GENEReviews

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Hereditary Paraganglioma-Pheochromocytoma Syndromes

[*Includes:SDHD-Related Hereditary Paraganglioma-Pheochromocytoma Syndrome (Paragangliomas 1), SDHB-Related Hereditary Paraganglioma-Pheochromocytoma Syndrome (Paragangliomas 4), SDHC-Related Hereditary Paraganglioma-Pheochromocytoma Syndrome (Paragangliomas 3)*]

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Summary

Disease characteristics. Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas (tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis) and by pheochromocytomas (paragangliomas that are confined to the adrenal medulla). Sympathetic paragangliomas hypersecrete catecholamines; parasympathetic paragangliomas are most often nonsecretory. Extra-adrenal parasympathetic paragangliomas are located predominantly in the head and neck; approximately 95% of such tumors are nonsecretory. In contrast, sympathetic extra-adrenal paragangliomas are generally confined to the thorax, abdomen, and pelvis, and are typically secretory. Pheochromocytomas, which arise from the adrenal medulla, typically hypersecrete catecholamines. Symptoms of PGL/PCC result either from mass effects or catecholamine hypersecretion (e.g., sustained or paroxysmal elevations in blood pressure, headache, episodic profuse sweating, palpitations, pallor, and apprehension or anxiety). The risk of malignant transformation is greater for extra-adrenal sympathetic paragangliomas than for pheochromocytomas or head and neck paragangliomas.

Diagnosis/testing. The diagnosis of hereditary PGL/PCC syndromes is based on physical examination, family history, imaging studies, biochemical testing, and molecular genetic testing. *SDHD, SDHC,* and *SDHB,* the three nuclear genes responsible for the hereditary PGL/PCC syndromes, encode three of the four subunits of the mitochondrial enzyme succinate dehydrogenase (SDH). Molecular genetic testing for disease-causing variants in all three genes is clinically available.

Management.*Treatment of manifestations:* for secretory tumors including pheochromocytomas, antagonism of catecholamine excess followed by surgery; for nonsecretory head and neck paragangliomas, surgical resection. PGL/PCCs identified in *SDHB*-mutation-positive individuals require resection promptly because of the high risk for malignant transformation. *Prevention of secondary complications:* Early detection through surveillance and removal of tumors may prevent or minimize complications related to mass effects, catecholamine hypersecretion, and malignant transformation. *Surveillance:* Beginning at age ten years or at least ten years before the earliest age at diagnosis in the family, individuals at risk for hereditary PGL/PCC syndromes need to begin lifelong biochemical and clinical surveillance for signs and symptoms of PGL/PCC. *Agents/Circumstances to avoid:* hypoxia, cigarette smoking. *Testing of relatives at risk:* First-degree relatives (age ≥10 years) of an individual with a known *SDHD, SDHC,* or *SDHB* mutation 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 disease-causing mutation.

Genetic counseling. The hereditary PGL/PCC syndromes are inherited in an autosomal dominant manner. Mutations in *SDHD* (PGL1) demonstrate parent-of-origin effects and generally cause disease only when the mutation is inherited from the father. A proband with a hereditary PGL/PCC syndrome may have inherited the mutation from a parent or have a *de novo* mutation; the proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with a hereditary PGL/PCC syndrome has a 50% chance of inheriting the disease-causing mutation. An individual who inherits a *SDHD* mutation from his/her mother has a low but not negligible risk of developing disease; each of his/her offspring is at a 50% risk of inheriting the disease-causing allele. An individual who inherits an *SDHD* mutation from his/her father is at high risk of manifesting paragangliomas and, to a lesser extent, pheochromocytomas. Prenatal testing for pregnancies at increased risk is possible for families in which the disease-causing mutation is known; if no laboratories offering prenatal testing are listed in the GeneTests Laboratory Directory, such testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes should be considered in all individuals with paragangliomas and/or pheochromocytomas, particularly those with the following findings [Young 2008]:

- Tumors that are:
  - Multiple (i.e., more than one separate tumor or tumor type), including bilateral tumors
  - Multifocal with multiple synchronous or metachronous tumors
  - Recurrent
  - Early onset (i.e., age <40 years)
- A family history of such tumors

Note: Many individuals with a hereditary PGL/PCC syndrome may present with a solitary tumor of the head or neck, thorax, abdomen, adrenal, or pelvis and no family history of the disorder (i.e., they are simplex cases - a single known occurrence in a family) [Baysal et al 2002, Neumann et al 2002, Badenhop et al 2004, Amar et al 2005].

The 2004 WHO Classification of Endocrine Tumours [DeLellis et al 2004] classifies paragangliomas/pheochromocytomas by location and, directly or indirectly, secretory status (i.e., sympathetic [hypersecrete catecholamines] versus parasympathetic [do not hypersecrete catecholamines]).

The following discussion of tumor types is based on the World Health Organization Classification of endocrine tumors [Kimura et al 2004a, Kimura et al 2004b, Lloyd et al 2004, McNicol et al 2004, Thompson et al 2004, Tischler & Komminoth 2004].

Paragangliomas (paraganglion tumors) arise from neuroendocrine tissues (paraganglia) symmetrically distributed along the paravertebral axis from their predominant location at the base of the skull and neck to the pelvis:

- Paragangliomas in the head and neck are primarily associated with the parasympathetic nervous system and generally do not hypersecrete catecholamines or other hormones. Approximately 5% of head and neck paragangliomas hypersecrete catecholamines.
- Paragangliomas in the thorax, abdomen, and pelvis are typically associated with the sympathetic nervous system and usually hypersecrete catecholamines.

  Note: Sympathetic paragangliomas located along the paravertebral axis (and not in the adrenal gland) are called "extra-adrenal sympathetic paragangliomas."

Pheochromocytomas are catecholamine-secreting paragangliomas confined to the adrenal medulla. Pheochromocytomas are also known as adrenal chromaffin tumors.

Note: "Chromaffin cells/tumors" is another term for any sympathetic (catecholamine-secreting) neuroendocrine cells/tumors regardless of location. Chromaffin refers to the brown-black color that results from oxidization and polymerization of catecholamines contained in the cells/tumors by chromium salts (such as potassium dichromate).

The diagnosis of paragangliomas and pheochromocytomas is based on physical examination, imaging studies, and biochemical testing (see Testing).

Patient evaluation includes the following:

- Detailed family history, including specific knowledge of any relatives with unexplained or incompletely explained sudden death
- Personal medical history for the following:
  - Symptoms of catecholamine excess that can include sustained or paroxysmal elevations in blood pressure, headache, episodic profuse sweating, palpitations (perceived episodic, forcible, often rapid heart beat), pallor, and apprehension or anxiety
  - Paroxysmal symptoms that may be triggered by changes in body position, increases in intra-abdominal pressure, medications (e.g., metoclopramide), exercise, or micturition in the case of urinary bladder paragangliomas. Urinary bladder paragangliomas may also be accompanied by painless hematuria
  - Evidence of head and neck paragangliomas. These tumors may present as enlarging masses that are asymptomatic or associated with symptoms of mass effects from the size and/or location of the tumors. Associated symptoms may include unilateral hearing loss, pulsatile tinnitus, cough,

hoarseness of voice, pharyngeal fullness, swallowing difficulty, pain, and/or problems with tongue motion.

- Physical examination directed toward signs suggestive of PGL/PCC:
  - For sympathetic paragangliomas and pheochromocytomas, signs may include documentation of elevated blood pressure, tachyarrhythmias or other arrhythmias, and palpable abdominal masses.
  - For head and neck paragangliomas, signs may include head and neck masses:
    - A carotid body tumor is likely to be vertically adherent and may be associated with bruits or palpable thrills.

      Note: 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.
    - A jugulotympanic tumor may be visible as a blue-colored pulsating mass behind the intact tympanic membrane [Gujrathi & Donald 2005].

Imaging studies

For diagnosis and tumor localization, the following studies can be used [Lenders et al 2005, Young 2006, Pacak et al 2007].

MRI/CT

- Paragangliomas may be identified anywhere along the paravertebral axis from the head to the pelvis, including the paraortic sympathetic chain. 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.
- Chromaffin tumors usually exhibit high signal intensity on T2-weighted MRI, which helps distinguish pheochromocytomas from benign adrenal cortical adenomas.
- Multiple tumors can be present.
- The diagnostic sensitivities and specificities of CT and MRI are equivalent, approximately 90%-100% and 70%-80%, respectively.
- Whole-body short tau inversion recovery (STIR) MRI with targeted MRI for positive tumors may be a reasonable approach for both diagnosis and monitoring. This strategy minimizes radiation exposure associated with CT scanning, while taking advantage of the high sensitivity of T2-weighted MRI.

Note: MRI and CT are also used for tumor staging [Lenders et al 2005, Young 2006, Pacak et al 2007].

Sonography. B-mode sonography coupled with color-coded Doppler sonography is useful for diagnosis of carotid body and vagal paragangliomas.

Digital subtraction angiography (DSA)

- 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.

To detect metastases, the following studies can be used [Gujrathi & Donald 2005].

^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, a technique that measures tumor uptake of a catecholamine analog radioisotope:

- MIBG has greater specificity for localization than CT and MRI, but lower sensitivity.
- It may be used to:
  - Further characterize masses detected by CT or MRI
  - Look for additional sites of disease
  - Identify tumors when CT or MRI results are negative [Young 2008]

Octreotide scintigraphy, a technique that measures tumor uptake of a somatostatin analog radioisotope, can be used in addition to MIBG scintigraphy as some MIBG-negative tumors are positive with octreotide scintigraphy.

2-^{18}F-fluoro-2-deoxy-D-glucose position emission tomography (FDG-PET), or PET using other imaging compounds, can also assist in detecting metastatic disease.

Testing

Biochemical testing

Catecholamines hypersecreted by PGL/PCC can be any of the following:

- Epinephrine (adrenaline)
- Norepinephrine (noradrenaline)
- Dopamine

When a catecholamine-secreting tumor is suspected, plasma and/or 24-hour urinary fractionated metanephrines or catecholamines are evaluated for catecholamine hypersecretion.

Note: (1) Measurement of fractionated metanephrine concentrations in plasma or urine is preferred, as it is more sensitive than measurement of catecholamine concentrations [Young 2008]. (2) False positive results may be reduced by follow-up testing for plasma chromogranin A and/or urine fractionated metanephrine levels when plasma fractionated metanephrine concentrations are less than fourfold above the reference range [Algeciras-Schimnich et al 2008]. (3) The secretion of norepinephrine with little or no epinephrine suggests an extra-adrenal paraganglioma or a pheochromocytoma associated with von Hippel-Lindau syndrome [Pacak et al 2007].

Biopsy

Biopsy of head and neck paragangliomas is not normally required and may be contraindicated because this invasive procedure has the risk of precipitating a hypertensive crisis, hemorrhage, and tumor cell seeding.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant*

any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Molecular Genetic Testing—Genes. The three nuclear genes responsible for the hereditary PGL/PCC syndromes encode three of the four subunits of the mitochondrial enzyme succinate dehydrogenase (SDH), which catalyzes the conversion of succinate to fumarate in the Krebs cycle and serves as complex II of the electron transport chain.

The individual hereditary PGL/PCC syndromes and their associated genes:

- PGL1: *SDHD* [Baysal et al 2000]
- PGL3: *SDHC* [Niemann & Muller 2000]
- PGL4: *SDHB* [Astuti et al 2001]

Other loci. The absence of known mutations in families with multiple affected members supports the probability of additional PGL/PCC susceptibility genes.

An additional locus (PGL2) has been mapped to chromosome 11q13 in a Dutch pedigree with familial paraganglioma [Mariman et al 1995].

Clinical testing

Sequence analysis. Sequence analysis of the eight coding exons of *SDHB*, the six coding exons of *SDHC*, and four coding exons of *SDHD,* and their respective intron-exon junctions can be used to detect point mutations in these genes. Approximately 70% of familial cases of head and neck paraganglioma are believed to be caused by germline mutations in one of these three genes [Baysal et al 2002]:

- Of 56 individuals with familial PGL/PCC or other syndromes discussed in the Differential Diagnosis section (i.e., NF, von Hippel-Lindau disease, and multiple endocrine neoplasia type 2 [MEN2]), 12 (21.4%) had mutations in *SDHB* or *SDHD* [Amar et al 2005]. In central Europe and the US, *SDHD* and *SDHB* mutations occur in roughly equal proportions, whereas *SDHC* mutations are rare [Baysal et al 2002, Neumann et al 2004, Schiavi et al 2005].
- In a German and Polish registry of individuals with PGL/PCC with either a *SDHD* or *SDHB* mutation, mutations in *SDHB* and *SDHD* were detected in equal proportions [Neumann et al 2004]
- In ten US families with head and neck paraganglioma, *SDHD* mutations were found in five (50%) and *SDHB* mutations in two (20%); two *SDHD* mutations (5%) and one *SDHB* mutation (3%) were detected among 37 simplex cases [Baysal et al 2002].

Research testing

Deletion analysis. Because deletion testing is available on a research basis only, data regarding the frequency of exonic, multiexonic, or whole-gene deletions in *SDHB*, *SDHC,* and *SDHD* are limited. However, such deletions have been reported [Baysal 2004, McWhinney et al 2004, Cascón et al 2006]. One study found gross deletions in *SDHB* in 12% of individuals in whom sequence analysis failed to identify a causative mutation [Cascón et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

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

Gene Symbol (Locus Name)	Proportion of Hereditary PGL/PCC Attributed to Mutations in This Gene	Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method	Test Availability
SDHD (PGL1)	~50% [1] ~13% [2]	Sequence analysis	Sequence variants [3]	70%-100%	Clinical Testing
SDHB (PGL4)	~20% [1] ~24% [2]	Sequence analysis	Sequence variants	70%-90%	Clinical Testing
		Deletion analysis [4]	Partial- and whole-gene deletions	~10%	Research only
SDHC (PGL3)	4% [5]	Sequence analysis	Sequence variants	~70%-100%	Clinical Testing

1. Pedigrees with familial/syndromic presentations of head and neck PGL [Baysal et al 2002]

2. Pedigrees with inherited and extra-adrenal sympathetic PGL and PCC [Amar et al 2005]

3. In the Netherlands, 94% of inherited head and neck PGL is caused by two *SDHD* founder mutations (p.Asp92Tyr and p.Leu139Pro) [Taschner et al 2001].

4. Detects exonic, multiexonic, or whole-gene deletions using a variety of methods including Southern blot analysis, relative quantitative polymerase chain reaction (PCR) techniques, and multiplex ligation-dependent probe amplification (MLPA)

5. Five of 121 individuals included in a European Head and Neck Paraganglioma Registry were found to have *SDHC* mutations [Schiavi et al 2005].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirmation of the diagnosis in a proband. Molecular genetic testing for *SDHB,SDHC,* and *SDHD* is indicated in all individuals known to have or suspected of having a PGL/PCC syndrome. Features such as young age at onset, presence of bilateral, extra-adrenal or multiple tumors, or malignancy suggest an inherited disorder [Gimenez-Roqueplo et al 2006, Pacak et al 2007]:

Note: The absence of family history or other features suggestive of a hereditary syndrome should not preclude genetic testing for *SDHB*, *SDHD*, and *SDHC* mutations.

- Persons with nonsecretory (parasympathetic) or secretory (sympathetic) head and neck paragangliomas should initially be tested for mutations in *SDHD*, followed by *SDHB* and *SDHC*. *SDHC* mutations have been reported in a few families, usually (but not exclusively) in association with nonsecretory head and neck paragangliomas [Schiavi et al 2005, Mannelli et al 2007, Pasini et al 2008, Peczkowska et al 2008].
- Because of the relatively low age-related penetrance, the tendency of chromaffin tumors to undergo malignant transformation, and the adverse prognosis associated with malignant paragangliomas and pheochromocytomas [Amar et al 2007], testing for *SDHB* mutations should be considered for all simplex cases, particularly those with extra-adrenal tumors.
- Persons with extra-adrenal sympathetic paragangliomas should initially be tested for mutations in *SDHB,* followed by *SDHD*, and then *VHL*.

  Note: A substantial proportion of individuals with an *SDHB* mutation present as simplex cases [Amar et al 2005, Timmers et al 2007, Klein et al 2008].

- Persons with pheochromocytomas without evidence for neurofibromatosis type I, von Hippel-Lindau syndrome (caused by mutation of *VHL*), or multiple endocrine neoplasia type 2 (MEN2, caused by mutation of *RET*) should be evaluated for *SDHB* and *SDHD* mutations. (See Differential Diagnosis):
  - Individuals with *VHL*- and *RET*-related disease especially tend to present at younger ages.
  - Bilateral pheochromocytoma is particularly associated with von Hippel-Lindau disease and MEN2 [Gimenez-Roqueplo et al 2006].
  - The First International Symposium on Pheochromocytoma has identified early age of onset as an important consideration in the decision to test for mutations in disease-causing genes, and has endorsed a stepwise approach to genetic testing, which includes the type of catecholamine produced by the tumor.
  - Pheochromocytomas in individuals with von Hippel-Lindau appear to universally produce norepinephrine, whereas those in individuals with MEN2 always produce epinephrine [Pacak et al 2007].
- An individual with a malignant tumor should initially be tested for mutation in *SDHB*.

Predictive testing for at-risk asymptomatic family members should be preceded by prior identification of the disease-causing mutation in the family whenever possible.

Note: Identification of the disease-causing mutation (or the absence thereof) in an affected individual is essential for interpretation of negative molecular genetic test results in an at-risk asymptomatic relative.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Recent evidence suggests that the Carney-Stratakis dyad, which includes paragangliomas and gastrointestinal stromal tumors (GISTs), may be caused by *SDHB*, *SDHD*, or *SDHC* mutations in some individuals [Pasini et al 2008].

No other disorders have been associated with mutations in *SDHB*, *SDHD*, or *SDHC*.

Clinical Description

Natural History

In the hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes tumors arise within the paraganglia, collections of neural crest cells symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis.

Paraganglia in the head and neck are generally associated with the parasympathetic nervous system, with the largest tissue collections located in the areas surrounding the carotid body, vagus nerve, and jugulotympanic region. Paragangliomas in these sites typically do not hypersecrete catecholamines. Most head and neck paragangliomas do not metastasize; their untoward consequences are typically the result of mass effects:

- **Carotid body paragangliomas** classically present as asymptomatic, enlarging lateral neck masses. Affected individuals may experience mass effects, including cranial

nerve and sympathetic chain compression, with resulting neuropathies. 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].

Paraganglia in the thorax, abdomen, and pelvis are normally associated with the sympathetic nervous system, and thus hypersecrete catecholamines. The adrenal medulla has the largest collection of sympathetic paraganglion cells.

Pheochromocytomas and extra-adrenal sympathetic paragangliomas in PGL/PCC syndromes present in a manner similar to those in persons with sporadic (i.e., not inherited) tumors, most often coming to medical attention in the following four clinical settings:

- Signs and symptoms associated with catecholamine hypersecretion, including elevations in blood pressure and pulse, headaches, palpitations, excessive sweating, and anxiety. Nausea, emesis, fatigue, and weight loss can also be seen. Symptoms are often episodic [Lenders et al 2005, Young 2006].
- Signs and symptoms related to mass effects from the neoplasm
- Incidentally discovered mass on MRI/CT performed for other reasons
- Screening at-risk relatives [Young 2008]

Extra-adrenal sympathetic paragangliomas have an increased likelihood of malignant transformation [Proye et al 1992]. Malignancy is much less likely in pheochromocytomas but does occur (see Genotype-Phenotype Correlations).

Manifestations of PGL/PCCs. Compared to persons with sporadic tumors, individuals with germline mutations in *SDHD* and *SDHB* tend to present at younger ages and to be more likely to have multifocal, bilateral, and recurrent disease, or to have multiple synchronous neoplasms.

Because *SDHC* mutations are rare, data on phenotypic characteristics associated with *SCHC* mutations are limited. In a review of 22 *SDHC*-positive individuals with head and neck paragangliomas (15 from the literature, 7 from an internally evaluated series), Schiavi et al (2005) found no clinical, pathologic, or demographic features that clearly differentiated *SDHC* mutation-positive persons from 88 index cases and two simplex cases from the literature with head and neck paragangliomas in whom mutations in *SDHD*, *SDHB*, *SDHC*, *VHL*, and *RET* were not detected.

Benign PGL/PCCs are generally slow growing—approximately 0.5 to 1.0 cm increase in diameter per year [Young 2007]. By contrast, malignant tumors are typically more aggressive, although malignant tumors with indolent courses have been documented [Young et al 2002].

No reliable studies are available to distinguish benign PGL/PCC from malignant PGL/PCC. Consequently, establishing the malignant nature of a tumor relies on the presence of metastases to nonchromaffin sites, the most common of which are bone, lung, liver, and lymph nodes.

Having to wait for evidence of metastasis to establish the malignant nature of a tumor may have introduced bias into present understanding of the natural history of these tumors.

For PGL/PCCs that have not metastasized, operative treatment can be curative. However, once metastases have occurred the disease is uniformly fatal, with only 50% of affected individuals surviving beyond five years [Thompson et al 2004, Young 2008].

Other tumors

- **Gastrointestinal stromal tumors** may occur inindividuals with hereditary PGL/PCC syndromes caused by mutations in one of the three genes encoding the SDH subunits [Pasini et al 2008].
- **Renal clear cell carcinoma** and **papillary thyroid carcinoma** have been reported with mutations in the three genes encoding the SDH subunits [Neumann et al 2002, Neumann et al 2004, Vanharanta et al 2004]. However, the significance of these findings is unclear.

Longevity. With palliative care some affected individuals have lived with their disease for 20 or more years [Young et al 2002].

Genotype-Phenotype Correlations

Although persons with *SDHB,SDHD,* and *SDHC* mutations can develop pheochromocytomas or paragangliomas within any paraganglion tissue, the following correlations between the gene involved and tumor location are used to guide diagnostic testing and, in some instances, patient care:

- Germline mutations in *SDHB* are strongly associated with extra-adrenal sympathetic paragangliomas [Gimenez-Roqueplo et al 2003, Neumann et al 2004, Benn et al 2006, Young 2006]. Chromaffin tumors in persons with germline *SDHB* mutations are sixfold more likely to be extra-adrenal than chromaffin tumors in general [Van Nederveen et al 2006].
- Mutations in *SDHD* and *SDHC* are more frequently associated with parasympathetic head and neck paragangliomas than other tumor types [Neumann et al 2004]:
  - Persons with a germline *SDHD* mutation have an odds ratio of approximately 24 of developing a head and neck paraganglioma compared with persons with a germline *SDHB* mutation [Benn et al 2006].
  - Persons with a germline *SDHD* mutation have an odds ratio of 0.28 of developing abdominal paragangliomas compared with persons with a germline *SDHB* mutation [Benn et al 2006].
- Paragangliomas in persons with a germline *SDHB* mutation are more likely to become malignant than sporadic paragangliomas or those that develop in persons with germline *SDHD* and *SDHC* mutations. *SDHB* mutations may also predict a shorter survival in persons with malignant pheochromocytomas and paragangliomas [Amar et al 2007]. However, persons with a germline *SDHD* mutation can develop malignant disease at any paraganglion site [Young et al 2002, Gimenez-Roqueplo et al 2003, Neumann et al 2004, Benn et al 2006, Jimenez et al 2006].
- Up to 50% of persons with malignant extra-adrenal paragangliomas have a germline *SDHB* mutation [Brouwers et al 2006, Klein et al 2008]. Because extra-adrenal sympathetic paragangliomas have long been known to have a greater predisposition to malignancy than pheochromocytomas and head and neck paragangliomas [Proye

et al 1992], it is not clear whether this effect is the result of location, mutation status, or both [Lima et al 2007, Klein et al 2008].

- Although less common than malignant extra-adrenal sympathetic paragangliomas, malignant pheochromocytomas do occur, and may be more common in individuals with a germline *SDHB* mutation than in those with a germline *SDHD* or *SDHC* mutation or with a sporadic pheochromocytoma.
- Head and neck paragangliomas in persons with a germline *SDHD* mutation, in particular, are more likely to be multifocal than in persons with sporadic tumors or those with a germline *SDHB* mutation [Boedeker et al 2005]. However, phenotypes vary among individuals and even among family members with the same mutation.

  Note: Despite the common association of *SDHD* mutations with head and neck paragangliomas, variation in the prevalence, penetrance, and phenotypic expression of SDH subunit gene mutations may be population specific [Lima et al 2007].
- Germline *SDHC* mutations appear to be primarily (but not exclusively) associated with head and neck paragangliomas [Schiavi et al 2005, Mannelli et al 2007, Pasini et al 2008, Peczkowska et al 2008].
- Approximately 75% of pheochromocytomas and sympathetic paragangliomas in persons with germline *SDHD* mutations reportedly occur when the mutation is in the 5' portion of the gene [Eng et al 2003].
- A possible relationship between *SDHB* exon 1 deletions and abdominal extra-adrenal PGLs was recently proposed [Cascón et al 2008]

Penetrance

Age-related penetrance. Mutations in the genes encoding the subunits of SDH appear to have a high but age-related penetrance (Table 2). Data, however, are limited [Neumann et al 2004,Benn et al 2006].

Table 2. Estimated Age-Related Penetrance for *SDHD* and *SDHB* Mutations

SDHD		SDHB		Reference
Age in Years	Penetrance	Age in Years	Penetrance	
30	48%	30	29%	Benn et al [2006] [1]
31	50%	35	50%	Neumann et al [2004][2]
40	73%	40	45%	Benn et al [2006] [1]
50	86%	50	77%	Neumann et al [2004][2]

1. The age-related penetrance was higher in persons with a germline *SDHD* mutation than in persons with a germline *SDHB* mutation.
2. The difference in age-related penetrance between individuals with *SDHB* and *SDHD* mutations was not statistically significant.

Site-related penetrance. Estimated penetrance for head and neck paragangliomas and extra-adrenal abdominal or thoracic tumors is shown in Table 3 [Benn et al 2006].

Table 3. Estimated Site-Related Penetrance for *SDHD* and *SDHB* Mutations

Tumor Sites	Mutation	Penetrance
Head and neck paragangliomas [1]	*SDHD*	68%
	SDHB	15%
Extra-adrenal abdominal or thoracic tumors [2]	*SDHD*	35%
	SDHB	69%

1. By age 40 years
2. By age 60 years

Anticipation

Anticipation is not observed in the PGL/PCC syndromes.

Nomenclature

The PGL/PCC syndromes were initially referred to as the hereditary paraganglioma syndromes prior to the discovery of their association with pheochromocytomas.

The diseases included in the designation PGL/PCC syndromes are named for the specific loci involved: PGL1 (*SDHD*), PGL3 (*SDHC*), and PGL4 (*SDHB*).

Prevalence

The prevalence of pheochromocytoma/paraganglioma is not precisely known. The incidence of these tumors appears to be approximately one in 300,000/year.

Three *SDHD* mutations (p.Asp92Tyr, p.Leu95Pro, p.Leu139Pro) are responsible for almost all cases of hereditary paraganglioma in the Dutch population [Taschner et al 2001, Dannenberg et al 2002]. The mutations p.Asp92Tyr and p.Leu139Pro were identified in 30 of 32 Dutch families with familial head and neck paragangliomas (94%) and 20/55 (36%) of simplex cases [Taschner et al 2001].

Two recurrent *SDHD* mutations (p.Pro81Leu, p.Arg38X) identified in the US appear to have arisen independently in some families [Taschner et al 2001, Baysal et al 2002].

It has been proposed that the *SDHD* mutation, p.Met1Ile, is a founder mutation in the Chinese population [Lee et al 2003].

A whole-exon deletion of *SDHB* exon 1 appears to be a founder mutation in the Spanish population [Cascón et al 2008].

See Table 4.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Most inherited paragangliomas and pheochromocytomas are attributable to mutations in *VHL, RET, NF1, SDHD, SDHB,* and *SDHC*.

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are within the differential diagnosis for all individuals with paragangliomas and pheochromocytomas. A

mutation in one of the genes encoding three of the four subunits of SDH may be present in 40% of individuals with head and neck paragangliomas [Badenhop et al 2004] and at least 10% of individuals with extra-adrenal sympathetic paragangliomas and pheochromocytomas [Amar et al 2005]:

- Approximately 12% of individuals with pheochromocytoma or paraganglioma from a German and Polish registry, without known family histories or evidence of other syndromes in which PGL/PCC can be seen (i.e., NF, von Hippel-Lindau syndrome, and MEN2), had a germline mutation in *SDHD* or *SDHB*. Mutations in *SDHB* and *SDHD* were detected in equal proportions [Neumann et al 2004]
- Among 314 French persons with pheochromocytomas or extra-adrenal sympathetic paragangliomas, 10% had a germline mutation in *SDHD* or *SDHB* [Amar et al 2005].
- Fourteen of 34 (41%) Australian individuals with head and neck paragangliomas had mutations in *SDHD* (79%) or *SDHB* (21%), including 10/11 of the familial cases (91%) [Badenhop et al 2004].

Given the high cost of molecular genetic testing, testing of *SDHD, SDHB,* and *SDHC* should proceed in a stepwise manner based on tumor location, hormonal status, presence or absence of malignancy, existence of multifocal tumors, family history, and clinical signs and symptoms associated with the four conditions (neurofibromatosis type 1, von Hippel-Lindau disease, multiple endocrine neoplasia type 2, and Carney syndrome) discussed in the following paragraphs [Young 2006, Pacak et al 2007]. *SDHB* mutations should be sought in malignant pheochromocytoma [Pacak et al 2007].

Pheochromocytomas and catecholamine-secreting paragangliomas are also found in the following disorders:

- **Neurofibromatosis type I(NF1),** an autosomal dominant disorder caused by mutation of *NF1*. Prevalence is estimated at 1:3000 to 1:4000. Major features of NF1 include neurofibromas, café au lait spots, iris hamartomas referred to as Lisch nodules, and axillary and inguinal freckling. Gastrointestinal stromal tumors (GISTs) [Stewart DR et al 2007] and carcinoid tumors [Stewart W et al 2007] have also been reported in individuals with NF1.

  Although pheochromocytomas are rare in NF1, their frequency is as high as 20%-50% in individuals with NF1 and hypertension. Most (84%) pheochromocytomas are unilateral. Extra-adrenal sympathetic paragangliomas can occur. These tumors are benign in most cases.

  Because the *NF1* gene is large and there do not appear to be discrete mutation "hot spots" associated with development of pheochromocytoma [Bausch et al 2007], genetic testing for *NF1* mutations is not routinely available. However, NF1 is usually diagnosed clinically at an early age, and generally is easily distinguished from the hereditary PGL/PCC syndromes [Jimenez et al 2006].
- **von Hippel-Lindau syndrome(VHL),** an autosomal dominant disorder caused by mutation of *VHL*. Prevalence is approximately 1:36,000 live births. Features of VHL include retinal angiomas, central nervous system hemangioblastomas, clear cell renal cell carcinoma, pancreatic endocrine tumors, endolymphatic sac tumors, renal, pancreatic, and epididymal cysts, and pheochromocytomas.

The frequency of pheochromocytoma in individuals with VHL is 10%-20% overall but varies by disease subtype. The mean age of onset of pheochromocytoma in VHL is approximately 30 years, although some individuals present with this neoplasm before age ten years [Lonser et al 2003]. Pheochromocytomas occur in only 6%-9% of individuals with VHL type 1; the prevalence rises to 40%-59% in persons with type 2 disease. In type 2C VHL, pheochromocytomas are the sole manifestation of the syndrome and may present as simplex cases.

Approximately 50% of pheochromocytomas are bilateral. Pheochromocytomas in VHL secrete primarily norepinephrine and normetanephrine. Approximately 5% of VHL-related catecholamine-secreting tumors become malignant, most commonly extra-adrenal sympathetic paragangliomas [Maher 2004]. Extra-adrenal sympathetic paragangliomas occur infrequently [Jimenez et al 2006, Pacak et al 2007].

VHL can be distinguished from hereditary PGL/PCC syndromes on clinical grounds in many instances, but may require molecular genetic testing [Jimenez et al 2006]. When sequence analysis and deletion analysis are used, the sensitivity of molecular genetic testing for VHL approaches 100% [Lonser et al 2003].

- **Multiple endocrine neoplasia type 2(MEN2),** an autosomal dominant syndrome caused by mutation of the *RET* protooncogene. MEN2 prevalence is estimated at 1:30,000. The MEN2A subtype is characterized by medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism; MEN2A accounts for more than 80% of cases of MEN2. The MEN2B subtype lacks hyperparathyroidism but includes mucocutaneous neuromas and/or diffuse ganglioneuromatosis of the gastroenteric mucosa, slender body habitus, joint laxity, and skeletal malformations. MEN2B accounts for approximately 5% of MEN2. The subtype familial medullary thyroid carcinoma (FMTC) has medullary thyroid carcinoma as its only feature.

  Approximately 50% of individuals with MEN2A and MEN2B develop pheochromocytoma; it is the first manifestation of disease in 25% of affected individuals. Pheochromocytomas are bilateral in 50%-80% of cases but are almost always benign. The tumors primarily secrete epinephrine and metanephrine. Sympathetic extra-adrenal paragangliomas rarely occur in MEN2 [Erickson et al 2001, Jimenez et al 2006, Marini et al 2006, Pacak et al 2007].

  Medullary thyroid cancer is the most common presenting feature of MEN2. MEN2 is often suspected on the basis of family history; individuals with pheochromocytomas infrequently present as simplex cases. Molecular genetic testing is available clinically.

- **Carney triad** is an extremely rare disorder that primarily affects young women. As initially described in 1977, the classic Carney triad included extra-adrenal sympathetic paraganglioma, gastric stromal sarcoma, and pulmonary chondroma. Pheochromocytoma, adrenal cortical adenoma, and esophageal leiomyoma were later shown to be associated with the syndrome. Carney found that 78% of affected individuals had two of the three classic tumors and 22% had all three neoplasms [Carney 1999]. The additional neoplasms comprising this syndrome should differentiate it from the hereditary PGL/PCC syndromes.

  Carney triad may be familial; a causative gene has yet to be identified. Matyakhina

et al (2007) failed to find mutations in *SDHB*, *SDHC, SDHD*, *KIT*, and *PDGFRA* in 34 females and three males with Carney triad. However, they found chromosomal changes that appeared to correlate with the syndrome, including possible loss of regions on the short arm (1p) and the long arm (1q) of chromosome 1.

- **Carney-Stratakis dyad** (Carney-Stratakis syndrome) is the association of paragangliomas and GISTS described in Carney & Stratakis 2002. Carney-Stratakis dyad appears to be distinct from the Carney triad. Carney & Stratakis (2002) described five families with paragangliomas and GISTs that appeared to be inherited in an autosomal dominant manner with incomplete penetrance. Paragangliomas occurred in the head and neck, thorax, and abdomen. Both secretory and nonsecretory tumors were identified. In six individuals from six unrelated families with the Carney-Stratakis dyad, McWhinney et al (2007) reported mutations in *SDHB* in three, *SCHC* in two, and *SDHD* in one. The significance of these findings is not yet clear.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome, the following are recommended:

- Imaging studies using MRI/CT, ^{123}I-MIBG, and possibly PET to localize tumors and quantify the disease burden
- Evaluation of individuals with extra-adrenal sympathetic paragangliomas and pheochromocytomas for blood pressure elevations, tachycardia, and other signs and symptoms of catecholamine hypersecretion that must be controlled prior to definitive therapy
- Consideration of evaluation for GISTs in children, adolescents, or young adults who have unexplained gastrointestinal symptoms such as abdominal pain, upper gastrointestinal bleeding, nausea, vomiting, difficulty swallowing, or who experience unexplained intestinal obstruction or anemia [Pasini et al 2008]

Treatment of Manifestations

The management of tumors in individuals with hereditary PGL/PCC syndromes resembles management of sporadic tumors [Young 2008]; however, persons with hereditary PGL/PCC syndromes are more likely to have multiple tumors and multifocal and/or malignant disease than are those with sporadic tumors.

For secretory tumors, treatment is directed toward containing the disease through antagonism of catecholamine excess prior to surgical removal; treatment for malignant tumors is directed toward surgical removal and mitigation of the deleterious effects of metastatic spread [Eisenhofer et al 2004, Lenders et al 2005].

For nonsecretory head and neck paragangliomas, early detection allows for timely surgical resection and is believed to reduce operative morbidity and improve prognosis [Rinaldo et al 2004, Gujrathi & Donald 2005].

- **For carotid body and low vagal paragangliomas,** surgical resection is the treatment of choice in almost all cases. Most are benign and can be completely excised.

  Note: In elderly individuals or those with clinically important comorbidities, surgery may be delayed and tumors monitored by serial imaging. Radiation therapy can also be used with these patients [Gujrathi & Donald 2005].

- **For jugulotympanic paragangliomas,** small tumors can usually be removed without difficulty; resection of larger tumors may be associated with CSF leak, meningitis, stroke, hearing loss, cranial nerve palsy, or even death. Therefore, close observation with symptomatically guided surgery may be prudent. Radiation therapy can also be used, but potential long-term risks include malignant transformation of the primary tumor and other radiation-induced malignancies. In selected patients, stereotactic radiosurgery may also be performed [Gujrathi & Donald 2005].

For pheochromocytomas, surgery, preferably laparoscopic, is the treatment of choice [Lenders et al 2005, Young 2008].

- **Preoperative**. The chronic and acute effects of catecholamine hypersecretion of adrenal chromaffin tumors must be reversed preoperatively. Combined α- and β-adrenergic blockade is required to control blood pressure and prevent intraoperative hypertensive crises. Using the following approach, only 7% of patients undergoing catecholamine-secreting tumor resection at the Mayo Clinic needed postoperative hemodynamic management [Young 2006, Young 2008]:
  - Alpha-adrenergic blockade starting at least seven to ten days preoperatively to allow for normalization of blood pressure and volume expansion
  - A liberal sodium diet
  - Once adequate α-adrenergic blockade is achieved, initiation of β- adrenergic blockade (e.g., 3 days prior to surgery)
- **Postoperative.** Approximately one to two weeks after surgery, 24-hour urinary fractionated metanephrines and catecholamines and/or plasma fractionated metanephrines should be measured.
  - If the levels are normal, resection of the biochemically active paraganglioma should be considered complete.
  - If the levels are increased, an unresected second tumor and/or occult metastases should be suspected.

In individuals with *SDHB* mutations. Paragangliomas or pheochromocytomas should be resected as soon as possible after tumor discovery. Prompt resection is particularly important for extra-adrenal sympathetic paragangliomas because of their tendency to metastasize.

Prevention of Secondary Complications

Early detection through surveillance and removal of tumors may prevent or minimize complications related to mass effects, catecholamine hypersecretion, and malignant transformation.

Surveillance

Individuals known to have a hereditary PGL/PCC syndrome, individuals without clinical manifestations of a hereditary PGL/PCC syndrome but known to have a disease-causing *SDHD, SDHC,* or *SDHB* mutation, 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.

Screening should begin at age ten years or at least ten years before the earliest age at diagnosis in the family. Benn et al (2006) estimated that if lifelong screening were to begin at age ten years, disease would be detected in all persons with *SDHD* mutations and 96% of persons with *SDHB* mutations.

Although no clear consensus has been developed on when, how, and how often biochemical studies and imaging should be done in at-risk individuals, it is reasonable to consider lifelong annual biochemical and clinical surveillance. The findings of these evaluations should guide imaging studies [Mannelli 2006, Pacak et al 2007]. Monitoring includes the following:

- Twenty-four hour urinary excretion of fractionated metanephrines and catecholamines, and/or plasma fractionated metanephrines to detect metastatic disease, tumor recurrence, or the development of additional tumors
- Follow-up imaging by CT, MRI, 123I-MIBG, or FDG-PET if the fractionated metanephrine and/or catecholamine levels become elevated, or if the original tumor had minimal or no catecholamine/fractionated metanephrine excess. In some individuals the image modality that was most effective in identifying the original tumor may prove to be equally effective in surveillance.
- In persons with *SDHD* and *SDHC* mutations, periodic (e.g., every 2 years) MRI or CT of the head and neck to detect paragangliomas and periodic (e.g., every 4 years) body MRI or CT and ^{123}I-MIBG scintigraphy to detect paragangliomas or metastatic disease that may occur beyond the neck and skull base
- In persons with *SDHB* mutations, periodic (e.g., every 2 years) MRI or CT of the abdomen, thorax, and pelvis to detect paragangliomas and periodic (e.g., every 4 years) ^{123}I-MIBG scintigraphy to detect paragangliomas or metastatic disease that may not be detected with MRI or CT
- In individuals (especially children, adolescents, or young adults) who have unexplained gastrointestinal symptoms (e.g., abdominal pain, upper gastrointestinal bleeding, nausea, vomiting, difficulty swallowing) or who experience unexplained intestinal obstruction or anemia, consideration of evaluation for GISTs [Pasini et al 2008]

Agents/Circumstances to Avoid

Penetrance of hereditary PGL/PCC syndromes may be increased in those who live in high altitudes or are chronically exposed to hypoxic conditions [Pacheco-Ojeda et al 1988, Astrom et al 2003]. Avoidance of habitation at high altitudes and activities that promote long-term exposure to hypoxia should be considered.

Activities such as cigarette smoking that predispose to chronic lung disease should be discouraged in persons who have a mutation in *SDHD, SDHC,* or *SDHB*.

Testing of Relatives at Risk

By age ten years or at least ten years before the earliest age at diagnosis in the family, presymptomatic testing, including genetic testing, should be offered to all first-degree relatives of an individual in whom a mutation in *SDHD, SDHC,* or *SDHB* has been detected.

Use of molecular genetic testing for early 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 disease-causing mutation. Early detection of tumors can facilitate surgical removal, decrease related morbidity, and potentially result in removal prior to malignant transformation or metastasis [Young et al 2002]:

- In families with a previously identified mutation, relatives who do not have the family-specific mutation are spared the cost and anxiety associated with regular clinical, biochemical, and imaging studies.

- Family members who have the family-specific mutation can be informed of their heightened risks for paragangliomas and pheochromocytomas and encouraged to undergo biochemical and imaging studies as described in Surveillance.

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

Therapies Under Investigation

Attempts to inhibit or regulate the effects of hypoxia-inducible factor (HIF) activation, for example by enhancing prolyl hydroxylase activity, are being investigated and could provide the basis for useful therapy in the hereditary PGL/PCC syndromes [Lee et al 2005, Selak et al 2005]:

- One compound, R59949, enhances prolyl hydroxylase activity, preventing HIF1α accumulation in cell lines under both normal and hypoxic conditions [Temes et al 2005].
- Other drugs that cause downregulation of HIF include mTOR inhibitors, HSP90 inhibitors, HDAC inhibitors, thioredoxin-1 inhibitors, and some microtubule inhibitors.

Vascular endothelial growth factor (VEGF) receptor inhibitors (e.g., SU11248 and BAY43-9006) could potentially be useful in treating hereditary PGL/PCC syndromes [Kaelin 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are inherited in an autosomal dominant manner. Mutations in *SDHD* (PGL1) demonstrate parent-of-origin effects, and cause disease almost exclusively when they are paternal in origin [Baysal 2004].

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with a hereditary PGL/PCC syndrome have inherited the mutation from a parent. However, the age-dependent penetrance and variable expressivity of *SDHD, SDHC,* and *SDHB* mutations, as well as the parent-of-origin effects associated with *SDHD* mutations, predict that a substantial number of individuals who have inherited a *SDHD, SDHC,* or *SDHB* mutation will be simplex cases.
- A proband with a hereditary PGL/PCC syndrome may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown. In one study a *de novo* mutation was identified in 2/24 persons with *SDHD* mutations; no *de novo* mutations were identified in 25 persons with *SDHB* mutations [Neumann et al 2004].
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility in simplex cases.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include testing for the mutation identified in the proband. Evaluation of parents may determine that one parent is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: (1) Although many individuals diagnosed with a hereditary PGL/PCC syndrome have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. (2) If the parent is the individual in whom the mutation first occurred s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected, although this has not been reported in the hereditary PGL/PCC syndromes.

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 or has a disease-causing mutation, the risk to the sibs of inheriting the disease-causing mutation is 50%.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with a hereditary PGL/PCC syndrome has 50% chance of inheriting the disease-causing mutation:

- An individual who inherits an *SDHD* mutation from his/her mother is usually not at risk of developing disease (although each of his/her offspring is at 50% risk of inheriting the disease-causing allele). However, exceptions occur: Pigny et al (2008) reported an 11-year-old boy with a maternally inherited *SDHD* mutation associated with head and neck paraganglioma.
- An individual who inherits an *SDHD* mutation from his/her father is at high risk of manifesting paragangliomas and, to a lesser extent, pheochromocytomas.

Other family members of a proband. The risk to other family members depends on the mutation status of the proband's parents and the biological relationship to the proband. If a parent is affected or has a mutation in one of the three genes encoding SDH subunits, risk can be determined by pedigree analysis and/or molecular genetic testing.

Related Genetic Counseling Issues

See Management, Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100% or all of the genes in which disease-causing mutations occur have not been identified. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for hereditary PGL/PCC syndrome caused by mutations in *SDHD* is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories listed in the GeneTests Laboratory Directory offer molecular genetic testing for prenatal diagnosis of *SDHC*- and *SDHB*-related hereditary PGL/PCC syndrome. However, prenatal testing may be available for pregnancies at increased risk in families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hereditary Paraganglioma-Pheochromocytoma Syndromes

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
PGL1	*SDHD*	11q23	Succinate dehydrogenase [ubiquinone] cytochrome b small subunit
PGL2	Unknown	11q13.1	Unknown
PGL3	*SDHC*	1q21	Succinate dehydrogenase cytochrome b560 subunit
PGL4	*SDHB*	1p36.1-p35	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hereditary Paraganglioma-Pheochromocytoma Syndromes

115310	PARAGANGLIOMAS 4; PGL4
168000	PARAGANGLIOMAS 1; PGL1
185470	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT B, IRON SULFUR PROTEIN; SDHB
601650	PARAGANGLIOMAS 2; PGL2
602413	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT C, INTEGRAL MEMBRANE PROTEIN, 15-KD; SDHC
602690	SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT D, INTEGRAL MEMBRANE PROTEIN; SDHD
605373	PARAGANGLIOMAS 3; PGL3

Table C. Genomic Databases for Hereditary Paraganglioma-Pheochromocytoma Syndromes

Locus Name	Gene Symbol	Locus Specific	Entrez Gene	HGMD
PGL1	*SDHD*	SDH	6392 (MIM No. 602690)	SDHD
PGL2	Unknown		5235 (MIM No. 601650)	
PGL3	*SDHC*		6391 (MIM No. 602413)	SDHC
PGL4	*SDHB*		6390 (MIM No. 185470)	SDHB

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

It is believed that *SDHD*, *SDHB*, and *SDHC* act as tumor suppressor genes in accordance with the Knudson two-hit hypothesis. Thus, the first hit (an inactivating mutation in the first allele of a causal gene) is inherited as a germline mutation, whereas the second hit (an inactivating mutation in the remaining allele of the same causal gene) occurs during mitosis of cells in somatic tissue(s). The second mutation may be caused by gross chromosomal rearrangements, recombination, point mutations, or epigenetic changes that result in allelic inactivation.

The common neural crest derivation of head and neck paragangliomas, sympathetic extra-adrenal paragangliomas, and pheochromocytomas accounts for their association within a single syndrome. Competing and possibly complementary theories propose to explain the relationship between succinate dehydrogenase/mitochondrial complex II mutations and tumor formation.

The protein products of the genes implicated in hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes represent three of the four subunits of the mitochondrial enzyme succinate dehydrogenase. Succinate dehydrogenase catalyzes the conversion of succinate to fumarate in the Krebs cycle and serves as complex II of the electron transport chain and acts as a link between the two. The nuclear genes *SDHD* and *SDHC* code for two membrane-spanning proteins, subunits D and C that anchor the catalytic site to the inner mitochondrial

membrane. Subunit B, an iron-sulfur protein encoded by the nuclear gene *SDHB*, is required for catalytic activity. This protein transfers the electrons released during the conversion of succinate to fumarate to coenzyme Q, which is bound to subunits D and C within the inner mitochondrial membrane [Eng et al 2003, Gottlieb & Tomlinson 2005].

One hypothesis for the mechanism of tumorigenesis mediated by homozygous inactivating mutations in *SDHB*, *SDHC*, or *SDHD* proposes the generation of a pseudohypoxic state within cells resulting from elevations in cellular succinate concentrations and/or the increased production of reactive oxygen species. Increased succinate concentrations appear to stabilize the transcription factor HIF1α by inhibiting prolyl hydroxylases. HIF1α is thought to be continuously produced and degraded within the cell. Prolyl hydroxylase function is necessary for VHL protein-mediated ubiquitination, which leads to HIF1α degradation. By inhibiting prolyl hydroxylases, increased intracellular succinate concentrations result in increased HIF1α levels and upregulation of cellular hypoxia/angiogenesis pathways. Increased levels of HIF1α enhance glucose uptake and increase expression of angiogenic, growth, and mitogenic factors such as VEGF and platelet-derived growth factor β polypeptide (PDGFβ), erythropoietin, and transforming growth factor α (TGFα) [Maher 2004, Gottlieb & Tomlinson 2005, Pollard et al 2005, Selak et al 2005].

Succinate inhibition of prolyl hydroxylases may also cause a decrease in the apoptosis of neural crest precursors that normally occurs during development in response to reduction in nerve growth factor levels. Cells within this residual pool are hypothesized to subsequently undergo malignant transformation [Lee et al 2005]. The kinesin KIF1Bβ was recently shown to act downstream of the prolyl hydroxylase, EG1N3, and to be necessary and sufficient for neuronal apoptosis. *KIF1Bβ* maps to chromosome 1p36.2, which is frequently deleted in neural crest-derived tumors, providing further support for this hypothesis [Schlisio et al 2008].

Note: Autosomal recessive mutations in *SDHA*, the gene encoding the fourth SDH subunit, are associated with late-onset optic atrophy and Leigh syndrome (see Mitochondrial Disorders Overview for a discussion of Leigh syndrome caused by mtDNA mutations), a neurodegenerative disorder characterized by early-onset, progressive encephalopathy. Mutations in *SDHA* have not been associated with hereditary PGL/PCC syndromes.

SDHB

Normal allelic variants.*SDHB* comprises eight exons and is approximately 40 kb in length. It encodes an 1162-bp transcript (reference sequence NM_003000.2). There are known normal allelic variants in the *SDHB* gene along with variants of undetermined clinical significance. A database of normal and pathologic variants for the SDH subunit genes is maintained by the Leiden University Medical Center (see Genomic Databases table)

Pathologic allelic variants. Nonsense, missense, and splice-site mutations, intragenic deletions and insertions, and whole-gene *SDHB* deletions have been reported in individuals/pedigrees affected with hereditary paraganglioma syndromes. More than 100 pathologic sequence variants have been described for *SDHB*. A database of normal and pathologic variants for the SDH subunit genes is maintained by the Leiden University Medical Center (see Genomic Databases table). *SDHB* variants are predominantly found in exons 1-7.

Normal gene product.*SDHB* encodes succinate dehydrogenase [ubiquinone] iron-sulfur subunit, a 280-amino-acid protein (reference sequence NP_002991.2).

Abnormal gene product. Mutations in *SDHB* result in reduced or absent succinate dehydrogenase function because of loss or dysfunction of the affected subunit, or failure of the SDH heterotetramer to assemble.

SDHC

Normal allelic variants.*SDHC* has six exons and is more than 35 kb in length. It codes for a 2858-bp transcript (reference sequence NM_003001.3). There are known normal allelic variants in *SDHC* along with variants of undetermined clinical significance. A database of normal and pathologic variants for the SDH subunit genes is maintained by the Leiden University Medical Center (see Genomic Databases table).

Pathologic allelic variants. Nonsense, missense, splice-site, regulatory, and exon deletion *SDHC* mutations have been reported in individuals and pedigrees affected with hereditary paraganglioma syndromes. Approximately 14 pathologic sequence variants have been described for *SDHC*. The pathologic variants are found throughout the coding region of the gene, with the exception of exon 3.

Normal gene product.*SDHC* encodes the succinate dehydrogenase cytochrome b560 subunit, a 169-amino-acid protein (reference sequence NP_002992.1).

Abnormal gene product. Mutations in *SDHC* result in reduced or absent succinate dehydrogenase function because of loss or dysfunction of the affected subunit or failure of the SDH heterotetramer to assemble.

SDHD

Normal allelic variants.*SDHD* consists of four exons and produces a 1313-bp transcript. There are known normal allelic variants in *SDHD* along with variants of undetermined clinical significance. A database of normal and pathologic variants for the SDH subunit genes is maintained by the Leiden University Medical Center (see Genomic Databases table).

Pathologic allelic variants. See Table 4. Nonsense, missense, splice-site, intragenic insertions and deletions, and a whole-gene deletion have been reported in *SDHD* in individuals and pedigrees affected with hereditary paraganglioma syndromes. More than 70 pathologic sequence variants have been described for *SDHD* (see Genomic Databases table). *SDHD* pathologic variants are distributed throughout the four exons of the gene. Three *SDHD* founder mutations identified in the Dutch population account for most cases of hereditary PGL/PCC syndrome in this population (p.Asp92Tyr, p.Leu139Pro, p.Leu95Pro). Additional founder mutations have been proposed in other population groups.

Table 4. *SDHD* Pathologic Allelic Variants Discussed in this *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.3G>C	p.Met1Ile	NM_003002.1 NP_002993.1
c.112C>T	p.Arg38X	
c.242C>T	p.Pro81Leu	
c.274G>T	p.Asp92Tyr	
c.284T>C	p.Leu95Pro	
c.416T>C	p.Leu139Pro	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

Normal gene product.*SDHD* encodes succinate dehydrogenase (ubiquinone) cytochrome b small subunit, a 159-amino-acid protein.

Abnormal gene product. Mutations in *SDHD* result in reduced or absent succinate dehydrogenase function because of loss or dysfunction of the affected subunit or failure of the SDH heterotetramer to assemble.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Paraganglioma

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

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