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Hereditary Paraganglioma-Pheochromocytoma Syndromes

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Summary

Clinical characteristics

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas (tumors that arise from neuroendocrine tissues distributed along the paravertebral axis from the base of the skull to the pelvis) and pheochromocytomas (paragangliomas that are confined to the adrenal medulla). Sympathetic paragangliomas cause catecholamine excess; parasympathetic paragangliomas are most often nonsecretory. Extra-adrenal parasympathetic paragangliomas are located predominantly in the skull base and neck (referred to as head and neck paragangliomas [HNPGLs]) and sometimes in the upper mediastinum; approximately 95% of such tumors are nonsecretory. In contrast, extra-adrenal sympathetic paragangliomas are generally confined to the lower mediastinum, abdomen, and pelvis, and are typically secretory. Pheochromocytomas, which arise from the adrenal medulla, typically lead to catecholamine excess. Symptoms of PGL/PCCs result from either mass effects or catecholamine hypersecretion (e.g., sustained or paroxysmal elevations in blood pressure, headache, episodic profuse sweating, forceful palpitations, pallor, and apprehension or anxiety). The risk for developing metastatic disease is greater for extra-adrenal sympathetic paragangliomas than for pheochromocytomas. Additional tumors reported in individuals with hereditary PGL/PCC syndromes include gastrointestinal stromal tumors (GISTs), pulmonary chondromas, and clear cell renal cell carcinoma.

Diagnosis/testing

A diagnosis of a hereditary PGL/PCC syndrome is strongly suspected in an individual with multiple, multifocal, recurrent, or early-onset paraganglioma or pheochromocytoma and/or a family history of paraganglioma or pheochromocytoma. The diagnosis is established in a proband with a personal or family history of

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paraganglioma or pheochromocytoma and a germline heterozygous pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* identified by molecular genetic testing.

Management

Treatment of manifestations: SDHB-related PGL/PCCs are typically treated with surgical resection because of the higher risk for metastatic disease. In general, most HNPGLs (carotid body, glomus jugulotympanicum, vagal, and jugular paragangliomas) are nonsecretory and may be treated with active observation, surgical resection, or radiation therapy. For secretory PGL/PCCs, alpha-adrenergic receptor blockade followed by surgical resection. All individuals with HNPGLs should be evaluated for catecholamine excess before surgical resection, which, if present, can suggest an additional primary PGL/PCC. Metastatic PGL/PCCs are treated with blood pressure control, surgical debulking, radiation therapy especially for bony lesions, liver-directed therapy, systemic chemotherapy, or radionuclide therapy. GIST treatment includes surgical resection and/or tyrosine kinase inhibitor. Clear cell renal cell carcinoma treatment is early surgical resection and standard treatments for metastatic disease.

Surveillance: Individuals at risk for hereditary PGL/PCC syndromes should have annual clinical assessment for manifestations of PGL/PCCs and GISTs, plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines every two years in childhood and then annually in adults, and whole-body MRI every two to three years. Age of initiation for screening varies by gene. Consider endoscopic evaluation for GISTs in individuals with unexplained anemia and gastrointestinal symptoms.

Agents/circumstances to avoid: As for all cancer predisposition syndromes, activities such as cigarette smoking that predispose to chronic lung disease should be discouraged. Hypoxic conditions (e.g., cyanotic heart disease, cigarette smoking) may increase tumor incidence and promote tumor growth, although data are extremely limited.

Evaluation of relatives at risk: First-degree relatives of an individual with a hereditary PGL/PCC syndrome and a known *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* pathogenic variant should be offered molecular genetic testing to clarify their genetic status to improve diagnostic certainty and reduce the need for costly screening procedures in those who have not inherited the pathogenic variant.

Genetic counseling

Hereditary PGL/PCC syndromes are inherited in an autosomal dominant manner. Most individuals diagnosed with a hereditary PGL/PCC syndrome inherited a PGL/PCC-related pathogenic variant from a parent; rarely, a proband with a hereditary PGL/PCC syndrome has the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with a hereditary PGL/PCC syndrome-causing pathogenic variant has a 50% chance of inheriting the pathogenic variant. Pathogenic variants in *SDHD*, *SDHAF2*, and possibly *MAX* demonstrate parent-of-origin effects and cause disease almost exclusively when they are paternally inherited: an individual who inherits an *SDHD* or *SDHAF2* pathogenic variant from the individual's father is at high risk of manifesting PGLs and PCCs; an individual who inherits an *SDHD* or *SDHAF2* pathogenic variant from the individual's mother is usually not at risk of developing disease – however, exceptions occur. Once the PGL/PCC syndrome-related pathogenic variant has been identified in an affected family member, predictive molecular genetic testing for at-risk family members and prenatal and preimplantation genetic testing are possible.

Diagnosis

The Endocrine Society guidelines for pheochromocytoma and paraganglioma [Lenders et al 2014], American College of Medical Genetics guidelines for cancer predisposition [Hampel et al 2015], and North American Neuroendocrine Tumor Society guidelines for metastatic or unresectable pheochromocytoma and

paraganglioma [Fishbein et al 2021] recommend that all individuals with paraganglioma or pheochromocytoma (PGL/PCC) be referred for molecular genetic testing to evaluate for a hereditary PGL/PCC syndrome.

Suggestive Findings

A hereditary PGL/PCC syndrome **should be suspected** in any individual with a paraganglioma or pheochromocytoma, particularly individuals with the following findings [Lenders et al 2014, Hampel et al 2015, Fishbein et al 2021, Horton et al 2022]:

- Tumors that are:
  - Multiple (i.e., >1 paraganglioma or pheochromocytoma), including bilateral adrenal pheochromocytoma
  - Multifocal, with multiple synchronous or metachronous tumors
  - Recurrent
  - Early onset (i.e., age <45 years)
  - Extra-adrenal
  - Metastatic
- A family history of paraganglioma or pheochromocytoma, or relatives with unexplained or incompletely explained sudden death

  Note: Many individuals with a hereditary PGL/PCC syndrome may present with a solitary tumor of the skull base or neck, thorax, abdomen, adrenal medulla, or pelvis and no family history of paraganglioma or pheochromocytoma.

The following clinical and laboratory features suggest a paraganglioma or pheochromocytoma. Note that many paragangliomas and pheochromocytomas are discovered incidentally on imaging done for other reasons.

- **Clinical features**
  - Signs and symptoms of catecholamine excess, including classic signs and symptoms (e.g., sustained or paroxysmal elevations in blood pressure, headache, palpitations, arrhythmia, profuse sweating, apprehension or anxiety), and non-classic signs and symptoms (e.g., pallor, nausea/vomiting, and sudden change in glycemic control)

    Symptoms may be triggered by changes in body position, increases in intra-abdominal pressure, medications (e.g., metoclopramide), anesthesia induction, exercise, or micturition.
  - Palpable abdominal mass
  - Enlarging mass of the skull base or neck
  - Compromise of cranial nerves (VII, IX, X, XI) and sympathetic nerves in the head and neck area (e.g., hoarseness, dysphagia, soft palate paresis, Horner syndrome)
  - Tinnitus
- **Laboratory findings.** Elevated fractionated metanephrines and/or catecholamines in plasma and/or a 24-hour urine sample can include any of the following:
  - Metanephrine or its precursor epinephrine (adrenaline)
  - Normetanephrine or its precursor norepinephrine (noradrenaline)
  - Dopamine and its major metabolite 3-methyoxytyramine

Note: (1) Measurement of fractionated metanephrine concentrations in plasma or urine is preferred, as it is more sensitive than measurement of catecholamine concentrations [Eisenhofer et al 2023]. (2) False positive results may be reduced by follow-up testing for 24-hour urine fractionated metanephrines when plasma normetanephrine concentrations are less than twofold above the reference range [Eisenhofer et al 2023]. (3) The secretion of epinephrine with little norepinephrine excess suggests an adrenal pheochromocytoma, which may be associated with multiple endocrine neoplasia type 2 [Young 2011].

Establishing the Diagnosis

The diagnosis of a **hereditary PGL/PCC syndrome should be strongly suspected** in an individual with multiple, multifocal, recurrent, or early-onset paraganglioma or pheochromocytoma and/or a family history of paraganglioma or pheochromocytoma.

The diagnosis of **hereditary PGL/PCC syndromes is established** in a proband with a personal or family history of paraganglioma or pheochromocytoma and a germline heterozygous pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1 identified by molecular genetic testing.

Note: (1) Some families have multiple individuals with a paraganglioma or pheochromocytoma and no identifiable pathogenic variant in a known susceptibility gene. These families likely have a hereditary PGL/PCC syndrome either from a pathogenic variant in a regulatory element not found through standard molecular analysis or from a pathogenic variant in an unidentified susceptibility gene. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (3) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

Molecular genetic testing approaches include the use of a **multigene panel** and **single-gene testing** depending on the phenotype.

- **A multigene panel** that includes *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Single-gene testing.** Given the cost-effectiveness of multigene panel testing and overlap of phenotype in hereditary PGL/PCC syndromes, single-gene testing is not commonly used. However, in certain situations, it may be more cost-effective to use single-gene testing. Prioritized genetic testing may be pursued as single-gene testing based on clinical features:
  - *SDHB* in an individual with a metastatic pheochromocytoma or paraganglioma

- *SDHD* in individuals with head and neck paragangliomas (HNPGLs); *SDHD* germline pathogenic variants account for 40%-50% of HNPGLs.

Table 1. Molecular Genetic Testing Used in Hereditary Paraganglioma-Pheochromocytoma Syndromes

Gene [1, 2]	Proportion of Hereditary PGL/PCC Syndromes Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [3, 5]	Gene-targeted deletion/ duplication analysis [3, 6]
MAX	~4%	~90%	~10%
SDHA	~4%	~98%	1 reported
SDHAF2	~1%	~100%	None reported
SDHB	50%-55% [7]	~85%-95%	~5%-15%
SDHC	~8%	~85%	~15%
SDHD	~20%-25% [8]	90%-95%	5%-10%
TMEM127	~5% [3]	~100%	None reported
Unknown [9]	NA		

PGL = paraganglioma; PCC = pheochromocytoma
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
4. See Molecular Genetics for information on variants detected in this gene.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Due to pseudogenes, many labs do not perform *SDHA* deletion/ duplication analysis.
7. An *SDHB* pathogenic variant is identified in 24%-44% of individuals with chest, abdomen, or pelvic PGL/PCCs [Amar et al 2005, Burnichon et al 2009] and 12%-20% of individuals with HNPGLs [Baysal et al 2002, Burnichon et al 2009].
8. An *SDHD* pathogenic variant is identified in 15% of individuals with chest, abdomen, or pelvic PGL/PCCs [Amar et al 2005, Burnichon et al 2009] and 40%-50% of individuals with HNGPLs [Baysal et al 2002, Burnichon et al 2009].
9. This table includes the core genes associated with hereditary paraganglioma-pheochromocytoma syndromes. *FH* and *MDH2* are likely susceptibility genes (see Differential Diagnosis). *EGLN1*, *EGLN2, EPAS1*, *KIF1B*, *KMT2D*, and additional genes have been reported to be associated with hereditary PGL/PCC; their clinical significance is as yet unclear.

Tumor Immunohistochemistry

If germline molecular genetic testing for hereditary PGL/PCC syndromes is not readily available, the results of immunohistochemical tumor analysis may suggest the presence of an underlying germline pathogenic variant. When any component of the mitochondrial respiratory chain complex 2 is completely inactivated, often the entire complex becomes unstable, resulting in degradation of the SDHB subunit. Therefore, negative immunohistochemistry staining for SDHB appears to occur when a germline pathogenic variant in *SDHA*, *SDHB*, *SDHC*, or *SDHD* is accompanied by inactivation of the normal allele [van Nederveen et al 2009, Gill et al 2010, Pai et al 2014, Udager et al 2018]. Germline pathogenic variants in *SDHA* show loss of staining for SDHA, in addition to loss of staining for SDHB [Korpershoek et al 2011, Papathomas et al 2015].

For these reasons, some recommend SDHB immunohistochemistry in individuals with familial and apparently sporadic PGL/PCC to guide molecular genetic testing; however, evidence is currently insufficient to advocate for the routine use of immunohistochemistry to guide molecular testing, as several nonconcordant cases have been reported [Santi et al 2017, Wallace et al 2020, Ding et al 2022]. Pathogenic variants in *VHL* also appear to contribute to difficulty in interpreting SDHB immunohistochemistry results. Therefore, since there are still

challenges in interpreting SDHB immunohistochemistry, and the procedure is not widely available, it is unclear whether it should be routinely performed on PGL/PCC tumor tissue.

Clinical Characteristics

Clinical Description

In individuals with hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes, tumors arise within the paraganglia – collections of neural crest cells distributed along the paravertebral axis from the base of the skull to the pelvis – as well as in some visceral locations. The 2022 World Health Organization (WHO) Classification of Endocrine Tumours classifies paragangliomas by location and (directly or indirectly) secretory status (adrenal paraganglioma [called pheochromocytoma], sympathetic abdominal paraganglioma, sympathetic head and neck paraganglioma, and parasympathetic paraganglioma) [Mete et al 2022].

Paragangliomas (paraganglion tumors) arise from neuroendocrine tissues (paraganglia) distributed along the paravertebral axis from their predominant location at the skull base to the pelvis.

Head and neck paragangliomas (HNPGLs) and those in the upper mediastinum are primarily associated with the parasympathetic nervous system and typically do not secrete catecholamines or other hormones. Approximately 5% of HNPGLs secrete catecholamines. The rare secretory tumors in the head and neck area are either a subset of carotid body tumors or arise from the cervical sympathetic chain. Most HNPGLs do not metastasize, although there are many exceptions. Clinical complications of HNPGLs are typically the result of mass effect.

- **Carotid body paragangliomas** often present as asymptomatic, enlarging lateral neck masses. (The carotid bodies are located at or near the bifurcations of the carotid arteries, in the lateral upper neck at approximately the level of the fourth cervical vertebra.) Affected individuals may experience mass effects, including cranial nerve and sympathetic chain compression, with resulting neuropathies (e.g., hoarseness, Horner syndrome). On physical examination masses are vertically (but not horizontally) fixed; bruits and/or thrills may be present.
- **Vagal paragangliomas** present in a manner similar to carotid body paragangliomas. Signs and symptoms include neck masses, hoarseness, pharyngeal fullness, dysphagia, dysphonia (impaired use of the voice), pain, cough, and aspiration. Dysphonia may be caused by mass effects within the throat or by pressure on nerves supplying the vocal cords or tongue.
- **Jugulotympanic paragangliomas** may present with pulsatile tinnitus, hearing loss, and other lower cranial nerve abnormalities. Blue-colored, pulsatile masses may be visualized behind the tympanic membrane on otoscopic examination [Gujrathi & Donald 2005].
- **Jugulare paragangliomas** may present with difficulty swallowing, hoarseness, dysphagia, dizziness, hearing loss or pulsations in the ear, facial nerve palsy, or pain.

Paragangliomas in the lower mediastinum, abdomen, and pelvis are typically associated with the sympathetic nervous system and usually secrete catecholamines. Sympathetic paragangliomas located along the paravertebral axis (and not in the adrenal gland) are called extra-adrenal sympathetic paragangliomas. Extra-adrenal sympathetic paragangliomas are associated with a higher risk of metastasizing [Ayala-Ramirez et al 2011].

Pheochromocytomas are catecholamine-secreting paragangliomas confined to the adrenal medulla. Metastatic disease is less likely in pheochromocytomas but can occur (see Phenotype Correlations by Gene).

Signs and symptoms of paraganglioma and pheochromocytoma are similar in individuals with hereditary PGL/PCC syndromes and individuals with sporadic (i.e., not inherited) tumors, most often coming to medical attention in the following four clinical settings:

- Signs and symptoms of catecholamine excess, including episodic or sustained elevations in blood pressure and pulse, headaches, palpitations (perceived episodic, forceful, often rapid heartbeat), arrhythmias, excessive sweating, pallor, apprehension, and anxiety. Nausea, emesis, fatigue, sudden alteration in glycemic control, and weight loss can also be seen. Paroxysmal symptoms may be triggered by changes in body position, increases in intra-abdominal pressure, medications (e.g., metoclopramide), anesthesia induction, exercise, or micturition in individuals with urinary bladder paragangliomas. Urinary bladder paragangliomas may also be accompanied by painless hematuria.
- Signs and symptoms related to mass effects from the neoplasm (particularly HNPGLs), which can compromise cranial nerves (e.g., VII, IX, X, XI) and sympathetic nerves in the head and neck area, leading to hoarseness, dysphagia, soft palate paresis, Horner syndrome, and/or tinnitus.
- Incidentally discovered mass on MRI/CT performed for other reasons
- Screening of at-risk relatives

Biochemical features of PGL/PCC. Catecholamines and metanephrines secreted by PGL/PCC can be any of the following:

- Metanephrine or its precursor epinephrine (adrenaline)
- Normetanephrine or its precursor norepinephrine (noradrenaline)
- Dopamine and its major metabolite 3-methoxytyramine

Note: Plasma chromogranin A is not a catecholamine but is a protein often secreted by PGL/PCCs and can suggest a diagnosis of a PGL/PCC. However, elevation of plasma chromogranin A is not specific, as many other medical conditions (e.g., liver and kidney disease; gastrointestinal conditions such as atrophic gastritis, irritable bowel syndrome, and colon cancer; other malignancies and neuroendocrine tumors) and medications (e.g., proton pump inhibitors) can cause elevated plasma chromogranin A levels. Therefore, it is not recommended to measure plasma chromogranin A in those with suspected PGL/PCC.

Radiographic features of PGL/PCC. CT is often the imaging modality of choice to identify a PGL/PCC in a symptomatic person with suggestive biochemical testing, given its excellent spatial resolution of the thorax, abdomen, and pelvis [Lenders et al 2014]. MRI is a better option in individuals for whom radiation exposure must be limited, such as pregnant women, and for lifelong screening for biochemically silent PGL/PCC and other manifestations in those asymptomatic individuals with known germline pathogenic variants.

- Paragangliomas can be identified anywhere along the paravertebral axis from the skull base to the pelvis, including the para-aortic sympathetic chain, as well as some other visceral locations. Common sites of neoplasia are near the renal vessels and in the organ of Zuckerkandl (chromaffin tissues near the origin of the inferior mesenteric artery and the aortic bifurcation). A less common site is within the urinary bladder wall.
- PGL/PCCs usually exhibit high signal intensity on T_2-weighted MRI and have no loss of signal intensity on in- and out-of-phase imaging, which helps distinguish pheochromocytoma from benign adrenal cortical adenomas. On CT examination these tumors are characterized by heterogeneous appearance with cystic areas, high unenhanced CT attenuation (density, Hounsfield units >10), increased vascularity on contrast-enhanced CT, and slow contrast washout.
- Multiple tumors can be present.
- Digital subtraction angiography (DSA) is sensitive for the detection of small paragangliomas and can be diagnostically definitive. DSA is essential if preoperative embolization or carotid artery occlusion is to be performed.
- Some experts suggest using ^{68}Ga-DOTATATE PET-CT in individuals with hereditary PGL/PCC syndromes [Taïeb et al 2023] given high sensitivity and specificity for this imaging.

Distinguishing localized and metastatic PGL/PCCs. No reliable pathology studies are available to distinguish a localized PGL/PCC from a metastatic PGL/PCC. Furthermore, biopsy of PGL/PCCs is contraindicated because this carries the risk of precipitating a hypertensive crisis, hemorrhage, and tumor cell seeding [Vanderveen et al 2009]. The pathology of the primary tumor cannot reliably predict the development of metastatic disease [Wu et al 2009].

The most common sites of PGL/PCC metastases are bone, lung, liver, and lymph nodes.

For PGL/PCCs that have not metastasized, operative treatment can be curative. However, once metastases have occurred there is no cure, with a five-year survival rate of 50%-69% [Hescot et al 2013, Asai et al 2017, Fishbein et al 2017, Hamidi et al 2017].

To detect metastases, the following radiographic studies can be used:

- **^{68}Ga-DOTATATE PET-CT** is a more sensitive modality to detect somatostatin receptor-positive disease, especially in individuals with metastatic disease [Janssen et al 2015, Chang et al 2016, Janssen et al 2016, Patel et al 2022].
- **^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy** is a technique that measures tumor uptake of a catecholamine analog radioisotope. MIBG has greater specificity for localization than CT and MRI but significantly lower sensitivity. For this reason, it is typically not used for detection of metastatic PGL/PCCs but will be used to determine if the metastatic disease can be treated with I-131-MIBG radionuclide therapy.
- **Octreotide scintigraphy** has been largely replaced by ^{68}Ga-DOTATATE PET-CT, where available, because of the significantly higher sensitivity.
- **2-deoxy-2-(^{18}F)-fluoro-D-glucose position emission tomography (FDG-PET),** or PET using other imaging compounds, can also assist in detecting metastatic disease.

Other tumors

- **Gastrointestinal stromal tumors (GISTs).** The majority of GISTs associated with hereditary PGL/PCC syndromes occur in individuals with a germline pathogenic variant in *SDHA* or *SDHC* but can also occur in individuals with a germline pathogenic variant in *SDHB* or *SDHD*. Molecular genetic testing of *SDHA*, *SDHB*, *SDHC*, and *SDHD* should be considered in individuals with a wild type GIST (those that lack *KIT* or *PDGFRA* pathogenic variants) either by immunohistochemistry on tumor tissue or germline genetic testing. Children with GISTs are more likely to have a germline pathogenic variant in a PGL/PCC susceptibility gene than an adult with a GIST. Most GISTs associated with hereditary PGL/PCC syndromes occur in the stomach and are often multifocal (>40%).
- **Pulmonary chondromas** have been described in individuals with a germline pathogenic variant in an *SDHx* gene [Boikos et al 2016].
- **Clear cell renal cell carcinoma** is more common in individuals with a pathogenic variant in *SDHB* or *SDHD* [Ricketts et al 2010]. The lifetime risk of developing a clear cell renal cell carcinoma for individuals with an *SDHB* pathogenic variant is 4.7%, compared to 1.7% in the general population [Andrews et al 2018].
- Other tumors including papillary thyroid carcinoma, pituitary adenomas, and neuroendocrine tumors have been described in individuals with *SDHx* germline pathogenic variants. However, whether there is an increased risk of developing these other tumors has not been established.

Prognosis. With staged tumor-targeted treatment modalities, some affected individuals have lived with metastatic disease for more than 20 years [Fishbein et al 2017, Hamidi et al 2017].

Phenotype Correlations by Gene

Although persons with *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* pathogenic variants can develop pheochromocytomas and/or paragangliomas within any paraganglial tissue, the following correlations between the gene involved and tumor location are used to guide testing (see also Table 2).

MAX. Germline *MAX* pathogenic variants have most commonly been reported in association with pheochromocytomas; all individuals with *MAX*-related hereditary PGL/PCC presented initially with pheochromocytoma. Some individuals also had paragangliomas [Comino-Méndez et al 2011, Burnichon et al 2012, Bausch et al 2017].

SDHA. Germline *SDHA* pathogenic variants have been identified in individuals with pheochromocytomas and paragangliomas (sympathetic and parasympathetic) [Burnichon et al 2010, Korpershoek et al 2011, Bausch et al 2017].

SDHAF2. Germline *SDHAF2* pathogenic variants have been identified in individuals with HNPGLs [Hao et al 2009, Bayley et al 2010, Kunst et al 2011, Piccini et al 2012, Currás-Freixes et al 2015, Zhu et al 2015, Bausch et al 2017].

SDHB. Germline pathogenic variants in *SDHB* are generally associated with higher morbidity and mortality than pathogenic variants in genes encoding the other SDH subunits [Ricketts et al 2010, Andrews et al 2018]. They are strongly associated with extra-adrenal sympathetic paragangliomas with an increased risk of metastatic disease and, less frequently, pheochromocytomas and parasympathetic paragangliomas [Andrews et al 2018]. Up to 45% of persons with metastatic extra-adrenal paragangliomas have a germline *SDHB* pathogenic variant [Fishbein et al 2013].

SDHC. Germline *SDHC* pathogenic variants appear to be most often associated with HNPGLs. However, up to 10% of *SDHC*-related tumors are observed in the thoracic cavity [Peczkowska et al 2008, Else et al 2014].

SDHD. *SDHD* pathogenic variants are mainly associated with HNPGL, although extra-adrenal paragangliomas and pheochromocytomas also occur [Ricketts et al 2010, Andrews et al 2018]. Seventy-five percent of persons with a germline *SDHD* pathogenic variant have multifocal primary paraganglioma [Taïeb et al 2023].

TMEM127. Germline *TMEM127* pathogenic variants are associated with pheochromocytoma but can also be associated with HNPGLs and extra-adrenal paragangliomas [Armaiz-Pena et al 2021]. Clear cell renal cell carcinoma has also been associated [Qin et al 2014].

Table 2. Distinguishing Clinical Features of Hereditary PGL/PCC Syndromes by Genetic Etiology

Gene	Distinguishing Clinical Features [1]				
	Most frequent tumor type	Frequency of multiple or bilateral tumors	Biochemical phenotype	Metastatic risk	MOI
MAX	PCC	~60% bilateral	Mixed	25%	Possibly paternal [2]
SDHA	PGL, PCC	Single	Mixed	Low	AD
SDHAF2 [3]	PGL (skull base & neck)	~90% multiple	Unclear	Low	Paternal [2]
SDHB	PGL	~20% multiple	Norepinephrine/ normetanephrine, nonsecreting	24% -58%	AD
SDHC	PGL	~20% multiple	Norepinephrine/ normetanephrine	Low	AD
SDHD	PGL (skull base & neck most common)	~75% multiple	Norepinephrine/ normetanephrine, often nonsecreting	<5%	Paternal [4]

Table 2. continued from previous page.

Gene	Distinguishing Clinical Features [1]				
	Most frequent tumor type	Frequency of multiple or bilateral tumors	Biochemical phenotype	Metastatic risk	MOI
TMEM127	PCC, rarely PGL	~25% bilateral	Mixed	Low	AD

AD = autosomal dominant; MOI = mode of inheritance; PCC = pheochromocytoma; PGL = paraganglioma
1. General rules of thumb; exceptions exist.
2. Mode of inheritance is likely paternal; only a few pedigrees have been described.
3. Phenotype is not well described as only a few families have been reported.
4. Maternal transmission has been rarely reported.

Genotype-Phenotype Correlations

No consistent genotype-phenotype correlations have been identified.

Penetrance

Age-related penetrance. Penetrance estimates vary (see Table 3). Penetrance was initially believed to be quite high, but larger studies with less bias from probands suggest a much lower penetrance. No reliable penetrance data are currently available for *MAX*, *SDHAF2*, or *TMEM127* pathogenic variants.

Table 3. Estimated Penetrance for *SDHx* Pathogenic Variants

Gene	Penetrance of PGL/PCC		By Age	Reference(s)
	In non-probands	In probands & non-probands		
SDHA	10%	50%	70 years	van der Tuin et al [2018]
SDHB	21.8%-26.4%	23.9%-57.6%	60 years	Jochmanova et al [2017], Andrews et al [2018]
SDHC	25% [1]	Unknown	60 years	Andrews et al [2018]
SDHD	43.2%	Unknown	60 years	

PCC = pheochromocytoma; PGL = paraganglioma
1. This estimate is higher than expected based on clinical experience.

Nomenclature

The hereditary PGL/PCC syndromes were initially referred to as the hereditary paraganglioma syndromes before the discovery of their association with pheochromocytomas. Hereditary paragangliomas of the head and neck have also been referred to as familial glomus tumors and familial nonchromaffin paragangliomas.

Prior to the identification of the genes underlying hereditary PGL/PCC syndrome loci, the syndromes were referred to by their locus (i.e., PGL1, PGL2, PGL3, PGL4, and PGL5). A dyadic gene and phenotype-based naming approach is now preferred (e.g., *SDHB*-related hereditary PGL/PCC syndrome).

In 2017 WHO replaced the term "malignant pheochromocytoma" with "metastatic pheochromocytoma" to avoid confusion in the definition. PGL/PCCs are now considered localized or metastatic, not benign or malignant.

Carney-Stratakis syndrome (OMIM 606864) and Carney triad (OMIM 604287) are largely historical terms predating the use of a molecular-driven nomenclature and are best reserved for individuals with the clinical features but without *SDHx* germline pathogenic variants.

Pheochromocytomas are tumors of the adrenal medulla, which is a specialized paraganglion. Paragangliomas arise from paraganglial tissue anywhere in the body, usually as head and neck paragangliomas (HNPGLs; e.g., carotid body tumor, glomus jugulare tumor, glomus tympanicum tumor, glomus vagale tumor), as thoracic

paragangliomas either arising from paraganglia associated with the large arteries or the paraspinal sympathetic chain, or as abdominal paragangliomas (e.g., organ of Zuckerkandl, para-adrenal, bladder wall). The term "chromaffin" tumor is largely historical and refers to positive staining by chromium salts, which react with catecholamines. Therefore, usually only catecholamine-secreting tumors, such as pheochromocytomas and sympathetic paragangliomas, are truly chromaffin, while most parasympathetic tumors are silent.

Prevalence

The incidence of hereditary PGL/PCC syndromes is not precisely known. The incidence of pheochromocytoma is approximately 0.6 in 100,000 per year [Berends et al 2018]. About 25% of all pheochromocytomas arise in individuals with a hereditary predisposition. The incidence of paragangliomas is lower, but these tumors are more often associated with a hereditary predisposition. Altogether, about 35%-40% of all PGL/PCCs are associated with a hereditary predisposition.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *MAX*, *SDHAF2*, *SDHC*, or *TMEM127*.

Other phenotypes associated with germline pathogenic variants in *SDHA*, *SDHB*, and *SDHD* are summarized in Table 4.

Table 4. Allelic Disorders

Gene	MOI	Disorder
SDHA	AR	Dilated cardiomyopathy reported in 15 homozygous individuals of Bedouin ancestry (OMIM 613642)
	AR	Complex II-deficient Leigh syndrome (See Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview.)
	AD	Neurodegeneration w/ataxia & late-onset optic atrophy (OMIM 619259)
SDHB	AR	Mitochondrial complex II deficiency nuclear type 4 (OMIM 619224)
SDHD	AR	Mitochondrial complex II deficiency nuclear type 3 (OMIM 619167)

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Differential Diagnosis

The differential diagnosis of hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes includes sporadic pheochromocytoma and sporadic paraganglioma or other syndromes that predispose to pheochromocytomas or paragangliomas.

Sporadic pheochromocytoma. The incidence of all pheochromocytoma is ~0.6 in 100,000, and 75% are thought to be sporadic (not associated with hereditary predisposition).

Sporadic paraganglioma. The incidence of sporadic paraganglioma is not known. It is believed to be less common than sporadic pheochromocytoma, but the association with hereditary predisposition is higher than for pheochromocytoma.

Several genetic disorders (see Table 5) associated with an increased risk of pheochromocytomas and/or paragangliomas have additional clinical features that are not seen in individuals with hereditary PGL/PCC syndromes.

Table 5. Disorders to Consider in the Differential Diagnosis of Hereditary Paraganglioma-Pheochromocytoma Syndromes

Gene	Disorder	MOI	Typical Clinical Features of Disorder [1]	
			Overlapping w/Hereditary PGL/PCC	Distinguishing From Hereditary PGL/PCC
EPAS1	Polycythemia-paraganglioma-somatostatinoma syndrome [1]	See footnote 2.	PGL	• Mainly in females • Polycythemia • Somatostatinoma
FH	*FH* tumor predisposition syndrome (hereditary leiomyoma renal cell carcinoma syndrome)	AD	PCC/PGL are rare.	• Cutaneous & uterine leiomyomas • Other types of renal carcinoma
MEN1	Multiple endocrine neoplasia type 1	AD	PCC/PGL are rare.	• Parathyroid tumors • Pituitary tumors • Foregut neuroendocrine tumors, incl pancreatic, lung, & duodenal neuroendocrine tumors • Adrenocortical adenomas
NF1	Neurofibromatosis 1	AD	• PCC that secrete epinephrine &/or norepinephrine • PGL are rare.	• Café au lait macules • Axillary & inguinal freckling • Neurofibromas (cutaneous & plexiform) • Long bone dysplasia • Optic glioma
RET	Multiple endocrine neoplasia type 2	AD	• PCC that secrete epinephrine/metanephrine &/or norepinephrine/ normetanephrine • PGL are rare.	MEN2A: • Medullary thyroid carcinoma • Hyperparathyroidism MEN2B: • Medullary thyroid carcinoma • Mucocutaneous neuromas • Ganglioneuromatosis • Slender body habitus • Joint laxity • Skeletal malformations
VHL	Von Hippel-Lindau disease	AD	• PCC that secrete norepinephrine/ normetanephrine • PGL are infrequent. • Clear cell renal cell carcinoma	• CNS hemangioblastomas • Renal, pancreatic, epididymal, & broad ligament cysts • Pancreatic neuroendocrine tumors • Endolymphatic sac tumors

AD = autosomal dominant; CNS = central nervous system; MOI = mode of inheritance; PCC = pheochromocytoma; PGL = paraganglioma

1. Yang et al [2015]

2. To date, the majority of reported individuals with polycythemia-paraganglioma-somatostatinoma syndrome have the disorder as the result of a somatic mosaic pathogenic variant (i.e., a pathogenic variant not inherited from a parent).

Management

Clinical practice guidelines for the management of individuals with hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes due to *SDHx* pathogenic variants have been published [Lenders et al 2014, Amar et al 2021, Hanson et al 2023, Taïeb et al 2023].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a hereditary PGL/PCC syndrome, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Hereditary Paraganglioma-Pheochromocytoma Syndromes: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
General	Refer to expert on hereditary PGL/PCC syndromes (e.g., endocrinologist, oncologist); the specialist w/expertise in PGL/PCC should then complete the evaluations in this table.	Referral to other subspecialists (e.g., ENT, cardiology, gastroenterology) as needed
In those w/symptoms or biochemical findings of PGL/PCC	• Cross-sectional imaging (CT/MRI) is preferred method to define tumor extent. • Functional studies, such as somatostatin receptor-based imaging (e.g., ^{68}Ga- DOTATATE PET-CT) or less commonly other functional studies (e.g., FDG-PET) can aid in defining cross-sectional imaging findings as PGL/PCC or allow for defining therapeutic options for metastatic disease.	CT or MRI may be preferable based on suspected tumor location: • HNPGLs are often best characterized by MRI. • Thoracic PGLs are best characterized by CT. • Abdominal tumors by either MRI or CT
In those w/symptoms of GIST	Clinical eval (incl EGD) for GISTs in children, adolescents, or young adults who have unexplained GI symptoms (e.g., abdominal pain, upper GI bleeding, nausea, vomiting, difficulty swallowing) or who experience unexplained intestinal obstruction or anemia	
Cardiovascular	Evaluate for hypertension & tachycardia.	These need to be controlled prior to initiation of therapy.
For at-risk asymptomatic individuals	• Plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) to screen for secreting PGL/PCC • Whole-body MRI for PGL, PCC, renal cell carcinoma, & GIST	See Table 8 for gene-specific surveillance guidelines.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of hereditary PGL/PCC syndromes to facilitate medical & personal decision making

EGD = esophagogastroduodenoscopy; GI = gastrointestinal; GIST = gastrointestinal stromal tumor; HNPGL = head and neck paraganglioma; MOI = mode of inheritance; PCC = pheochromocytoma; PGL = paraganglioma

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The management of tumors in individuals with hereditary PGL/PCC syndromes resembles management of sporadic tumors; however, persons with hereditary PGL/PCC syndromes are more likely to have multiple tumors and multifocal and/or metastatic disease than are those with sporadic tumors [Fishbein et al 2021, NCCN 2022, Taïeb et al 2023].

Table 7. Hereditary Paraganglioma-Pheochromocytoma Syndromes: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
***SDHB*-related PGL/PCC**	• Surgical resection is recommended due to risk for metastases. Prompt resection is particularly important for extra-adrenal sympathetic PGLs because of their tendency to metastasize. • Perioperative alpha-adrenergic blockade is typically required.	There may be no difference in metastatic potential between *SDHB*-assoc & sporadic HNPGLs [Richter et al 2022].
Nonsecretory HNPGL	Treatment options: • Active observation • Surgical resection • Radiation therapy Because most HNPGLs are nonsecretory, persons w/HNPGLs should be evaluated for catecholamine excess before surgical resection; if present, this can suggest an additional primary PGL/PCC.	Early detection allows for a timely decision re treatment or surveillance. Active observation & radiation therapy are often equally beneficial or better approaches.
Carotid body, jugulotympanicum, & vagal PGL	Treatment options: • Active observation • Surgical resection • Radiation Treatment choice should be based on extent of tumor (e.g., Shamblin I & II carotid body tumors are good candidates for surgery), assoc risks (e.g., resection of glomus vagal tumors almost invariably leads to loss of ipsilateral vagal & recurrent laryngeal nerve), & presumed metastatic potential (e.g., ***SDHB*-assoc tumors** could be considered for more aggressive therapy).	Radiation therapy is an option, & there is currently no evidence for ↑ incidence of secondary malignancies in this population due to underlying genetic condition. [1]
Jugular paragangliomas	Treatment options: • Surgical resection • Active observation • Radiation therapy or stereotactic radiosurgery in selected persons [1]	• Small tumors may potentially be removed w/o complications or permanent nerve injuries. • Resection of larger tumors is often assoc w/CSF leak, meningitis, stroke, hearing loss, cranial nerve palsy, or even death. • Close observation w/ symptomatically guided surgery may be prudent. • Gamma knife stereotactic surgery is a good option to prevent morbidity from resection.

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Catecholamine-secreting tumors	Treatment is directed toward containing the effect of catecholamines through antagonism of catecholamine excess w/pharmacologic adrenergic blockade prior to surgical removal. [2]	
Pheochromocytomas	**Preoperative:** • Alpha-adrenergic blockade (w/prazosin/doxazosin) starting ≥7-10 days preoperatively to normalize BP & allow volume expansion. The dose of the α-blocker is adjusted for a low-normal systolic BP for age. • Calcium channel blockers (e.g., amlodipine, nicardipine) as needed for second-line treatment of BP control [2] • A liberal sodium diet & fluid intake to allow for plasma volume expansion. • Once adequate α-adrenergic blockade or BP control w/ calcium channel blockers is achieved, initiation of beta-adrenergic blockade may be required to control reflex tachycardia. The dose of the β-blocker is adjusted for a target heart rate of 80 beats per minute.	Treat chronic & acute effects of catecholamine excess. Alpha-adrenergic blockade is required to control BP & prevent intraoperative hypertensive crises. The Endocrine Society guidelines have an algorithm for medication titration. [1]
	Surgical resection, preferably laparoscopic, is the treatment of choice. [1]	
	Postoperative: • ~2-8 wks after surgery, assess 24-hour urine fractionated metanephrines &/or plasma-free metanephrines. • If the levels are normal, resection of the biochemically active PCC should be considered complete. • If the levels are ↑, an unresected 2nd tumor &/or occult metastases should be suspected.	
Metastatic PGL/PCC	Treatment options: • BP control w/α-blocker to ↓ symptoms from high catecholamine levels in persons w/sympathetic tumors • Surgical debulking to ↓ tumor burden due to mass effect or catecholamine secretion • Active observation for nonprogressing, nonsecreting disease • Radiation therapy, esp for bony lesions • Liver-directed therapy • Systemic therapy w/chemotherapy (e.g., cyclophosphamide, vincristine, dacarbazine) • I-131-MIBG therapy	
Metastatic or unresectable PGL/PCC – radionucleotide therapies	I-131-MIBG; reserved for those requiring systemic therapy who have uptake in sites of disease on MIBG imaging.	
	Lutathera® (Lu-177-DOTATATE therapy; peptide receptor radionuclide therapy [PRRT])	Lutathera® is FDA approved for gastroenteropancreatic neuroendocrine tumors but not yet FDA approved for PGL/PCC (see Therapies Under Investigation).

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
GIST	• Surgical resection of localized disease, particularly if tumor is bleeding, causing obstruction, >2 cm, or ↑ in size • Tyrosine kinase inhibitor (TKI) for adjuvant therapy after surgical resection or as first-line therapy in those w/metastatic disease. However, SDH-deficient GISTs are largely resistant to TKIs.	There are no standard recommendations other than expert opinion. [3]
Pulmonary chondroma	Active observation for these benign tumors unless they cause bronchial compression.	
Clear cell renal cell carcinoma	• Early surgical intervention • Partial nephrectomy in persons w/solitary tumor at early stage • Standard treatment for metastatic disease	There are no standard recommendations other than expert opinion. [4]

BP = blood pressure; CSF = cerebrospinal fluid; MIBG = metaiodobenzylguanidine; PCC = pheochromocytoma; PGL = paraganglioma
1. Taïeb et al [2014]
2. Lenders et al [2014]
3. Neppala et al [2019]
4. Wang & Rao [2018]

Surveillance

Individuals known to have a hereditary PGL/PCC syndrome and relatives at risk based on family history who have not undergone DNA-based testing need regular clinical monitoring by a physician or medical team with expertise in treatment of hereditary PGL/PCC syndromes.

Although no clear data regarding when to start, best method, and how frequent biochemical studies and imaging should be done in at-risk individuals exist, it is reasonable to consider surveillance for all at-risk individuals [Amar et al 2021]. Surveillance recommendations should take into account the associated gene and penetrance. Gene-specific recommendations from expert consensus groups have been published but are based on limited data (see Table 8) [Hanson et al 2023, Taïeb et al 2023].

Table 8. Hereditary Paraganglioma-Pheochromocytoma Syndromes: Surveillance for Individuals at Risk and Affected Individuals

Gene	Evaluation	Frequency [1]	
SDHA	Clinical assessment for manifestations of PGL/PCC & GIST	Annually	Beginning at age 6-15 yrs [2]
	Plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) for secreting PGL/PCC	Every 2 yrs in childhood; then annually in adults	
	Whole-body MRI to assess for PGL, PCC, RCC, & GIST	Every 2-3 yrs	
	EGD for those w/unexplained anemia & GI symptoms	As needed	
	Note: Surveillance is not recommended in persons w/*SDHA* pathogenic variant & no personal or family history of PGL/PCC or other *SDHA*-related tumors (i.e., incidental finding) due to low penetrance (see Table 3) [Hanson et al 2023].		

Table 8. continued from previous page.

Gene	Evaluation	Frequency [1]	
SDHB	Clinical assessment for manifestations of PGL/PCC & GIST	Annually	Beginning at age 6-10 yrs [3]
	Plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) for secreting PGL/PCC	Every 2 yrs in childhood; then annually in adults	
	Whole-body MRI for PGL, PCC, RCC, & GIST	Every 2-3 yrs	
	EGD for those w/unexplained anemia & GI symptoms	As needed	
SDHC	Clinical surveillance for clinical manifestations of PGL/PCC & GIST	Annually	Beginning at age 6-15 yrs [3]
	Plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) for secreting PGL/PCC	Every 2 yrs in childhood; then annually in adults	
	Whole-body MRI for PGL, PCC, RCC, & GIST	Every 2-3 yrs	
	EGD for those w/unexplained anemia & GI symptoms	As needed	
SDHD [4]	Clinical assessment for manifestations of PGL/PCC & GIST	Annually	Beginning at age 6-15 yrs [3, 6, 7]
	Plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) for secreting PGL/PCC	Every 2 yrs in childhood; then annually in adults	
	• Whole-body MRI for PGL, PCC, RCC, & GIST • Note: Some also suggest PET-CT, preferably w/ radiolabeled somatostatin analogues. [5, 6]	Every 2-3 yrs	
	EGD for those w/unexplained anemia & GI symptoms	As needed	

Table 8. continued from previous page.

Gene	Evaluation	Frequency [1]	
MAX [4] *SDHAF2* [4] *TMEM127*	Clinical assessment for manifestations of PGL/PCC & GIST	Annually	Beginning at age 6-8 yrs
	Plasma-free fractionated metanephrines or 24-hour urine fractionated metanephrines (optional dopamine or 3-methoxytyramine) for secreting PGL/PCC	Every 2 yrs in childhood; then annually in adults	
	• Whole-body MRI for PGL, PCC, RCC, & GIST • Note: Current guidelines do not provide surveillance recommendations for at-risk persons w/*MAX*, *SDHAF2*, or *TMEM127* pathogenic variants. [3] Given that persons w/*MAX* pathogenic variants are primarily at risk for PCC & persons w/*SDHAF2* pathogenic variants are primarily at risk for HNPGL, targeted imaging can be considered.	Every 2-3 yrs	
	EGD for those w/unexplained anemia & GI symptoms	As needed	

EGD = esophagogastroduodenoscopy; GI = gastrointestinal; GIST = gastrointestinal stromal tumor; PCC = pheochromocytoma; PGL = paraganglioma; RCC = renal cell carcinoma

1. The wide age range of when to initiate these recommendations is due to multiple consensus guidelines [Rednam et al 2017, Amar et al 2021]. A patient-centered approach given all available information is recommended to determine the specific age to initiate recommendations.

2. Hanson et al [2023]

3. Amar et al [2021]

4. Recommendations apply to individuals with a paternally inherited pathogenic variant in these genes.

5. Taïeb et al [2023]

6. Although some guidelines suggest using PET-CT in combination with MRI as first-line imaging for tumor screening, there is little data for its use in screening (as opposed to defining suspected tumors), and cost and radiation exposure must be considered.

7. Rednam et al [2017], NCCN [2022]

Agents/Circumstances to Avoid

Activities such as cigarette smoking that predispose to chronic lung disease should be discouraged.

There is some limited evidence that the penetrance of hereditary PGL/PCC syndromes may be increased in those who live in high altitudes or are chronically exposed to hypoxic conditions [Astrom et al 2003]. However, no recommendation can be based on this very limited evidence.

Evaluation of Relatives at Risk

Evaluation of apparently asymptomatic older and younger at-risk relatives of an individual with hereditary PGL/PCC syndrome is recommended. Identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited a pathogenic variant. Early detection of tumors can facilitate surgical removal, decrease related morbidity, and potentially result in removal prior to the development of metastatic disease. Evaluations can include the following:

- **Predictive molecular genetic testing.** If the pathogenic variant in the family is known, predictive molecular genetic testing should be offered to at-risk family members. Because the recommended gene-specific ages for initiation of surveillance is in childhood for all hereditary PGL/PCC-related genes (see Table 8), predictive molecular genetic testing is offered to at-risk children and adolescents. (Note: The frequency and intensity of surveillance should be tailored for the individual and family.)

Pathogenic variants in *SDHD* and *SDHAF2* (and possibly *MAX*) demonstrate parent-of-origin effects and cause disease almost exclusively when they are paternally inherited. In the case of maternal inheritance, predictive molecular genetic testing of family members can be deferred until age 18 years, at which time the individual can make an autonomous decision regarding predictive testing. However, a thorough family history and risk assessment should be used in determining surveillance strategies in these families regardless of suspected parent-of-origin effects.

- **Surveillance.** If the pathogenic variant in the family is not known, surveillance for PGL/PCC can be considered in families with more than one individual with PGL/PCC. Of note, there are only very rare families with more than one individual with PGL/PCC in which no germline pathogenic variant was found.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

There are no published consensus management guidelines for the diagnosis and management of hereditary PGL/PCC syndromes during pregnancy. A high index of suspicion for these tumors in pregnant women is indicated, since there are other more common causes of hypertension during pregnancy (e.g., preeclampsia). Secretory PGL/PCCs are more likely to present at any time during pregnancy (whereas preeclampsia is more common in the second or third trimester) and are typically not associated with weight gain, edema, proteinuria, or thrombocytopenia. Individuals with PGL/PCCs are more likely to present with palpitations, sweating, pallor, orthostatic hypotension, and glucosuria, and the hypertension may be episodic. A retrospective multicenter cohort study of pregnancy outcomes in women with PGL/PCCs showed better outcomes for the woman and the fetus in women treated with alpha-adrenergic blockade [Bancos et al 2021].

Every individual with a hereditary PGL/PCC syndrome should be evaluated for an active catecholamine-secreting tumor prior to planned pregnancy or as soon as pregnancy is known. This evaluation can be done by measurement of fractionated metanephrines and catecholamines in a 24-hour urine sample or measurement of plasma-free metanephrines. There is no consensus regarding the frequency of follow-up biochemical evaluation during pregnancy, but obtaining levels during the second trimester (preferred window for surgery) and prior to delivery should be considered. The retrospective multicenter cohort study did not show improved outcomes with surgery in the second trimester compared to medical therapy with alpha-adrenergic blockade [Bancos et al 2021]. MRI without gadolinium administration should be the first-line test used to localize a tumor, as CT examination will expose the fetus to radiation. Radioisotope imaging studies should be deferred until after pregnancy in nonlactating mothers for similar reasons.

Surgery is the definitive treatment for these tumors, with appropriate alpha-adrenergic and (if needed) subsequent beta-adrenergic blockade to prevent a hypertensive crisis. For intra-abdominal PGL/PCCs, a laparoscopic surgical approach is ideal if the tumor size allows. After 24 weeks' gestation, surgery may need to be delayed until fetal maturity is reached (~34 weeks) because of issues with tumor accessibility. An open surgical approach combined with elective cesarean section may be necessary in these situations. A good outcome with vaginal delivery has only been described in those with appropriate alpha-adrenergic blockade [Bancos et al 2021].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

For metastatic PGL/PCC, several therapies are under investigation. Preliminary studies with peptide receptor radionuclide therapy (PRRT) have shown clinical and biochemical responses that suggest increased survival [Kong et al 2017]. There are currently ongoing clinical trials with PRRT (Lutathera®) and newer alpha-emitting

molecules (see ClinicalTrials.gov). There is also an ongoing clinical trial with the HIF2α inhibitor belzutifan that has closed for recruitment and analysis is pending. Furthermore, tyrosine kinase inhibitors such as cabozantinib are under investigation (see ClinicalTrials.gov), and sunitinib showed a modest increase in progression-free survival [Ayala-Ramirez et al 2012]. There are a number of open studies in North America and Europe.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are inherited in an autosomal dominant manner.

Pathogenic variants in *SDHD*, *SDHAF2*, and possibly *MAX* demonstrate parent-of-origin effects and cause disease almost exclusively when they are paternally inherited [Hensen et al 2004, Kunst et al 2011, Burnichon et al 2012, Hoekstra et al 2015]. It is notable that *SDHAF2*- and *MAX*-related hereditary PGL/PCC syndromes are rare, and information is limited; therefore, a thorough family history and risk assessment should be used in determining surveillance strategies in these families regardless of suspected parent-of-origin effects.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a hereditary PGL/PCC syndrome inherited a PGL/PCC-related pathogenic variant from a parent.
- Rarely, a proband with a hereditary PGL/PCC syndrome has the disorder as the result of a *de novo* pathogenic variant [Imamura et al 2016, Mauer et al 2020]. The proportion of individuals with a hereditary PGL/PCC syndrome caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The age-dependent penetrance and variable expressivity of *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* pathogenic variants, as well as the parent-of-origin effects associated with *SDHD*, *SDHAF2*, and possibly *MAX* pathogenic variants, predict that a substantial number of individuals who have inherited these pathogenic variants will appear to be simplex cases (i.e., appear to have a negative family history). Therefore, an apparently negative family history cannot be confirmed without appropriate

clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, sibs of a proband are still at increased risk for a hereditary PGL/PCC syndrome because of the possibility of (age-related) reduced penetrance in a heterozygous parent or parent-of-origin effects.

Offspring of a proband. Each child of an individual with a hereditary PGL/PCC syndrome has a 50% chance of inheriting the pathogenic variant.

- An individual who inherits an *SDHD* or *SDHAF2* pathogenic variant from the individual's father is at high risk of manifesting PGL and PCC.
- An individual who inherits an *SDHD* or *SDHAF2* pathogenic variant from the individual's mother is usually not at risk of developing disease (although each of the individual's offspring is at a 50% risk of inheriting the pathogenic variant). However, exceptions occur:
  - Yeap et al [2011] identified a woman age 26 years with pathologically confirmed pheochromocytoma who had an *SDHD* pathogenic variant inherited from her mother, and also had a right glomus jugulare tumor.
  - Bayley et al [2014] and Burnichon et al [2017] also identified examples of *SDHD* tumor susceptibility from maternal-origin variants.
- It is unclear whether the same parent-of-origin effect holds true for pathogenic variants in *MAX*. The total number of individuals identified with *MAX* pathogenic variants is limited, but thus far, tumor formation has not occurred in individuals who inherited a *MAX* pathogenic variant on the maternal allele.

Other family members

- The risk to other family members depends on the genetic status of the proband's parents and the biological relationship to the proband.
- If a parent of the proband is affected and/or has a pathogenic variant, risk can be determined by pedigree analysis and, if the familial pathogenic variant is known, molecular genetic testing.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic individuals. Consideration of molecular genetic testing of young, at-risk family members is appropriate. Identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited a pathogenic variant (see Management, Surveillance and Evaluation of Relatives at Risk).

- Molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members if a clinically diagnosed relative has undergone molecular genetic testing and is found to have a germline PGL/PCC-related pathogenic variant.
- Because the recommended gene-specific ages for initiation of surveillance is in childhood for all hereditary PGL/PCC-related genes (see Table 8), molecular genetic testing is offered to at-risk children and adolescents. Special consideration should be given to education of the children and their parents prior to genetic testing, and older children and adolescents should be given the option of assenting to the test. A

plan should be established for the manner in which results are to be given to the parents and their children.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – health professional version (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- For those with a known hereditary PGL/PCC syndrome, screening for sympathetic PGL/PCC prior to conception is optimal. Otherwise, at a minimum, screening during pregnancy should be done to allow for optimal medical management for both the mother and the fetus (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the PGL/PCC syndrome-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Pheo Para Alliance**

  Our mission is to empower patients with pheochromocytoma or paraganglioma, their families and medical professionals through advocacy, education and a global community of support, while helping to advance research that accelerates treatments and cures.

  www.pheopara.org

- **MedlinePlus**

  Hereditary paraganglioma-pheochromocytoma

- **National Cancer Institute (NCI)**

  Pheochromocytoma

- **NeuroEndocrine Cancer Australia**

  Australia

Email: info@neuroendocrine.org.au

www.neuroendocrine.org.au

- **AMEND Research Registry**

  Association for Multiple Endocrine Neoplasia Disorders

  United Kingdom

  Email: jo.grey@amend.org.uk

  UK National MEN1 & PNET Research Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Paraganglioma-Pheochromocytoma Syndromes: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MAX	14q23.3	Protein max	MAX @ LOVD	MAX	MAX
SDHA	5p15.33	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	TCA Cycle Gene Mutation Database (SDHA)	SDHA	SDHA
SDHAF2	11q12.2	Succinate dehydrogenase assembly factor 2, mitochondrial	SDHAF2 @ LOVD	SDHAF2	SDHAF2
SDHB	1p36.13	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial	TCA Cycle Gene Mutation Database (SDHB)	SDHB	SDHB
SDHC	1q23.3	Succinate dehydrogenase cytochrome b560 subunit, mitochondrial	TCA Cycle Gene Mutation Database (SDHC)	SDHC	SDHC
SDHD	11q23.1	Succinate dehydrogenase [ubiquinone] cytochrome b small subunit, mitochondrial	TCA Cycle Gene Mutation Database (SDHD)	SDHD	SDHD
TMEM127	2q11.2	Transmembrane protein 127	TMEM127 gene homepage - transmembrane protein 127	TMEM127	TMEM127

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Paraganglioma-Pheochromocytoma Syndromes (View All in OMIM)

115310	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 4; PPGL4
154950	MAX PROTEIN; MAX
168000	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 1; PPGL1
171300	PHEOCHROMOCYTOMA
185470	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT B, IRON SULFUR PROTEIN; SDHB
600857	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT A, FLAVOPROTEIN; SDHA
601650	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 2; PPGL2

Table B. continued from previous page.

602413	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT C, INTEGRAL MEMBRANE PROTEIN, 15-KD; SDHC
602690	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT D, INTEGRAL MEMBRANE PROTEIN; SDHD
605373	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 3; PPGL3
613019	SUCCINATE DEHYDROGENASE COMPLEX ASSEMBLY FACTOR 2; SDHAF2
613403	TRANSMEMBRANE PROTEIN 127; TMEM127
614165	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 5; PPGL5

Molecular Pathogenesis

SDHA, *SDHB*, *SDHC*, and *SDHD* are four nuclear genes responsible for hereditary PGL/PCC syndromes. They encode the four subunits of the mitochondrial enzyme succinate dehydrogenase (SDH). SDH catalyzes the conversion of succinate to fumarate in the Krebs cycle and serves as complex II of the electron transport chain. A fifth nuclear gene, *SDHAF2* (also known as *SDH5*), encodes a protein that appears to be necessary for flavination of another SDH subunit, SDHA, as well as stabilization of the SDH complex. These five genes are collectively known as the *SDHx* genes.

SDHA, *SDHAF2*, *SDHB*, *SDHC*, and *SDHD* are tumor suppressor genes. Somatic second-hit variants in tumors include gross chromosomal rearrangements, recombination, single-nucleotide variants, or epigenetic changes that result in allelic inactivation.

The common neural crest derivation of skull base and neck paragangliomas, sympathetic extra-adrenal paragangliomas, and pheochromocytomas characterize this syndrome.

Inactivation of *SDHA*, *SDHB*, *SDHC*, or *SDHD* may cause the generation of a pseudohypoxic cellular state due to elevation of cellular succinate concentrations and/or the increased production of reactive oxygen species. Increased succinate in the cell can competitively inhibit the 2-oxoglutarate-dependent dioxygenases such as HIF prolyl-hydroxylases and histone and/or DNA demethylases. This can lead to increases in HIF1α-stimulating hypoxia pathways and epigenetic modifications such as hypermethylation [Pollard et al 2005, Letouzé et al 2013].

Much less is known about the role of *TMEM127* and *MAX* in PGL/PCC tumorigenesis. TMEM127 is a transmembrane-spanning protein involved in regulating the mTOR pathway. MAX is a transcription factor that heterodimerizes with MYC to regulate transcription of downstream genes involved in tumorigenesis.

Mechanism of disease causation. Loss of function

Table 9. Hereditary Paraganglioma-Pheochromocytoma Syndromes: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
MAX	Pathogenic variants in *MAX* may exhibit parent-of-origin effects.
SDHA	*SDHA* has ≥4 pseudogenes reported that may interfere w/interpretation of sequence analysis data.
SDHAF2	Pathogenic variants in *SDHAF2* exhibit parent-of-origin effects.
SDHC	*SDHC* has ≥5 pseudogenes reported that may interfere w/interpretation of sequence analysis data.
SDHD	• Pathogenic variants in *SDHD* demonstrate parent-of-origin effects & generally cause disease only when the pathogenic variant is inherited from the father. • *SDHC* has ≥7 pseudogenes reported that may interfere w/interpretation of sequence analysis data.

1. Genes from Table 1 in alphabetic order.

Table 10. Hereditary Paraganglioma-Pheochromocytoma Syndromes: Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
SDHAF2	NM_017841.1 NP_060311.1	c.232G>A	p.Gly78Arg	Founder variant in persons of Dutch ancestry [Hensen et al 2012]

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Tobias Else (telse@med.umich.edu), Samantha Greenberg (samantha.greenberg@utsouthwestern.edu), and Lauren Fishbein (lauren.fishbein@cuanschutz.edu) are actively involved in clinical research regarding individuals with hereditary PGL/PCC syndromes. They would be happy to communicate with persons who have any questions regarding diagnosis of a hereditary PGL/PCC syndrome or other considerations.

Tobias Else (telse@med.umich.edu), Samantha Greenberg (samantha.greenberg@utsouthwestern.edu), and Lauren Fishbein (lauren.fishbein@cuanschutz.edu) are also interested in hearing from clinicians treating families affected by a hereditary PGL/PCC syndrome in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in hereditary PGL/PCC syndromes.

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