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Hereditary Paraganglioma-Pheochromocytoma Syndrome: *SDHD* Mutations

SDHD-Associated Tumor Risks

Mutations in the *SDHD* gene are primarily associated with increased risks for neuroendocrine tumors called paragangliomas (PGL) and pheochromocytomas (PCC). While many of these tumors are not cancerous, there is a risk for malignant transformation or other complications such as high blood pressure or stroke, so early detection is important.

SDHD-associated tumors are typically multi-focal, parasympathetic PGLs with a low risk of malignancy and present, on average, in the 4th decade of life.[1-4] *SDHD* mutations almost exclusively demonstrate a parent of origin effect, in that only individuals who inherit a mutation from their father (paternal transmission) are at an increased risk of tumor development. However, rare cases of tumor development in maternal transmission have been reported.[5-7]

Paraganglioma (PGL): Paragangliomas (PGLs) are neuroendocrine tumors that arise from paraganglia. Paraganglia are a collection of neuroendocrine tissue that are distributed throughout the body, from the middle ear and base of the skull to the pelvis. The lifetime risk of PGLs for individuals with a paternally inherited *SDHD* mutation has been estimated at 86-90%, with the majority of affected individuals developing multiple PGLS.[3,4] *SDHD* mutations are more frequently associated with head and neck paragangliomas.[1-4]

- **Head and Neck PGL:** Generally located in the areas surrounding the carotid body, vagus nerve, and jugulotympanic region.[8] While typically nonfunctioning, 5% may hypersecrete catecholamines. Individuals may present with enlarging lateral neck masses, cranial nerve and sympathetic chain compression, dysphonia, hoarseness, pain or cough (depending on the PGL location).[8] Jugulotympanic paragangliomas can present with tinnitus or hearing loss and otoscopic examination may reveal blue-colored masses behind the tympanic membrane.[9]

- **Thoracic, Abdominal, and Pelvic PGL:** Intra-abdominal and thoracic sympathetic-associated PGLs are generally functionally active with excess catecholamine production; however, 10% are biochemically silent. PGLs in these sites often present with symptoms associated with catecholamine hypersecretion, including elevations in blood pressure and pulse, headaches, palpitations, excessive sweating, and anxiety. [10,11]

Pheochromocytoma (PCC): These are catecholamine-secreting PGLs confined to the adrenal medulla. It is estimated that 23-53% of individuals with *SDHD* mutations will develop a PCC.[1,3,4] These often present with symptoms associated with catecholamine hypersecretion, including elevations in blood pressure and pulse, headaches, palpitations, excessive sweating, and anxiety. [11]

Other Risks: Gastrointestinal stromal tumors (GIST), renal cancer, pituitary adenomas and papillary thyroid cancer have all been reported in individuals with mutations in the four genes encoding the *SDH* subunit.[3,4,12-14]

SDHD Risk Management

It is suggested that individuals with hereditary paraganglioma-pheochromocytoma syndrome have regular clinical monitoring by a physician or medical team with expertise in the treatment of hereditary GIST and PGL/PCC syndromes. A consultation with an endocrine surgeon, endocrinologist, and otolaryngologist is also recommended to establish an individualized care plan.

The Endocrine Society has published Pheochromocytoma and Paraganglioma Clinical Practice Guidelines.[11] Recommended screening is outlined below. In general, imaging modalities should be at the discretion of the managing provider due to conflicting data regarding the utility and efficacy of the various options. **Per the AACR Pediatric Oncology Series, routine screening should begin between the ages of 6 to 8 years.[15]**

	SDHD Surveillance Recommendations[1,11,14,15]	Frequency
Physical Exam	• Physical exam (including blood pressure and evaluation for arrhythmia and/or palpable abdominal masses)	Annually (at minimum)
Biochemical Screening for PGL/PCC	• 24 hour urine fractionated metanephrines and catecholamines and/or plasma free fractionated metanephrines ○ Follow-up imaging by CT, MRI, I-MIBG, or FDG-PET if levels become elevated or if the original tumor had minimal or no catecholamine/fractionated metanephrine excess • Plasma methoxytyramine	Annually
Imaging for PGL/PCC	• MRI/CT of skull base and neck, abdomen, thorax, and pelvis ○ Unless contraindicated, CT is generally recommended over MRI as a first-choice imaging modality due to its spatial resolution for the thorax, abdomen, and pelvis.	Every 2-4 years
	• Periodic 123I-MIBG (metaiodobenzylguanidine) scintigraphy may detect paragangliomas or metastatic disease that are not detected with MRI or CT	Every 2–4 years
Renal Cancer Screening	• Screening tests for renal cancer can include urinalysis (urine test) to screen for small amounts of blood in the urine or imaging tests (ultrasound, CT, MRI)	Consider at clinician discretion

Perioperative Medical Management: Patients should undergo appropriate perioperative medical management including preoperative blockade of hormonally active tumors to prevent perioperative cardiovascular complications.[11]

Treatment: The management of tumors in individuals with hereditary PGL/PCC syndromes resembles management of sporadic tumors;[11] however, individuals with a *SDHD* mutation are more likely to have multiple tumors and multifocal and/or malignant disease than are those with sporadic tumors.

Pregnancy Management: Evaluation for PGL/PCC should be performed prior to achieving pregnancy. However, after a diagnosis of PGL/PCC in pregnancy, it is important that delivery be in a tertiary hospital with an experienced obstetric, anesthetic and endocrine service as well as a neonatal intensive unit.[16]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *SDHD* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- *SDHD* mutations almost exclusively demonstrate a parent of origin effect, in that only individuals who inherit a mutation from their father (paternal transmission) are at an increased risk of tumor development. However, rare cases of tumor development in maternal transmission have been reported.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

Support Services for Hereditary PGL/PCC Syndrome

- Pheo Para Troopers (www.pheoparatroopers.org) is a national organization that offers resources, support and advocacy for families facing Hereditary PGL/PCC syndromes.

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