al. Parasympathetic paragangliomas are part of the Von Hippel-Lindau syndrome. J Clin Endocrinol Metab. 2009;94(11):4367–71. https://doi.org/10.1210/jc.2009-1479.

32. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011;19(6):617–23. https://doi.org/10.1038/ejhg.2010.175.
33. Ong KR, Woodward ER, Killick P, Lim C, Macdonald F, Maher ER. Genotype-phenotype correlations in von Hippel-Lindau disease. Hum Mutat. 2007;28(2):143–9. https://doi.org/10.1002/humu.20385.
34. Wells SA Jr. Advances in the management of MEN2: from improved surgical and medical treatment to novel kinase inhibitors. Endocr Relat Cancer. 2018;25(2):T1–T13. https://doi.org/10.1530/ERC-17-0325.
35. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610. https://doi.org/10.1089/thy.2014.0335.
36. Castinetti F, Qi XP, Walz MK, Maia AL, Sanso G, Peczkowska M, et al. Outcomes of adrenal-sparing surgery or total adrenalectomy in phaeochromocytoma associated with multiple endocrine neoplasia type 2: an international retrospective population-based study. Lancet Oncol. 2014;15(6):648–55. https://doi.org/10.1016/S1470-2045(14)70154-8.
37. Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. Cancer Cell. 2005;7(1):77–85. https://doi.org/10.1016/j.ccr.2004.11.022.
38. Xiao M, Yang H, Xu W, Ma S, Lin H, Zhu H, et al. Inhibition of alpha-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors. Genes Dev. 2012;26(12):1326–38. https://doi.org/10.1101/gad.191056.112.
39.• Rednam SP, Erez A, Druker H, Janeway KA, Kamihara J, Kohlmann WK, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res. 2017;23(12):e68–75. https://doi.org/10.1158/1078-0432.CCR-17-0547 **Expert recommendation guidelines for screening patients with hereditary paraganglioma-pheochromocytoma syndrome.**
40. Burnichon N, Briere JJ, Libe R, Vescovo L, Riviere J, Tissier F, et al. SDHA is a tumor suppressor gene causing paraganglioma. Hum Mol Genet. 2010;19(15):3011–20. https://doi.org/10.1093/hmg/ddq206.
41. Parfait B, Chretien D, Rotig A, Marsac C, Munnich A, Rustin P. Compound heterozygous mutations in the flavoprotein gene of the respiratory chain complex II in a patient with Leigh syndrome. Hum Genet. 2000;106(2):236–43.
42. Bausch B, Schiavi F, Ni Y, Welander J, Patocs A, Ngeow J, et al. Clinical characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. JAMA Oncol. 2017;3(9):1204–12. https://doi.org/10.1001/jamaoncol.2017.0223.
43. van der Tuin K, Mensenkamp AR, Tops CMJ, Corssmit EPM, Dinjens WN, van de Horst-Schrivers ANA, et al. Clinical aspects of SDHA-related pheochromocytoma and paraganglioma: a nationwide study. J Clin Endocrinol Metab. 2018;103(2):438–45. https://doi.org/10.1210/jc.2017-01762.
44. Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: a report from the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol. 2016;2(7):922–8. https://doi.org/10.1001/jamaoncol.2016.0256.
45. Horvath R, Abicht A, Holinski-Feder E, Laner A, Gempel K, Prokisch H, et al. Leigh syndrome caused by mutations in the flavoprotein (Fp) subunit of succinate dehydrogenase (SDHA). J Neurol Neurosurg Psychiatry. 2006;77(1):74–6. https://doi.org/10.1136/jnnp.2005.067041.
46. Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, et al. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. Am J Hum Genet. 2001;69(1):49–54. https://doi.org/10.1086/321282.
47. Pasini B, Stratakis CA. SDH mutations in tumorigenesis and inherited endocrine tumours: lesson from the phaeochromocytoma-paraganglioma syndromes. J Intern Med. 2009;266(1):19–42. https://doi.org/10.1111/j.1365-2796.2009.02111.x.
48.• Andrews KA, Ascher DB, Pires DEV, Barnes DR, Vialard L, Casey RT, et al. Tumour risks and genotype-phenotype correlations associated with germline variants in succinate dehydrogenase subunit genes SDHB, SDHC and SDHD. J Med Genet. 2018;55(6):384–94. https://doi.org/10.1136/jmedgenet-2017-105127. **This is one of the largest studies with index and non-index patients evaluating penetrance of *SDHx* gene pathogenic variants.**
49. Jochmanova I, Wolf KI, King KS, Nambuba J, Wesley R, Martucci V, et al. SDHB-related pheochromocytoma and paraganglioma penetrance and genotype-phenotype correlations. J Cancer Res Clin Oncol. 2017;143(8):1421–35. https://doi.org/10.1007/s00432-017-2397-3.
50. Jafri M, Whitworth J, Rattenberry E, Vialard L, Kilby G, Kumar AV, et al. Evaluation of SDHB, SDHD and VHL gene susceptibility testing in the assessment of individuals with non-syndromic phaeochromocytoma, paraganglioma and head and neck paraganglioma. Clin Endocrinol. 2013;78(6):898–906. https://doi.org/10.1111/cen.12074.
51. Niemeijer ND, Rijken JA, Eijkelenkamp K, van der Horst-Schrivers ANA, Kerstens MN, Tops CMJ, et al. The phenotype of SDHB germline mutation carriers: a nationwide study. Eur J Endocrinol. 2017;177(2):115–25. https://doi.org/10.1530/EJE-17-0074.
52. van Hulsteijn LT, Dekkers OM, Hes FJ, Smit JW, Corssmit EP. Risk of malignant paraganglioma in SDHB-mutation and SDHD-mutation carriers: a systematic review and meta-analysis. J Med Genet. 2012;49(12):768–76. https://doi.org/10.1136/jmedgenet-2012-101192.
53. Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D, Bosch A, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science. 2000;287(5454):848–51.
54. Neumann HP, Erlic Z. Maternal transmission of symptomatic disease with SDHD mutation: fact or fiction? J Clin Endocrinol Metab. 2008;93(5):1573–5. https://doi.org/10.1210/jc.2008-0569.
55. Yeap PM, Tobias ES, Mavraki E, Fletcher A, Bradshaw N, Freel EM, et al. Molecular analysis of pheochromocytoma after maternal transmission of SDHD mutation elucidates mechanism of parent-of-origin effect. J Clin Endocrinol Metab. 2011;96(12):E2009–13. https://doi.org/10.1210/jc.2011-1244.
56. Bayley JP, Oldenburg RA, Nuk J, Hoekstra AS, van der Meer CA, Korpershoek E, et al. Paraganglioma and pheochromocytoma upon maternal transmission of SDHD mutations. BMC Med Genet. 2014;15:111. https://doi.org/10.1186/s12881-014-0111-8.
57. Ricketts CJ, Forman JR, Rattenberry E, Bradshaw N, Lalloo F, Izatt L, et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. Hum Mutat. 2010;31(1):41–51. https://doi.org/10.1002/humu.21136.
58. Niemann S, Muller U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. Nat Genet. 2000;26(3):268–70. https://doi.org/10.1038/81551.
59. Else T, Marvin ML, Everett JN, Gruber SB, Arts HA, Stoffel EM, et al. The clinical phenotype of SDHC-associated hereditary

paraganglioma syndrome (PGL3). J Clin Endocrinol Metab. 2014;99(8):E1482–6. https://doi.org/10.1210/jc.2013-3853.
60. Bayley JP, Kunst HP, Cascon A, Sampietro ML, Gaal J, Korpershoek E, et al. SDHAF2 mutations in familial and sporadic paraganglioma and phaeochromocytoma. Lancet Oncol. 2010;11(4):366–72. https://doi.org/10.1016/S1470-2045(10)70007-3.
61. Kunst HP, Rutten MH, de Monnink JP, Hoefsloot LH, Timmers HJ, Marres HA, et al. SDHAF2 (PGL2-SDH5) and hereditary head and neck paraganglioma. Clin Cancer Res. 2011;17(2):247–54. https://doi.org/10.1158/1078-0432.CCR-10-0420.
62. Qin Y, Yao L, King EE, Buddavarapu K, Lenci RE, Chocron ES, et al. Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. Nat Genet. 2010;42(3):229–33. https://doi.org/10.1038/ng.533.
63. Yao L, Schiavi F, Cascon A, Qin Y, Inglada-Perez L, King EE, et al. Spectrum and prevalence of FP/TMEM127 gene mutations in pheochromocytomas and paragangliomas. JAMA. 2010;304(23):2611–9. https://doi.org/10.1001/jama.2010.1830.
64. Qin Y, Deng Y, Ricketts CJ, Srikantan S, Wang E, Maher ER, et al. The tumor susceptibility gene TMEM127 is mutated in renal cell carcinomas and modulates endolysosomal function. Hum Mol Genet. 2014;23(9):2428–39. https://doi.org/10.1093/hmg/ddt638.
65. Burnichon N, Cascon A, Schiavi F, Morales NP, Comino-Mendez I, Abermil N, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. Clin Cancer Res. 2012;18(10):2828–37. https://doi.org/10.1158/1078-0432.CCR-12-0160.
66. Comino-Mendez I, Gracia-Aznarez FJ, Schiavi F, Landa I, Leandro-Garcia LJ, Leton R, et al. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. Nat Genet. 2011;43(7):663–7. https://doi.org/10.1038/ng.861.
67. Zhuang Z, Yang C, Lorenzo F, Merino M, Fojo T, Kebebew E, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922–30. https://doi.org/10.1056/NEJMoa1205119.
68. Comino-Mendez I, de Cubas AA, Bernal C, Alvarez-Escola C, Sanchez-Malo C, Ramirez-Tortosa CL, et al. Tumoral EPAS1 (HIF2A) mutations explain sporadic pheochromocytoma and paraganglioma in the absence of erythrocytosis. Hum Mol Genet. 2013;22(11):2169–76. https://doi.org/10.1093/hmg/ddt069.
69. Lorenzo FR, Yang C, Ng Tang Fui M, Vankayalapati H, Zhuang Z, Huynh T, et al. A novel EPAS1/HIF2A germline mutation in a congenital polycythemia with paraganglioma. J Mol Med (Berl). 2013;91(4):507–12. https://doi.org/10.1007/s00109-012-0967-z.
70. Yang C, Sun MG, Matro J, Huynh TT, Rahimpour S, Prchal JT, et al. Novel HIF2A mutations disrupt oxygen sensing, leading to polycythemia, paragangliomas, and somatostatinomas. Blood. 2013;121(13):2563–6. https://doi.org/10.1182/blood-2012-10-460972.
71. Buffet A, Smati S, Mansuy L, Menara M, Lebras M, Heymann MF, et al. Mosaicism in HIF2A-related polycythemia-paraganglioma syndrome. J Clin Endocrinol Metab. 2014;99(2):E369–73. https://doi.org/10.1210/jc.2013-2600.
72. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30(4):406–10. https://doi.org/10.1038/ng849.
73. Castro-Vega LJ, Buffet A, De Cubas AA, Cascon A, Menara M, Khalifa E, et al. Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. Hum Mol Genet. 2014;23(9):2440–6. https://doi.org/10.1093/hmg/ddt639.
74. Clark GR, Sciacovelli M, Gaude E, Walsh DM, Kirby G, Simpson MA, et al. Germline FH mutations presenting with pheochromocytoma. J Clin Endocrinol Metab. 2014;99(10):E2046–50. https://doi.org/10.1210/jc.2014-1659.
75. Calsina B, Curras-Freixes M, Buffet A, Pons T, Contreras L, Leton R, et al. Role of MDH2 pathogenic variant in pheochromocytoma and paraganglioma patients. Genet Med. 2018;20(12):1652–62. https://doi.org/10.1038/s41436-018-0068-7.
76. Cascon A, Comino-Mendez I, Curras-Freixes M, de Cubas AA, Contreras L, Richter S, et al. Whole-exome sequencing identifies MDH2 as a new familial paraganglioma gene. J Natl Cancer Inst. 2015;107(5):djv053. https://doi.org/10.1093/jnci/djv053.
77. Buffet A, Morin A, Castro-Vega LJ, Habarou F, Lussey-Lepoutre C, Letouze E, et al. Germline mutations in the mitochondrial 2-oxoglutarate/malate carrier SLC25A11 gene confer a predisposition to metastatic paragangliomas. Cancer Res. 2018;78(8):1914–22. https://doi.org/10.1158/0008-5472.CAN-17-2463.
78. Remacha L, Comino-Mendez I, Richter S, Contreras L, Curras-Freixes M, Pita G, et al. Targeted exome sequencing of Krebs cycle genes reveals candidate cancer-predisposing mutations in pheochromocytomas and paragangliomas. Clin Cancer Res. 2017;23(20):6315–24. https://doi.org/10.1158/1078-0432.CCR-16-2250.
79. Remacha L, Curras-Freixes M, Torres-Ruiz R, Schiavi F, Torres-Perez R, Calsina B, et al. Gain-of-function mutations in DNMT3A in patients with paraganglioma. Genet Med. 2018;20(12):1644–51. https://doi.org/10.1038/s41436-018-0003-y.
80. Remacha L, Pirman D, Mahoney CE, Coloma J, Calsina B, Curras-Freixes M, et al. Recurrent germline DLST mutations in individuals with multiple pheochromocytomas and paragangliomas. Am J Hum Genet. 2019;104(4):651–64. https://doi.org/10.1016/j.ajhg.2019.02.017.