SDHAF2 gene

Associated Syndrome Name: Hereditary pheochromocytoma-paraganglioma syndrome (hereditary PPGL syndrome)

SDHAF2 Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Endocrine	High Risk

SDHAF2 gene Overview

Hereditary pheochromocytoma-paraganglioma syndrome (hereditary PPGL syndrome) [1, 2, 3, 4, 5]

- Individuals with mutations in *SDHAF2* have hereditary pheochromocytoma-paraganglioma syndrome (hereditary PPGL syndrome).
- **The *SDHAF2* gene shows a parent of origin effect. In most cases, only individuals who inherit the *SDHAF2* gene mutation from their male parent are at increased risk to develop the disease manifestations associated with hereditary PPGL syndrome. When possible, genetic testing of parents may help predict the likelihood that this patient will be affected by hereditary PPGL syndrome. However, it is not yet certain that there is no risk when the *SDHAF2* gene mutation is inherited from the female parent.**
- Based on limited case reports, individuals with hereditary PPGL syndrome due to mutations in *SDHAF2* have a high risk for cancers of the nervous system (paragangliomas), which can be in the head, neck, upper body or abdomen. Paragangliomas can develop at young ages.
- Paragangliomas in individuals with hereditary PPGL syndrome may secrete hormones that can cause symptoms such as high blood pressure, rapid and/or abnormal heartbeat, headaches, sweating, nausea, fatigue and anxiety.
- Other genes associated with hereditary PPGL syndrome have an elevated risk for paragangliomas of the adrenal gland (pheochromocytomas), renal cancer, and gastrointestinal stromal tumors (GIST). However, the data are not conclusive as to whether *SDHAF2* mutations also cause an increased risk for these or other cancers at this time.
- It is appropriate to offer genetic counseling to individuals with hereditary PPGL syndrome who are of reproductive age to discuss reproductive risks and options. There are additional considerations before and during pregnancy for individuals with hereditary PPGL syndrome.
- Although there are high risks for cancers and other medical conditions in individuals with hereditary PPGL syndrome, it may be possible to reduce these risks with appropriate medical management. Guidelines for the medical management of patients with hereditary PPGL syndrome have been developed by the National Comprehensive Cancer Network (NCCN), American Association for Cancer Research (AACR), and international consensus. These are summarized below. Since hereditary PPGL syndrome is a complex condition, and management recommendations are likely to change over time, patients with *SDHAF2* mutations and a diagnosis of hereditary PPGL syndrome should be managed by a multidisciplinary team with expertise in medical genetics and the prevention and treatment of the complications associated with this condition.

SDHAF2 gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Paraganglioma	To age 80[4]	75% or higher, when paternally inherited	<0.1%

SDHAF2 Cancer Risk Management Table

The overview of medical management options provided is a summary of professional society guidelines. The most recent version of each guideline should be consulted for more detailed and up-to-date information before developing a treatment plan for a particular patient.

This overview is provided for informational purposes only and does not constitute a recommendation. While the medical society guidelines summarized herein provide important and useful information, medical management decisions for any particular patient should be made in consultation between that patient and his or her healthcare provider and may differ from society guidelines based on a complete understanding of the patient's personal medical history, surgeries and other treatments.

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Paraganglioma	Clinical monitoring, including blood pressure measurement[1, 3]	10 to 18 years	Annually
	Biochemical screening of blood and urine[1, 3]	10 to 18 years	Every 1 to 3 years, depending on symptoms and findings, or prior to any surgical procedure
	Whole-body MRI. If not available, consider chest CT and MRI of abdomen, pelvis, skull base, and neck.[1, 3, 5]	10 to 21 years	Every 2 to 5 years

Information for Family Members

The following information for Family Members will appear as part of the MMT for a patient found to have a mutation in the SDHAF2 gene.

This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.

Family members should talk to a healthcare provider about genetic testing. Close relatives such as parents, children, brothers and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance of carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention.

It is appropriate to offer genetic counseling to individuals with hereditary PPGL syndrome who are of reproductive age to discuss reproductive risks and options. There are additional considerations before and during pregnancy for individuals with hereditary PPGL syndrome.[2]

The *SDHAF2* gene shows a parent of origin effect. In most cases, only children who inherit the *SDHAF2* gene mutation from their male parent are at increased risk to develop the disease manifestations associated with hereditary PPGL syndrome. However, it is not yet certain that there is no risk when the *SDHAF2* gene mutation is inherited from the female parent.[1, 2, 4]

Since paternally inherited *SDHAF2* mutations carry a risk for complications in children and some screenings are recommended to begin as early as age 10 years, consideration should be given to mutation testing in childhood for offspring of male *SDHAF2* mutation carriers. Offspring of female *SDHAF2* mutation carriers can defer predictive testing until age 18.[1, 2]

References

1. Casey RT, et al. International consensus statement on the diagnosis and management of phaeochromocytoma and paraganglioma in children and adolescents. Nat Rev Endocrinol. 2024 Aug 15. PMID: 39147856.
2. Else T, et al. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2023 Sep 21. In: Adam MP, et al., editors. GeneReviews® [Internet]. PMID: 20301715.
3. Bergsland E, et al. NCCN Clinical Practice Guidelines in Oncology®: Neuroendocrine and Adrenal Tumors. V 2.2025. May 28. Available at https://www.nccn.org.
4. Kunst H, et al. *SDHAF2* (PGL2-SDH5) and Hereditary Head and Neck Paraganglioma. Clinical Cancer Res. 2011 Jan 15. PMID: 21224366.
5. Greer MC, et al. Update on Whole-Body MRI Surveillance for Pediatric Cancer Predisposition Syndromes. Clin Cancer Res. 2024 Nov 15;30(22):5021-5033. PMID: 39287924.

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