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# Genetics of Pheochromocytoma and Paraganglioma

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**Abstract:** Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that often develop on a background of predisposing genetic mutations. With the continuous expansion of genetic landscape of PPGL, new tools of genetic screening have been developed for simultaneous parallel sequencing of multiple genes, at faster rates and lower costs. Yet, next-generation sequencing techniques are not available worldwide and demand expertise to circumvent technical limitations and interpret results of uncertain significance, and thus a sequential genetic analysis driven by the clinical phenotype remains advisable for a successful diagnosis, and to save costs. In this chapter, we focus on the clinical features of patients with PPGLs as a framework for an optimized sequential genetic screening. We also describe new syndromes and genes that are expanding the genetic etiology of PPGLs.

**Keywords:** Genetic testing; Multifocal tumors; Paraganglioma; Pheochromocytoma; SDH mutation

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## INTRODUCTION

Pheochromocytomas (PHEO; MIM #171300) and paragangliomas (PGLs; MIM #168000) (pheochromocytomas and paragangliomas, PPGLs) are rare neuroendocrine tumors that arise in the adrenal medulla and in the ganglia of the sympathetic and parasympathetic nervous chains, respectively (1). The genetic landscape of PPGL has evolved over the years from the old “rule of tens” (10%) for a genetic etiology to a prevalence of more than 40% of genetic mutations associated with these tumors (2, 3). Besides von Hippel–Lindau (*VHL*), rearranged during transfection (*RET*), and neurofibromatosis type 1 (*NF1*) genes, new germline mutations in the following genes that predispose to PPGLs have been identified: the succinate dehydrogenase subunits *A/B/C/D/AF2* (*SDHx*), which cause paraganglioma syndrome types 1 to 5 (PGL1–5); Myc-associated protein X (*MAX*); transmembrane protein 127 (*TMEM127*), which causes the familial pheochromocytoma syndromes; hypoxia-inducible factor 2 alpha (*HIF2A*); fumarate hydratase (*FH*); prolyl hydroxylase types 1 and 2 (*PHD1* and *PHD2*); kinesin family member 1B (*KIF1B*); and malate dehydrogenase 2 (*MDH2*) (4–17).

Considering the high costs of genetic screening and the large and increasing number of PPGL-associated genes, it is advised that clinicians follow a phenotype-driven algorithm when ordering genetic tests for patients with PPGL (Table 1). Additionally, it may be inadequate to screen for mutations in genes that have never been associated with a particular PPGL phenotype (18, 19). Syndromic presentations, multifocal tumors, metastatic disease, bilateral pheochromocytoma (bPHEO), and pediatric PPGLs are clinical features associated with a higher likelihood of a gene mutation, and these scenarios may entail the selection of a specific genetic screening (20–22). Furthermore, the type of catecholamine secretion by the PPGL, the pattern of immunostaining in pathology surveys, and results from functional nuclear imaging provide clues to prioritize the sequential genetic screening (18, 23–27).

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## MOLECULAR PATHWAYS ASSOCIATED WITH PPGL

The molecular pathways involved in the development of PPGL are classified according to three main clusters: a pseudohypoxic cluster (cluster 1: mutations in *VHL*, *SDHx*, *HIF2A*, *PHD1/PHD2*, *FH*, and *MDH2*), a cluster of kinase receptor signaling and protein translation pathways (cluster 2: mutations in *RET*, *NF1*, *TMEM127*, *KIF1B*, and *MAX*), and a cluster related to a Wnt-altered pathway (28–30). This last cluster includes only mutations at the somatic level that cause an aggressive form of sporadic pheochromocytoma (30).

In the pseudohypoxic cluster, there is a common denominator to all PPGL-associated mutations and their altered pathways, that is, overexpression of hypoxia-inducible factor type 2 alpha (*HIF-2 $\alpha$* ), the predominant isoform of *HIF- $\alpha$*  in cells of neural crest origin (31, 32). Under hypoxia states, there is an overexpression of *HIF-2 $\alpha$*  which upregulates genes that are drivers of

**TABLE 1**  
**Clinical features of PPGL-associated genes**

PPGL-associated genes	Clinical features					Ancillary surveys	
	Frequency in cohorts of PPGL (%)	Prototypic tumors and features	Multifocal tumors	Bilateral PHEO	Metastatic PPGL	Biochemical phenotype	SDHA/B IHC
<i>VHL</i>	9.6–17.6	<ul style="list-style-type: none"> <li>– CNS hemangiomas</li> <li>– renal cysts</li> <li>– RCC</li> <li>– pNET</li> <li>– pancreatic cysts</li> <li>– abdominal PPGL</li> <li>– thoracic PGL</li> </ul>	0–18.8	29–43.5	Rare	NA	+ve/+ve
<i>RET</i>	5.4	<ul style="list-style-type: none"> <li>– MEN2A (MTC, PPGL, pHPT)</li> <li>– MEN2B (MTC, PPGL, marfanoid habitus, ganglioneuromatosis of the gut/oral mucosa)</li> </ul>	Rare	47–66	Rare	A	+ve/+ve
<i>NFI</i>	2.2–2.9	<ul style="list-style-type: none"> <li>– <i>café au lait</i> spots</li> <li>– axillary/inguienal freckling</li> <li>– neurofibromas</li> <li>– Lisch nodules of the iris</li> <li>– typical osseous lesions</li> <li>– optic glioma</li> <li>– carcinomas (breast, lung, colorectal)</li> <li>– sarcomas, GIST</li> <li>– melanoma</li> <li>– PPGL</li> </ul>	Rare	Rare	5.4–12	A	+ve/+ve

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**TABLE 1** Clinical features of PPGL-associated genes (Continued)

PPGL-associated genes	Frequency in cohorts of PPGL (%)	Clinical features				Ancillary surveys	
		Prototypic tumors and features	Multifocal tumors	Bilateral PHEO	Metastatic PPGL	Biochemical phenotype	SDHA/B IHC
SDHD	10.5	<ul style="list-style-type: none"> <li>- HN PGL</li> <li>- thoracic PGL</li> <li>- abdominal PPGL</li> <li>- Carney dyad</li> <li>- RCC</li> <li>- pituitary adenomas</li> </ul>	66.9	Rare	3.1	NA; D	+ve/-ve
SDHAF2	<1	<ul style="list-style-type: none"> <li>- HN PGL</li> <li>- thoracic PGL</li> <li>- PHEO</li> </ul>	46.8	NA	Rare	NA, A*	+ve/-ve
SDHC	4	<ul style="list-style-type: none"> <li>- HN PGL</li> <li>- thoracic PGL</li> <li>- PHEO</li> <li>- Carney dyad</li> </ul>	31.2	NA	Rare	NA; D	+ve/-ve
SDHB	20.6	<ul style="list-style-type: none"> <li>- abdominal PPGL</li> <li>- thoracic PGL</li> <li>- HN PGL</li> <li>- Carney dyad</li> <li>- RCC</li> <li>- pituitary adenomas</li> </ul>	20.8	Rare	37.0	NA; D	+ve/-ve
SDHA	3.0	<ul style="list-style-type: none"> <li>- HN PGL</li> <li>- abdominal PGL</li> <li>- PHEO</li> <li>- Carney dyad</li> <li>- pituitary adenomas</li> </ul>	Rare	Rare	11.0	NA; D	-ve/-ve

*Table continued on following page*

**TABLE 1** Clinical features of PPGL-associated genes (Continued)

PPGL-associated genes	Frequency in cohorts of PPGL (%)	Clinical features				Frequency (%)		Ancillary surveys	
		Prototypic tumors and features	Multifocal tumors	Bilateral PHEO	Metastatic PPGL	Biochemical phenotype	SDHA/B IHC		
HIF2A	5.3	- polycythemia since early childhood - abdominal PPGL - duodenal somatostatinomas - retinopathy	66	Rare	18	NA	+ve/+ve		
PHD1	U	- polycythemia - abdominal/thoracic PPGL	100*	U	U	NA	U		
PHD2	U	- polycythemia - abdominal/thoracic PPGL	100*	U	U	NA	U		
MAX	<2	- abdominal PPGL - thoracic PGL	21	66.7–73	10.5–25	NA; NA, A	+ve/+ve		
TMEM127	1.9	- PHEO	Rare	28.5–37	Rare	NA, A	+ve/+ve		
FH	~1	- cutaneous/uterine leiomyomas - RCC - abdominal PPGL - thoracic PGL	30*	U	30*	NA	+ve/+ve		
KIF1B	U	U**	U	66.6*	U	NA*	U		
MDH2	U	U†	U†	U	U†	NA†	U		

Abbreviations: -ve, negative; +ve, positive; A, adrenaline; CNS, central nervous system; FH, fumarate hydratase gene; GIST, gastrointestinal stromal tumor; HIF2A, hypoxia-inducible factor 2 alpha gene; IHC, immunohistochemistry; KIF1B/kinase family member 1B gene; MAX, Myc-associated Protein X gene; MDH2, malate dehydrogenase 2 gene; MEN2A, multiple endocrine neoplasia type 2A; MEN2B, multiple endocrine neoplasia type 2B; MTC, medullary thyroid carcinoma; NA, noradrenaline; NF1, Neurofibromatosis type 1 gene; PGL, paraganglioma; PHD1, prolyl hydroxylase type 1 gene; PHD2, prolyl hydroxylase type 2 gene; PHEO, pheochromocytoma; pHPT, primary hyperparathyroidism; pNET, pancreatic neuroendocrine tumor; PPGL, pheochromocytoma and paraganglioma; RCC, renal cell carcinoma; RET, rearranged during transfection gene; SDHA, succinate dehydrogenase subunit A gene; SDHA/F2, succinate dehydrogenase complex assembly factor 2; SDHB, succinate dehydrogenase subunit B gene; SDHC, succinate dehydrogenase subunit C gene; SDHD, succinate dehydrogenase subunit D gene; TMEM127, transmembrane protein 127 gene; VHL, von Hippel-Lindau gene; U, unknown.

\*Few cases reported (≤10patients).

†One patient developed bilateral pheochromocytoma, neuroblastoma, gangliocarcinoma, and pelvic leiomyosarcoma; one patient developed lung adenocarcinoma.

\*\*Only one patient reported to date with multifocal/metastatic paragangliomas.

erythropoiesis, glucose metabolism, proliferation, programmed cell survival, and angiogenesis. Pseudohypoxia is a state where there is a normal oxygen supply to the tissues but a disruption in the oxygen sensing pathways (caused by gene mutations and their non-synonymous structural translated proteins), leading to an abnormal overexpression of HIF-2 $\alpha$  that promotes oncogenesis, cancer invasion, and metastasis (31, 32). The SDH complex (formed by its catalytic subunits A and B, and anchorage subunits C and D) and the enzymes FH and MDH2 catalyze the conversion of succinate to fumarate, fumarate to malate, and malate to oxaloacetate in the tricarboxylic acid cycle, respectively. Loss-of-function mutations in *SDHx* (*SDHD*, MIM \*602690; *SDHAF2*, MIM \*613019; *SDHC*, MIM \*602413; *SDHB*, MIM \*185470; *SDHA*, MIM \*600857), *FH* (MIM \*136850), and *MDH2* (MIM \*154100) lead to the accumulation of Krebs cycle precursors such as fumarate and succinate, which act as oncometabolites: (i) they inhibit the PHD activity, which signals HIF-2 $\alpha$  for degradation; (ii) they inhibit the factor inhibiting HIF, resulting in activation by HIF-2 $\alpha$  (and other complexed molecules) of proteins that promote gene transcription; (iii) succinate inhibits the ten eleven translocation enzymes, which are key in repressing gene transcription by silencing promoter regions through methylation processes (33). Similarly, inactivating mutations in *PHD1* (MIM \*606424) and *PHD2* (MIM \*606425) lead to a decrease in the hydroxylation (by their corresponding enzymes, PHD1 and PHD2) of HIF-2 $\alpha$ , promoting its accumulation and proneoplastic activity (15, 32). *HIF2A* (MIM \*603349) mutations that predispose to PPGL cause electrostatic alterations in HIF-2 $\alpha$  that impair its hydroxylation and subsequent degradation by VHL proteins (34, 35). Finally, *VHL* (MIM \*608537) inactivating mutations lead to an excess of HIF-2 $\alpha$  due to the defective recognition of its hydroxylated isoform by the VHL protein and, ultimately, to cancer development and metastasis (34, 35).

The proto oncogene *RET* (MIM + 164761) encodes a tyrosine kinase transmembrane receptor that activates Ras/MAPK and PI3K/AKT pathways, which are involved in proliferation, survival, migration, and angiogenesis. Gain-of-function mutations in *RET* lead to a constitutive activation of the tyrosine kinase domain of its receptor, and to cancer initiation through deregulated proliferation and increased cell survival (36). *NF1* (MIM \*613113) is a tumor suppressor gene that encodes a GTPase activator—neurofibromin type 1. Neurofibromin type 1 normally inhibits Ras and its downstream activation through the mTOR kinase pathway (37). *TMEM127* (MIM \*613403) is also a tumor suppressor gene that translates a protein which directly inhibits the mTOR protein (38). Thus, loss-of-function mutations in *NF1* and *TMEM127* lead to an increased activation of the mTOR pathway and, ultimately, to enhanced cell proliferation and cancer development. *MAX* (MIM \*154950) gene encodes a nuclear protein that acts as a transcriptional repressor of Myc. PPGL-associated *MAX* mutations translate a protein that cannot bind Myc, thus allowing a Myc deregulated transcriptional activity that results in cell proliferation, repression of differentiation, and angiogenesis (39). *KIF1B* (MIM \*605995) encodes a protein that acts as a downstream effector of PHD3-induced apoptosis. Thus, loss-of-function mutations in *KIF1B* lead to PPGL development through cell death escape and enhanced survival (40, 41).

## SYNDROMIC PRESENTATIONS

PPGL may be part of one of the following syndromes: VHL, multiple endocrine neoplasia type 2 (MEN2), NF1, and those associated with mutations in *PHD1/PHD2* and *HIF2A*. VHL syndrome (MIM #193300) is an autosomal dominant disease characterized by central nervous system (CNS) and retinal hemangiomas (60–80%), renal cysts (50–70%), clear cell renal cell carcinoma (RCC) (30%), pancreatic neuroendocrine tumors (8–17%) and cysts (72%), PPGL (20%), endolymphatic sac tumors (6–15%), and epididymal (25–60%) and broad ligament cystadenomas (42–45). CNS hemangiomas are the most common prototypic lesions of VHL disease, and death is usually caused by RCC and complications of CNS tumors (42, 45). The mean age of presentation is in the third decade of life and the penetrance of the disease reaches 90% by 65 years old (yo), but patients can show retinal hemangioblastomas or pancreatic cysts as early as 1 yo (45). According to the patient's genotype, VHL disease may be classified as type 1 (large deletions and truncating mutations of *VHL* that predispose to CNS hemangiomas and RCC, but not PPGL) or type 2 (missense mutations that predispose to PPGL associated with hemangioblastomas: VHL disease type 2A; hemangioblastomas and RCC: VHL disease type 2B; or only PPGL: VHL disease type 2C) (44, 45). In large case series of patients with PPGL, a *VHL* mutation is present in 9.6–17.6% of cases (3, 46). The mean age of PPGL presentation is 30 yo (4–58), and patients develop PHEO much more frequently than PGL (19). PPGL may be the presenting feature of the syndrome (30–55%) and, as *de novo* mutations are frequent, patients may not have a remarkable personal and family history (19, 45, 47). Thus, clinicians should bear in mind the relative high frequency of *VHL* mutations (46) in patients with a seemingly sporadic PPGL when ordering their genetic screening.

MEN2 is an autosomal dominant syndrome caused by germline mutations in *RET*, and it is classified into two subtypes according to the patient's phenotype: MEN2A (MIM #171400) and MEN2B (MIM #162300) (48). MEN2A is the most common subtype (95%) and its prototypic lesions are medullary thyroid carcinoma (MTC, 97%), PPGL (68%), and primary hyperparathyroidism (14%). The mean age of presentation is 40 yo and the penetrance is virtually 100% by the 8th decade of life (48–50). MEN2B is a variant characterized by an aggressive form of MTC (100%), PPGL (59%), marfanoid habitus, and ganglioneuromatosis of the oral mucosa and gut. It usually develops earlier than MEN2A (mean age of presentation: 13–22 yo), and most patients have incurable MTC at diagnosis, as 75% of cases are sporadic and thus not amenable for cancer surveillance and timely treatment strategies (49, 51, 52). In MEN2, PPGL are usually diagnosed concomitantly or after MTC, and PHEO is the most frequent chromaffin cell tumor, whereas PGL occurs in a small proportion of patients (4.8%) (49). Specific mutations in *RET* codons 918, 883, 634, and 631 confer the highest risk for PHEO, whereas other affected codons are associated with a much lower penetrance (50, 53).

NF1 (MIM #162200) is a syndrome characterized by the progressive occurrence, since birth, of *cafe au lait* spots (~100%), axillary/inguinal freckling (90%), neurofibromas (84%), Lisch nodules of the iris (>70%), typical osseous lesions

(14%; scoliosis, sphenoid wing, and/or long bone dysplasia), and optic glioma (4%). NF1 also predisposes to breast, lung, and colorectal carcinomas (16%), PPGL (7.7%), sarcomas (7%), gastrointestinal stromal tumors, GIST (7%), melanoma (0.1–5.4%), and pancreatic neuroendocrine tumors (rare) (54–58). The clinical diagnosis of NF1 is usually easy to establish, as the penetrance of at least two NF1 prototypic lesions is close to 100% by 8 yo (54). Similar to VHL disease and MEN2, PHEO (93.6%) is much more frequent than PGL (6%) in patients with NF1, and the mean age of diagnosis of PPGL is 42 yo (19, 57).

*HIF2A* mutations cause a new PPGL-associated cancer syndrome described initially in 2012 (59). This syndrome is characterized by a set of clinical features, occurring either in isolation or in combination: polycythemia since early childhood, PPGL, duodenal somatostatinomas, and retinopathy. The “Pacak–Zhuang” syndrome is considered if the patient develops polycythemia, PPGL, and somatostatinoma (60). The relative frequency of the clinical phenotypes associated with *HIF2A* mutations is isolated polycythemia (45.0%), polycythemia and PPGL (14.5%), polycythemia, PPGL, and somatostatinoma (9.6%), isolated PPGL (22.6%), brain hemangiomas (4.8%, one with a concomitant PGL), and duodenal gangliocytic PGL (3.2%) (13, 60, 61–70). The prevalence of *HIF2A* mutations in cohorts of PPGL is estimated to be 5.3% (63, 65, 66), with a median age of diagnosis of PHEO of 40 yo (range: 13–78), whereas for PGL it is 20 yo (range: 8–78) (13, 60, 61–70). These tumors are initially benign and multiple, but they recur frequently, requiring repeated surgeries, and develop metastases, especially PGLs (60). Somatostatinomas occur only in females at the median age of diagnosis of 32 yo (range: 22–59) and they are located around duodenal ampulla. These tumors are associated with symptomatic gallbladder disease, occur in the duodenum (100.0%) and pancreas (50.0%), carry a considerable risk of recurrence (50.0%) and malignancy (50.0%), and are diagnosed after the development of PPGL (60). The majority of *HIF2A* mutations are somatic and thus the family history is negative. However, some patients have somatic mosaicism, where the mutation is found in tumor cells and in a fraction of normal tissues (61, 63, 65, 70). Thus, there may be a possibility of transmission of a *HIF2A* mutation to the next generation by an affected member who has mosaicism that includes the gametes. However, such cases have never been described until now (61). Additionally, there are seven familial cases of *HIF2A* mutations, but the majority had only polycythemia (60), and two non-related cases of germline mutations in adult patients with isolated PHEO (65). This evidence has led experts to develop recommendations regarding genetic testing and counseling, as well as clinical follow-up of patients with *HIF2A* mutations (60, 61).

Germline mutations in *PHD1/PHD2* were reported in patients with polycythemia and PPGL (15, 71). The syndromes caused by these mutations are characterized by polycythemia at a later age relative to *HIF2A* mutation carriers and recurrent PPGL (15, 71). To date, only two cases of *PHD2*- and one case of *PHD1*-associated PPGL have been reported in the literature (15, 71). The two patients with *PHD2* mutations were a female and a male with an unremarkable family history who developed polycythemia by the ages of 16 yo and 30 yo, and recurrent PPGL since 39 yo (bPHEO and recurrent PGL) and 43 yo (recurrent PGL), respectively. The single case of *PHD1*-associated PPGL was a female with no family history who presented with polycythemia diagnosed at 6 yo and developed PPGL (bPHEO and recurrent and metastatic PGL) since 14 yo (15, 71).

## MULTIFOCAL TUMORS

Multifocal PPGLs occur mainly in patients with *SDHx*, *HIF2A*, *PHD1/2*, and *FH* mutations and rarely in those with *MAX* and *VHL* mutations (11, 14, 15, 46, 60, 71, 72).

Germline *SDHD* mutations predispose carriers to PGL1 (MIM #168000) (9). This syndrome is characterized by parasympathetic head and neck (HN) PGL (89.0%), sympathetic thoracic PGL (16.0%), and/or PHEO (10.5%), with a particularly high incidence of multiple tumors (66.9%) and recurrence of new tumors (58.2%). The mean age of presentation is 28 yo, and the penetrance reaches >80.0% by 40 yo (72–74). Non-chromaffin cell tumors may also occur in patients with *SDHD* mutations (RCC: 8%; GIST: rare, isolated, or associated with PGL—Carney dyad or Carney–Stratakis syndrome—; and pituitary adenomas: rare) (75–80). PGL1 almost always manifests when the *SDHD* mutation is paternally inherited due to a selective somatic loss of the maternal chromosome 11. Lack of the paternal chromosome 11 does not lead to tumor initiation due to a maternal oncosuppressor locus in the 11p15 region (imprinted in the father) (81). Thus, the family history may show a “skip-generation” pattern of inheritance (73, 82, 83). Very rarely, loss of the paternal 11q (where *SDHD* allele is located) and a mitotic recombination of the maternal 11q (carrying an *SDHD* mutation) with the paternal 11p15 imprinted oncosuppressor region may lead to the phenotypic expression of the disease, inherited from the mother (73, 82, 83).

*SDHB* mutations cause PGL4 (MIM #115310) (7), an autosomal dominant disorder characterized mainly by the development of sympathetic abdominal (67.0%) and thoracic PGL (17.6%), parasympathetic HN PGL (27.5%), and/or PHEO (11.4%); multifocal tumors may develop in 20.8% of patients (72, 73). The mean age of presentation is 34 yo, and the penetrance reaches 65.0% by 40 yo (73). Although both *SDHB* and *SDHD* mutations predispose patients to multifocal tumors, the former are more likely when the phenotype is characterized by thoracic and abdominal PPGL (72, 73). *SDHB* mutations are also associated with the development of RCC (14%), GIST (2%; isolated or as part of Carney dyad/Carney–Stratakis syndrome), and pituitary adenomas (rare) (75–80).

PGL3 (MIM #506373) is caused by mutations in *SDHC* gene (84). This syndrome is inherited in an autosomal dominant pattern and clinical disease usually manifest at a mean age of 46 yo; the prevalence of PPGL associated with PGL3 is 4.0% (85). Carriers of *SDHC* mutations develop mainly HN PGL (87.5%) of carotid body and jugular/tympanojugular region, and less frequently thoracic PGL (12.5%) and PHEO (rare) (72, 85, 86). Although multifocal HN PGLs are more likely associated with *SDHD* mutations, this phenotype is found in 31.2% of patients with PGL3 (72). *SDHC* mutations are also associated with the development of RCC (rare), GIST (rare; isolated or as part of Carney dyad), and pituitary adenomas (rare) (75–80). Of interest, the epigenetic methylation of the promoter region of *SDHC* (at the somatic level) is the molecular signature of Carney triad—GIST, PGL, and pulmonary chondroma (78).

*SDHAF2* mutations were originally described in a large Dutch kindred with HN PGL, with half of the affected carriers manifesting multiple tumors (87, 88). PGL2 (MIM #601650) is inherited in an autosomal dominant pattern but similar to PGL1, as *SDHAF2* is maternally imprinted, clinical manifestations occur only

when mutations are inherited from the father (88). Since the description of PGL2 in the Dutch family, only a few additional reports have been published (10, 88, 89), and the prevalence of *SDHAF2* mutations in patients with PPGL is thus considered extremely rare (<1%) (90). Tumors develop as early as 20 yo, and the penetrance of the disease in carriers of paternally inherited mutations reaches 75% by the seventh decade of life (10, 73, 89). The majority of patients develop carotid HN PGL (56.3%), with multifocal tumors (HN region) detected in 46.8% of cases. Thoracic PGLs (co-occurring with HN PGL) and PHEO (single tumors) were also rarely described (10, 88, 89).

Patients with *HIF2A* mutations develop PPGL at a median age of 17 yo (8–39). These tumors are recurrent, localized in the abdomen in almost all cases, and PGLs are diagnosed before or simultaneously with PHEO in 66% of cases (13, 60, 61, 62). The three patients reported to date with *PHD1/PHD2* mutations developed a clinical phenotype similar to patients with *HIF2A* mutations (abdominal, recurrent PPGL) (15, 71). It is thus recommended that patients with *PHD1/PHD2/HIF2A* mutations should have a follow-up by imaging every 1–2 years (*HIF2A*: since 8 yo; *PHD1/PHD2*: unknown, youngest age reported is 14 yo) (60). Considering all available imaging methods, the most accurate examination to follow patients with *PHD1/PHD2/HIF2A* mutations is <sup>18</sup>F-fluoro dihydroxyphenylalanine (<sup>18</sup>F-FDOPA) positron emission tomography (PET)/computed tomography (CT), which reflects the importance of the genotype to individualize the care of patients with PPGL (60).

*FH* mutations, a cause of hereditary leiomyomatosis (cutaneous and uterine, 46%) and renal cell cancer (47%), were found recently to predispose carriers to PPGL (rarely, 0.83% of all PPGL) (14, 91). The 10 patients reported to date had a median age of diagnosis of 32 yo (6–69); eight patients developed PHEO and four patients developed PGL (three thoraco-abdominal and one head and neck) (14, 91–93). In a large collaborative cohort study, *FH* mutations were found to predispose to multifocal PPGL (30%) with a significantly higher rate than mutations in other PPGL-associated genes (14).

*MDH2* has been recently found as a new PPGL susceptibility gene in a 55 yo man with multiple recurrent thoracic and abdominal PGL (17). Although no further cases have been reported to date, it may be hypothesized that patients with PPGL and *MDH2* mutations manifest a phenotype similar to that of patients with *FH* mutations, as non-synonymous enzymes coded by these genes may generate a similar disruption of Krebs cycle and proneoplastic environment.

VHL disease is rarely associated with PGL. The majority are located in the abdomen and are usually solitary (42, 44, 94). The spectrum of prevalence of multifocal PPGL (abdominal PGL and PHEO) in VHL disease is wide across studies, from 0 to 18.8% (19, 47, 95). Considering that *VHL* is one of the most frequently mutated PPGL-associated genes (46), clinicians should take into account this gene as a cause of multifocal PPGL when patients have a negative genetic screening for *SDHx* mutations.

*MAX* mutations are a genetic cause of familial PHEO, which was discovered in 2011 in a cohort of young patients with bPHEO that tested negative to all of the main PPGL susceptibility genes (96). This finding was corroborated in a further cohort study that concluded that *MAX* mutations are a rare cause (<2%) of PPGL (11). Patients with *MAX* mutations have a median age of diagnosis of 30.5 years (range: 17–47) and the majority (73%) have developed the disease by 40 yo.

Family history is present in 37% of cases, and it shows a preferential paternal transmission of the disease (and a “skip-generation” pattern of heritability) (11, 96). Although no cases of multifocal PPGL were reported in the first published cohort of patients with *MAX* mutations (96), a further report comprising 23 PPGL patients with germline mutations in *MAX* showed a prevalence of thoracoabdominal PGL in association with PHEO in 21% of cases (11). Thus, although *MAX* is a rare cause of multifocal PPGL, it should also be considered in the genetic screening of patients with multifocal PPGL after more common gene mutations have been excluded.

## METASTATIC DISEASE

Malignant PPGL is considered when there is evidence of metastasis (e.g., bone, lymph node) (1). Its prevalence is reported to be 10.0%, considering all age groups (3, 19, 46), and tumors larger than 4 cm or extra-adrenal in location, pediatric age, and *SDHB* mutations are features that confer a higher risk of malignancy (97, 98). The majority of metastatic PPGLs are associated with *SDHB* mutations, and less frequently with *NF1*, *SDHA*, *HIF2A*, *MAX*, and *FH* mutations (5, 7, 11, 14, 19, 60, 72, 90, 99, 100).

PGL4 is associated with the development of metastatic PPGL in 37.0% of patients across the age spectrum (72, 73). Thoracic and abdominal sympathetic tumors carry the highest risk of metastasis, mainly to the lymph nodes, liver, lungs, and bones (7, 72). Thus, patients with *SDHB* mutations need a rigorous lifetime follow-up for timely detection of metastatic disease. When comparing all the available functional imaging techniques for this purpose, the most accurate for patients with *SDHx* mutations is [<sup>68</sup>Ga]-DOTA(0)-Tyr(3)-octreotate ([<sup>68</sup>Ga]-DOTATATE) PET/CT, followed by [<sup>18</sup>F]-fluoro-2-deoxy-D-glucose PET/CT (101). These data underline the importance of the patient genotype for the delivery of precision medicine.

*NF1* is a cause of PPGL in less than 3% of cohorts of patients with these tumors, but it is associated with a considerable rate of metastatic PPGL (5.4–12%) (19, 99, 100), with a large review of 148 patients with *NF1*-associated PPGL reporting 11.5% (5). The majority of cases present at diagnosis with metastasis in the liver, lungs, and bones (5, 19, 99, 100).

PGL5 (MIM #614165) is caused by mutations in the subunit A of the SDH complex (6), which are found in 3.0% of all PPGL patients (90). This syndrome has a median age of presentation of 33 yo, and the penetrance reaches 38% by 40 yo (6, 24, 90). *SDHA* mutations predispose patients to HN PGL (38.9%), abdominal PGL (27.8%), and unilateral PHEO (24.0%) (6, 24, 25, 90). *SDHA* mutations also confer susceptibility to GIST (isolated or as part of Carney dyad) and pituitary adenomas (rare) (75–80). In the largest case series (38 patients) of PPGL associated-*SDHA* mutations, the reported prevalence of metastatic PPGL was 11% (90).

*HIF2A* mutations are associated with metastatic PPGL in 18% of patients, and the few cases reported were abdominal PGL (13, 60–70). However, it seems that the aggressive behavior of metastatic PPGL seen in patients with *SDHB*-associated tumors is not present in patients with *HIF2A* mutations (60).

In patients with *MAX* mutations, the rate of metastatic PPGL is 10.5–25.0%, considering the two largest case series published. All cases occurred in patients with PHEO, and the majority showed metastasis at diagnosis (11, 96).

Taking into account the 10 reported patients with PPGL and *FH* mutations, metastatic disease was described in three of these cases (30%) (14, 91–93), and in a large cohort study of patients with PPGL, *FH* mutations were associated with a significantly higher risk of malignancy when compared with mutations in other PPGL susceptibility genes (14).

The single case of *MDH2*-associated multifocal PGL reported to date was also found to be malignant (17).

Thus, although patients with *NF1*, *SDHA*, *HIF2A*, *MAX*, *FH*, and *MDH2* mutations represent a minority among PPGL cases, clinicians should bear in mind the potential for metastatic behavior of tumors associated with these genotypes in the long-term care.

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## BILATERAL PHEOCHROMOCYTOMA

bPHEO often occurs in association with *MEN2* or *VHL* disease and is rarely associated with *MAX*, *TMEM127*, and *KIF1B* mutations (11, 16, 48–52, 95, 102–104).

Patients with *MEN2* are prone to bPHEO (synchronous or metachronous) in 47–66% of cases (48–52). The highest risk *RET* mutations for developing PHEO (those that affect *RET* codons 918, 883, 634, 631, and 618) are also associated with a high incidence of bPHEO (50, 53, 104). After adrenalectomy for a unilateral tumor, the mean follow-up time for a metachronous PHEO to develop is 3.6–5.2 years (49, 50, 105).

*VHL* disease is associated with bPHEO in 29–43.5% of cases (19, 47, 95); additionally, in patients presenting with a unilateral PHEO, a contralateral tumor may develop in 19% of cases at a mean follow-up time of 4 years (47, 94). Finally, *VHL* mutations are most likely in patients with an apparently nonsyndromic bPHEO included in large cohort studies, due to the higher incidence of *VHL* compared with *RET* mutations (46).

*TMEM127* mutations are a rare cause of PPGL (<2%) initially described in a cohort of patients older than the expected age for individuals with hereditary PPGL (12). In addition, it was found that family history was absent in nearly half of cases, which may hinder the suspicion for *TMEM127* mutations in clinical grounds (12). In larger case series, the median age of diagnosis was reported to be 41.5 yo (21–75), and the cumulative penetrance for clinical disease reached 32% by 65 yo (90, 102, 103). Patients with *TMEM127* mutations usually present with a unilateral PHEO, but have also a high rate of bPHEO (28.5–37%). They have a low incidence of PGL and metastatic disease (rare cases) (93, 102, 103).

*MAX* mutations are associated with a particularly high incidence of bPHEO (66.7–73%), considering the three largest case series published to date (11, 90, 96).

*KIF1B* germline mutations were initially reported in a family with bPHEO occurring in a female proband and her grandfather (age of diagnosis: 22 and 70 yo, respectively) (16). An additional case of a 54 yo female with a unilateral PHEO was reported later in a cohort of PPGL studied by targeted next-generation

sequencing (NGS) (106). Thus, although few cases of *KIF1B*-associated PPGL have been described to assume a propensity of patients with mutations in this gene to develop bPHEO, clinicians should bear in mind the possibility of a *KIF1B* mutation when more common genes associated with this phenotype have been found to be normal.

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## PEDIATRIC PPGL

Considering the largest case series of pediatric patients (363 patients  $\leq 18$  yo) with PPGL published to date, the prevalence of genetic mutations was found to be 66.8–80.4% (72, 107–109). The majority of PPGLs developing at a pediatric age occur in association with *SDHB*, *SDHD*, and *VHL* mutations (74, 107), and the higher frequency of hereditary cases at a pediatric compared with adult age is due to an excess of mutations in PPGL-susceptibility genes of cluster 1 (74). From a clinical point of view, it is worth noting that pediatric patients have a higher incidence of extra-adrenal, multifocal, recurrent, and metastatic tumors compared with adults (74). Thus, considering the very high prevalence of gene mutations in patients with PPGL at a pediatric age, all cases with  $\leq 18$  yo should be considered for genetic screening (18, 107, 109).

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## BIOCHEMICAL PHENOTYPE

The pattern of catecholamine secretion by the PPGL is recognized as a signature of its genetic background. Indeed, cluster 1 gene mutations are associated with a noradrenergic and/or dopaminergic phenotype of tumoral secretion, whereas gene mutations in cluster 2 are associated with an adrenergic and/or noradrenergic phenotype (110). Under hypoxia (or pseudohypoxia) states, HIF-2 $\alpha$  activates enzymes (e.g., tyrosine hydroxylase, dopamine  $\beta$ -hydroxylase, and dopa decarboxylase) that favor the production of norepinephrine in the catecholamine production pathway and, in parallel, decreases the expression of phenylethanolamine N-methyltransferase, the enzyme that converts norepinephrine to epinephrine (110). In agreement with these findings, PPGLs associated with *VHL*, *SDHx*, *HIF2A/PHD1/PHD2*, *FH*, and *MDH2* mutations produce and secrete predominantly norepinephrine/normetanephrine, but rarely epinephrine/metanephrine (PPGL-associated with *VHL* mutations do not secrete epinephrine/metanephrine) (14, 17, 23, 60). However, PHEOs associated with *SDHx* mutations also produce and/or secrete dopamine/methoxytyramine, which is rarely detected in *VHL* disease (23). On the contrary, PPGLs associated with *RET* or *NF1* mutations (cluster 2) induce an increase in phenylethanolamine N-methyltransferase and usually produce and secrete norepinephrine/normetanephrine and epinephrine/metanephrine (23, 110). The discriminatory rate between the pattern of catecholamine secretion between cluster 1 (*VHL/SDHx*-associated PPGL—normetanephrine but not metanephrine) and cluster 2 (*NF1/RET*-associated PPGL—normetanephrine and metanephrine) genes was found to be 99.0%. *VHL* and *SDHx*-associated PPGLs can be further discriminated in 78.0% of cases by the levels of

methoxytyramine (elevated only in *SDHx*-associated PPGL) (23). *MAX*-associated PPGLs secrete high levels of normetanephrine and moderate levels of metanephrine (11, 18). *TMEM127*-associated PPGLs have a mixed pattern of catecholamine secretion (normetanephrine and metanephrine) (102).

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## IMMUNOHISTOCHEMICAL PHENOTYPE

The immunohistochemical analysis of SDHA and SDHB protein expression in tumor samples may be very useful to individualize the genetic screening of patients with PPGL (24–26). Negative staining for SDHB immunohistochemistry (IHC) suggests an *SDHx* mutation, whereas a negative staining for SDHA IHC implies an *SDHA* mutation (24, 111). False negatives (positive or weakly positive staining) may occur in *SDHD*-related tumors for SDHB staining (112), and *SDHD* IHC may aid in these cases (positive staining predicts *SDHx* mutations) (113). *RET*, *HIF2A*, *MAX*, *TMEM127*, *FH*, *NF1* (95.0%) and *VHL* (84.0%) associated-PPGLs show positive IHC for SDHA/B, and thus this is a useful tool to aid in the selection of genetic screening, considering the full clinical setting (24, 93, 111). Although the rarity of *FH*-associated PPGL precludes the validation of *FH* IHC, there is evidence that the pattern of *FH* staining may also aid with the decision to proceed with *FH* analysis, as tumor samples with known mutations in this gene have negative staining for *FH*, whereas PPGLs associated with *SDHB/C/D*, *VHL*, and *RET* retain a positive staining for this enzyme (111).

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## FUNCTIONAL IMAGING

Functional imaging is used in the management of PPGL to (i) localize the primary tumor, (ii) define the tumor burden of a metastatic PPGL that may be missed on CT or MRI surveys, and (iii) characterize the metabolic activity of PPGL for therapeutic purposes (18, 114). The  $^{18}\text{F}$ -FDOPA PET/CT is a highly accurate functional imaging tool in the investigation of PPGL (27). However, false negative results may infrequently occur, mainly with abdominal tumors. These missed lesions on  $^{18}\text{F}$ -FDOPA PET/CT are often associated with *SDHB* and *SDHD* mutations, and it is worth to consider specific genetic screening for *SDHx* mutations in  $^{18}\text{F}$ -FDOPA PET/CT negative PPGL (27, 114).

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## NEXT-GENERATION SEQUENCING

Targeted NGS is a technology that processes DNA samples for simultaneous parallel sequencing of multiple genes (115, 116). Considering the high number of PPGL-related genes, NGS is attractive in this setting. Indeed, the application of this tool in cohorts of patients with PPGL has proved to be faster with lower costs compared with the conventional Sanger sequencing technique (117, 118), and NGS will probably replace the sequential genetic screening based on the clinical phenotype in a near future. However, some limitations of NGS may need to be

resolved before its full implementation in the everyday practice, namely, the clinical relevance of variants of uncertain significance or methodological errors induced by repetitive DNA sequences and pseudogenes (117–119). Additionally, in patients presenting with the full manifestations of a well-known syndrome, targeted conventional sequencing of the gene associated with that syndrome may be more appropriate instead of an NGS panel of several genes that have never been linked to that clinical scenario, and it may save costs. Finally, NGS is not yet available in or affordable by many countries, and thus the knowledge regarding PPGL genotype–phenotype correlations remains very useful for a cost-effective genetic screening.

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## CONCLUSIONS

Careful genetic screening is part of the standards of care of patients with PPGL. First, the possibility of a genetic mutation is close to 50%, and it reaches 80% in some age groups ( $\leq 18$ yo) (2, 3, 74, 107–109). Second, finding a specific genotype that is associated with a predisposition to the development of multifocal/recurrent (e.g., *SDHx*, *HIF2A/PHD1/PHD2*, and *FH* mutations) or metastatic PPGL (e.g., *SDHB*, *MAX*, and *FH* mutations), and other non-chromaffin cell tumors (e.g., duodenal somatostatinomas in *HIF2A* mutations; renal cell cancer in *VHL*), is paramount to tailor the diagnosis, treatment, and follow-up strategies in patients with PPGL (14, 18, 60). With the expanding genetic landscape of PPGL, new genes (e.g., *FH*, *MDH2*, and *HIF2A* mutations) are being added, which predispose patients to the development of chromaffin and non-chromaffin cell tumors with characteristic biological behaviors (14, 17, 60). This evidence emphasizes the importance of a comprehensive sequential genetic screening and the individualized strategies that may follow the discovery of a specific genotype in terms of diagnosis, treatment, long-term follow-up, and genetic counseling.

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