



## Hereditary paraganglioma-pheochromocytoma

Hereditary paraganglioma-pheochromocytoma is an inherited condition characterized by the growth of noncancerous (benign) tumors in structures called paraganglia. Paraganglia are groups of cells that are found near nerve cell bunches called ganglia. A tumor involving the paraganglia is known as a paraganglioma. A type of paraganglioma known as a pheochromocytoma develops in the adrenal glands, which are located on top of each kidney and produce hormones in response to stress. Other types of paraganglioma are usually found in the head, neck, or trunk. People with hereditary paraganglioma-pheochromocytoma develop one or more paragangliomas, which may include pheochromocytomas.

Pheochromocytomas and some other paragangliomas are associated with ganglia of the sympathetic nervous system. The sympathetic nervous system controls the "fight-or-flight" response, a series of changes in the body due to hormones released in response to stress. Sympathetic paragangliomas found outside the adrenal glands, usually in the abdomen, are called extra-adrenal paragangliomas. Most sympathetic paragangliomas, including pheochromocytomas, produce hormones called catecholamines, such as epinephrine (adrenaline) or norepinephrine. These excess catecholamines can cause signs and symptoms such as high blood pressure (hypertension), episodes of rapid heartbeat (palpitations), headaches, or sweating.

Most paragangliomas are associated with ganglia of the parasympathetic nervous system, which controls involuntary body functions such as digestion and saliva formation. Parasympathetic paragangliomas, typically found in the head and neck, usually do not produce hormones. However, large tumors may cause signs and symptoms such as coughing, hearing loss in one ear, or difficulty swallowing.

Although most paragangliomas and pheochromocytomas are noncancerous, some can become cancerous (malignant) and spread to other parts of the body (metastasize). Extra-adrenal paragangliomas become malignant more often than other types of paraganglioma or pheochromocytoma.

Researchers have identified several types of hereditary paraganglioma-pheochromocytoma. Each type is distinguished by its genetic cause. People with types 1, 2, and 3 typically develop paragangliomas in the head or neck region. People with type 4 usually develop extra-adrenal paragangliomas in the abdomen and are at higher risk for malignant tumors that metastasize. The other types are very rare. Hereditary paraganglioma-pheochromocytoma is typically diagnosed in a person's 30s.

Paragangliomas and pheochromocytomas can occur in individuals with other inherited disorders, such as von-Hippel Lindau syndrome, Carney-Stratakis syndrome,

and certain types of multiple endocrine neoplasia. These other disorders feature additional tumor types and have different genetic causes. Some paragangliomas and pheochromocytomas occur in people with no history of the tumors in their families and appear not to be inherited. These cases are designated as sporadic.

## Frequency

Hereditary paraganglioma-pheochromocytoma occurs in approximately 1 in 1 million people.

## Genetic Changes

Mutations in at least four genes increase the risk of developing the different types of hereditary paraganglioma-pheochromocytoma. Mutations in the *SDHD* gene predispose an individual to hereditary paraganglioma-pheochromocytoma type 1; mutations in the *SDHAF2* gene predispose to type 2; mutations in the *SDHC* gene predispose to type 3; and mutations in the *SDHB* gene predispose to type 4.

The *SDHB*, *SDHC*, and *SDHD* genes provide instructions for making three of the four subunits of an enzyme called succinate dehydrogenase (SDH). In addition, the protein made by the *SDHAF2* gene is required for the SDH enzyme to function. The SDH enzyme links two important cellular pathways called the citric acid cycle (or Krebs cycle) and oxidative phosphorylation. These pathways are critical in converting the energy from food into a form that cells can use.

As part of the citric acid cycle, the SDH enzyme converts a compound called succinate to another compound called fumarate. Succinate acts as an oxygen sensor in the cell and can help turn on specific pathways that stimulate cells to grow in a low-oxygen environment (hypoxia).

Mutations in the *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* genes lead to the loss or reduction of SDH enzyme activity. Because the mutated SDH enzyme cannot convert succinate to fumarate, succinate accumulates in the cell. As a result, the hypoxia pathways are triggered in normal oxygen conditions, which lead to abnormal cell growth and tumor formation.

## Inheritance Pattern

Hereditary paraganglioma-pheochromocytoma is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to increase the risk of developing tumors. An additional mutation that deletes the normal copy of the gene is needed to cause the condition. This second mutation, called a somatic mutation, is acquired during a person's lifetime and is present only in tumor cells.

The risk of developing hereditary paraganglioma-pheochromocytoma types 1 and 2 is passed on only if the mutated copy of the gene is inherited from the father. The

mechanism of this pattern of inheritance is unknown. The risk of developing types 3 and 4 can be inherited from the mother or the father.

### **Other Names for This Condition**

- familial paraganglioma-pheochromocytoma syndromes
- familial paraganglioma syndrome
- FPGL
- FPGL/PHEO
- hereditary paraganglioma-pheochromocytoma syndromes
- hereditary pheochromocytoma-paraganglioma
- paragangliomas 1
- paragangliomas 2
- paragangliomas 3
- paragangliomas 4

### **Diagnosis & Management**

#### Genetic Testing

- Genetic Testing Registry: Paragangliomas 1  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1868633/>
- Genetic Testing Registry: Paragangliomas 2  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866552/>
- Genetic Testing Registry: Paragangliomas 3  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1854336/>
- Genetic Testing Registry: Paragangliomas 4  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1861848/>
- Genetic Testing Registry: Paragangliomas 5  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3279992/>

#### Other Diagnosis and Management Resources

- GeneReview: Hereditary Paraganglioma-Pheochromocytoma Syndromes  
<https://www.ncbi.nlm.nih.gov/books/NBK1548>
- MedlinePlus Encyclopedia: Pheochromocytoma  
<https://medlineplus.gov/ency/article/000340.htm>
- National Cancer Institute: Pheochromocytoma and Paraganglioma  
<https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq>

### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

### **Additional Information & Resources**

#### MedlinePlus

- Encyclopedia: Pheochromocytoma  
<https://medlineplus.gov/ency/article/000340.htm>
- Health Topic: Pheochromocytoma  
<https://medlineplus.gov/pheochromocytoma.html>

#### Genetic and Rare Diseases Information Center

- Hereditary paraganglioma-pheochromocytoma  
<https://rarediseases.info.nih.gov/diseases/11984/hereditary-paraganglioma-pheochromocytoma>
- Pheochromocytoma  
<https://rarediseases.info.nih.gov/diseases/7385/pheochromocytoma>

#### Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development: Pheochromocytoma  
<https://www.nichd.nih.gov/health/topics/pheochrom>
- National Cancer Institute: Pheochromocytoma and Paraganglioma  
<https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq>

## Educational Resources

- Cleveland Clinic: Adrenal Cancer  
<https://my.clevelandclinic.org/health/articles/6152-adrenocortical-carcinoma>
- Disease InfoSearch: Paragangliomas 1  
<http://www.diseaseinfosearch.org/Paragangliomas+1/5578>
- Disease InfoSearch: Paragangliomas 2  
<http://www.diseaseinfosearch.org/Paragangliomas+2/5579>
- Disease InfoSearch: Paragangliomas 3  
<http://www.diseaseinfosearch.org/Paragangliomas+3/5580>
- Disease InfoSearch: Paragangliomas 4  
<http://www.diseaseinfosearch.org/Paragangliomas+4/5581>
- Disease InfoSearch: Paragangliomas 5  
<http://www.diseaseinfosearch.org/Paragangliomas+5/9075>
- MalaCards: hereditary paraganglioma-pheochromocytoma syndromes  
[http://www.malacards.org/card/hereditary\\_paraganglioma\\_pheochromocytoma\\_syndromes](http://www.malacards.org/card/hereditary_paraganglioma_pheochromocytoma_syndromes)
- Memorial Sloan-Kettering Cancer Center: Pheochromocytomas and Paragangliomas  
<https://www.mskcc.org/cancer-care/types/adrenal-tumors/about/types/pheochromocytomas-paragangliomas>
- My46 Trait Profile  
<https://www.my46.org/trait-document?trait=Hereditary%20Paraganglioma-Pheochromocytoma%20syndrome&type=profile>
- Orphanet: Hereditary pheochromocytoma-paraganglioma  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=29072](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=29072)
- The Children's Hospital of Philadelphia  
<http://www.chop.edu/conditions-diseases/hereditary-paraganglioma-pheochromocytoma-syndrome#.VE4-PsIn19Y>

## Patient Support and Advocacy Resources

- National Organization for Rare Disorders: Pheochromocytoma  
<https://rarediseases.org/rare-diseases/pheochromocytoma/>
- The Children's Hospital of Philadelphia: Paraganglioma-Pheochromocytoma Syndrome Resources  
<http://www.chop.edu/conditions-diseases/hereditary-paraganglioma-pheochromocytoma-syndrome/health-resources#.VFeLB8In19Y>

### GeneReviews

- Hereditary Paraganglioma-Pheochromocytoma Syndromes  
<https://www.ncbi.nlm.nih.gov/books/NBK1548>

### ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22hereditary+paraganglioma-pheochromocytoma%22+OR+%22Paraganglioma%22>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28hereditary+paraganglioma%5BTIAB%5D%29+OR+%28paragangliomas+1%5BTIAB%5D%29+OR+%28familial+paraganglioma%5BTIAB%5D%29+OR+%28hereditary+pheochromocytoma-paraganglioma%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

### OMIM

- PARAGANGLIOMAS 1  
<http://omim.org/entry/168000>
- PARAGANGLIOMAS 2  
<http://omim.org/entry/601650>
- PARAGANGLIOMAS 3  
<http://omim.org/entry/605373>
- PARAGANGLIOMAS 4  
<http://omim.org/entry/115310>
- PARAGANGLIOMAS 5  
<http://omim.org/entry/614165>

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