



Cancer Predisposition Clinic

Hereditary Paraganglioma-Pheochromocytoma Syndrome

Also called: familial glomus tumors, familial nonchromaffin paragangliomas, familial paraganglioma-pheochromocytoma syndromes, hereditary paraganglioma-pheochromocytoma syndromes, hereditary pheochromocytoma-paraganglioma

What is hereditary paraganglioma-pheochromocytoma syndrome?

Hereditary paraganglioma-pheochromocytoma syndrome is a condition in which tumors develop in structures called paraganglia. Paraganglia are bundles of cells of the peripheral nervous system (the nerves outside the brain and spinal cord). A tumor that develops in the paraganglia is called a paraganglioma.

There are two types of paragangliomas:

- **Sympathetic paragangliomas** — These produce and release catecholamines into the bloodstream. Catecholamines are certain kinds of hormones, such as epinephrine, norepinephrine and dopamine. Hormones are chemical messengers that send important instructions to different parts of the body. Normally, catecholamines are released into the bloodstream by the adrenal glands. The adrenal glands, located on top of each kidney, produce catecholamines in response to stress.
- **Parasympathetic paragangliomas** — These do not usually release catecholamines into the bloodstream.

Most paragangliomas are usually found in the head, neck or torso. A specific type of sympathetic paraganglioma, called a pheochromocytoma, develops in the adrenal glands.

Paragangliomas and pheochromocytomas can develop sporadically in people without a genetic syndrome. However, in families with a history of hereditary paraganglioma-pheochromocytoma syndrome, the risk of developing tumors can be passed from parents to children. Health care providers consider a diagnosis of hereditary paraganglioma-pheochromocytoma syndrome for all people with paragangliomas and pheochromocytomas, especially for those who have developed these types of tumors:

- Multiple tumors in different organs, such as bilateral tumors (tumors found in each of a pair of organs, such as one in each adrenal gland)
- Multifocal (more than one tumor in the same organ)
- Recurrent (tumors that grow back after removal)
- Early onset (tumors that develop earlier than age 40)
- Found in other family members

Not all of these descriptions will apply to every person with hereditary paraganglioma-pheochromocytoma syndrome. Many people with the syndrome may have only one tumor in the head, neck, torso, adrenal gland or pelvis. Many do not have any family history of similar tumors. Among people that do have a family history of the syndrome, the age of onset, number, location and severity of the tumors can be very different among family members.

What is the cancer risk for people with hereditary paraganglioma-pheochromocytoma syndrome?

The risk of developing paragangliomas and pheochromocytomas increases as people with the syndrome get older. At 30 years of age, about 29% to 50% of people with the syndrome have developed at least one tumor. This increases to 45% to 73% at age 40 years. Up to 86% of patients with the syndrome have developed at least one tumor by the age of 50 years.

In many cases, paragangliomas and pheochromocytomas are not cancerous (malignant). Sometimes the tumors do become cancerous and spread to other parts of the body (metastasize). The risk varies greatly among different people with this condition.

Doctors have found seven types of hereditary paraganglioma-pheochromocytoma syndrome, each of which has a different risk profile and each is related to different genes (shown in parentheses):

- **Type PGL1 (*SDHD*)**
 - Most people with Type PGL1 syndrome have multifocal head and neck paragangliomas that do not release catecholamines (hormones) into the bloodstream. Some people with Type PGL1 syndrome may have paragangliomas in the adrenal glands, torso or pelvis that do release catecholamines into the bloodstream.
 - The risk of the tumors becoming cancerous in people with Type PGL1 syndrome is less than 5%.
- **Type PGL2 (*SDHAF2*)**
 - This type is very rare. People with this type typically only have head and neck paragangliomas that do not release catecholamines (hormones) into the bloodstream. Although multifocal tumors and a young age of onset are common, many people with Type PGL2 syndrome do not have any symptoms.
 - The risk of the tumors becoming cancerous in people with Type PGL2 syndrome is not known because the type is so rare. However, the risk is very low.

- **Type PGL3 (*SDHC*)**
 - This type is also very rare. Most people with Type PGL3 syndrome only have head and neck paragangliomas that do not release catecholamines (hormones) into the bloodstream.
 - The risk of the tumors becoming cancerous in people with Type PGL3 syndrome is not known because the type is so rare. However, the risk is very low.
- **Type PGL4 (*SDHB*)**
 - Most people with this type develop paragangliomas that are not in the adrenal glands but which do release catecholamines (hormones) into the bloodstream. These tumors are usually found in the abdomen.
 - Some people with this type also develop pheochromocytomas.
 - The risk of the tumors becoming cancerous in people with Type PGL4 syndrome is high (34% to 97%).
- **Type PGL 5 (*SDHA*)**
 - This type is extremely rare. People with this type have had single paragangliomas or single pheochromocytomas.
 - The risk of the tumors becoming cancerous in people with Type PGL5 syndrome is not known because the type is so rare. However, the risk is very low.
- ***TMEM127*-Related PGL**
 - In this type tumors usually develop at older ages than seen with other types. The average age of tumor diagnosis is 42 years.
 - Most people with this type develop pheochromocytomas. Some develop abdominal or head and neck paragangliomas.
 - The risk of the tumors becoming cancerous in people with *TMEM127*-Related PGL syndrome is less than 5%.
- ***MAX*-Related PGL**
 - Only pheochromocytomas have been identified in the few people known to have this type. About 50% to 70% of people with this type have bilateral pheochromocytomas (tumors in both adrenal glands).
 - The risk of the tumors becoming cancerous in people with *MAX*-Related PGL syndrome is about 25%.

People with hereditary paraganglioma-pheochromocytoma syndrome are also at an increased risk to develop other types of tumors, including:

- Gastrointestinal stromal tumors (GIST) — a type of tumor found in the digestive tract
- Renal clear cell carcinoma — a type of tumor in the kidney
- Papillary thyroid carcinoma — a type of tumor in the thyroid gland

The exact tumor risks depend on which of the seven types of hereditary paraganglioma-pheochromocytoma syndrome a person has.

What are other symptoms seen in people with hereditary paraganglioma-pheochromocytoma syndrome?

Paragangliomas and pheochromocytomas can cause symptoms if they release catecholamines (hormones) into the bloodstream. These symptoms may include the following:

- Headache
- High blood pressure
- Excessive sweating
- Heart palpitations (pounding, skipping or fluttering heartbeats)
- Pale skin
- Anxiety

Paragangliomas can also cause symptoms if they grow to a large size. These symptoms may include the following:

- Trouble swallowing
- Coughing
- Hoarse voice
- Hearing loss

Not all patients with hereditary paraganglioma-pheochromocytoma syndrome will have all of these symptoms.

What causes hereditary paraganglioma-pheochromocytoma syndrome?

Genes carry information telling cells within the body how to function. Hereditary paraganglioma-pheochromocytoma syndrome is caused by changes in any one of a group of genes that includes *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* and *MAX*.

Most people without hereditary paraganglioma-pheochromocytoma syndrome carry two working copies of each of these genes in their cells. One copy of each gene is inherited from the mother and one copy of each gene is inherited from the father. Cells from people with hereditary paraganglioma-pheochromocytoma syndrome carry two working copies of each of these genes except one. For that one gene, the person's cells carry one working copy and one copy that is changed. This change causes the gene to not work properly. It is called a mutation.

As people with hereditary paraganglioma-pheochromocytoma syndrome get older, the remaining working copy of the gene with the mutation often becomes changed within some of their cells. When both copies of the gene are changed, a tumor can develop. The tumor may become cancerous. That is why people with hereditary paraganglioma-pheochromocytoma syndrome have a higher risk of developing tumors and cancer than people who do not have this condition.

Currently it is not known how many people with hereditary paraganglioma-pheochromocytoma syndrome inherit a gene mutation from a parent who also has the syndrome. Some people with the syndrome have a new gene mutation that did not come from a parent. These children have no history of the syndrome in their families. In these cases, the change either happened in an egg or sperm cell when the child was formed or in one of the child's cells during pregnancy. These children are the first in their families to have the syndrome.

All people with hereditary paraganglioma-pheochromocytoma syndrome have a 50% or 1 in 2 chance of passing their gene mutation to their children. Children who inherit a *SDHC*, *SDHB*, *SDHA* or *TMEM127* gene mutation from either parent will have hereditary paraganglioma-pheochromocytoma syndrome. In most cases, only children who inherit a *SDHAF2*, *SDHD* or *MAX* mutation from their fathers will have the syndrome.

How are people with hereditary paraganglioma-pheochromocytoma syndrome screened for tumors?

People with hereditary paraganglioma-pheochromocytoma syndrome should be managed by a health care provider who knows this condition well. Screening is recommended for all people with this condition. The goal of screening is finding and treating tumors early to allow the best outcome for patients.

Screenings should begin typically between the ages of 7-9 years, or if there are family members with the syndrome, screenings should begin at least 10 years before the earliest date that tumors developed in those family members.

Our recommended screenings for children with hereditary paraganglioma-pheochromocytoma syndrome include the following:

- **Yearly physical exams** by a health care provider who knows this condition well. The health care provider should pay special attention to symptoms such as high blood pressure, heart palpitations, anxiety, headache, coughing, hoarse voice, problems swallowing and hearing loss.
- **Blood tests** to screen for abnormally high levels of catecholamines (hormones). These should be repeated yearly.
- **Whole body and neck MRIs** every two years to check for tumors.

It is possible that recommended screenings may change over time as health care providers learn more about hereditary paraganglioma-pheochromocytoma syndrome. Parents should discuss all

screening options for their child with a health care provider who knows this condition well. Because hereditary paraganglioma-pheochromocytoma syndrome is a complex condition, it is important that parents seek out an experienced health care provider for their child.

How is genetic testing for hereditary paraganglioma-pheochromocytoma syndrome done?

The health care provider may suspect hereditary paraganglioma-pheochromocytoma syndrome after looking at a person's medical or family history. In most cases, a health care provider or genetic counselor will ask questions about a person's health and the health of other family members.

The genetic counselor or health care provider will record which family members have developed tumors, what types of tumors and at what ages tumors occurred. From this information they will create a family tree. Health care providers and genetic counselors will look at the family tree to find out:

- If there are more cancers than normal,
- If cancers occurred at younger-than-expected ages, and
- If the types of tumors match up with what might be seen in those with hereditary paraganglioma-pheochromocytoma syndrome.

If hereditary paraganglioma-pheochromocytoma syndrome is suspected in a child or other family members, the health care provider or genetic counselor will likely recommend genetic testing of one or more of the genes that are associated with the syndrome (*SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* and *MAX*).

Diagnostic genetic testing

If the health care provider or genetic counselor suspects that a person has hereditary paraganglioma-pheochromocytoma syndrome, diagnostic testing may take place as follows:

- A blood sample is collected.
- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- Both copies of the person's genes are checked for possible changes. A genetic specialist compares the two copies of the patient's genes to normal copies of the genes. If there are differences, the specialist decides if they might cause a certain condition such as hereditary paraganglioma-pheochromocytoma syndrome.
- If a mutation in one of the tested genes is found, the genetic counselor will work with the family in the following ways:
 - To help the family understand the cancer risks of hereditary paraganglioma-pheochromocytoma syndrome
 - To find out if other family members should consider testing
 - To help with decisions about prenatal genetic testing

It is important to remember that genetic testing does not always find a mutation in *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* and *MAX* for all people with hereditary paraganglioma-pheochromocytoma syndrome. A person can still have the syndrome even if no mutations in these genes are found. There are likely to be more, undiscovered genes that play a role in the development of this syndrome.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with a known family mutation in *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* or *MAX*. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of the testing. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy — Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for a known mutation in *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* or *MAX* before placing them into the uterus.

Testing that occurs during pregnancy — Testing can be used to see if a pregnancy is affected with a known mutation in *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* or *MAX*. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)** — during the first trimester (first three months)
- **Amniocentesis** — during the second trimester or later (last six months)

Collected tissue can be checked for the presence of a known mutation in *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* or *MAX* that has already been identified in the family.

Both of these tests carry minor risks and should be discussed with an experienced doctor or genetic counselor.

Special concerns

Genetic testing for hereditary paraganglioma-pheochromocytoma syndrome is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before testing is done. If they choose testing, they should review the test results with the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes children or adults with hereditary paraganglioma-pheochromocytoma syndrome can feel sad, anxious or angry. Parents who pass on a mutation in *SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *SDHA*, *TMEM127* or *MAX* to one or more of their children can feel guilty. Some people with a mutation in one of these genes could have trouble getting disability coverage, life insurance or

long-term care insurance in some states. More information about genetic discrimination can be found at www.ginahelp.org.

Are there other special health care needs for children with hereditary paraganglioma-pheochromocytoma syndrome?

People of any age with hereditary paraganglioma-pheochromocytoma syndrome have a higher risk of cancer. They should monitor their health and adopt healthy habits throughout life. It is important to continue to have regular physical checkups and screenings. That way, any cancer can be found early at the most treatable stage.

Other ideas to reduce the risk of cancer include the following:

- Eat a healthy diet with lots of fruits and vegetables
- Get regular exercise
- Avoid smoking or using tobacco products
- Avoid secondhand smoke
- Avoid excess sun exposure and always wear sunscreen, hat and protective clothing when out in the sun

People with hereditary paraganglioma-pheochromocytoma syndrome should watch closely for general signs or symptoms that could signal cancer:

- Unexplained weight loss
- Excessive sweating or feelings of anxiety
- Racing heart beat
- Unexplained high blood pressure
- Loss of appetite
- Pain in abdomen
- Blood in the stool or changes in bowel habits
- Aches, pains, lumps or swelling that cannot be explained
- Headaches or changes in vision or nerve function that do not go away

It is important to seek medical help if anything unusual appears.

What other information and resources are there for children with hereditary paraganglioma-pheochromocytoma syndrome and their families?

Resources about hereditary paraganglioma-pheochromocytoma syndrome:

- Pheo Para Troopers (www.pheoparatroopers.org)
- Genetics Home Reference (ghr.nlm.nih.gov/condition/hereditary-paraganglioma-pheochromocytoma#synonyms)
- National Organization for Rare Disorders: Pheochromocytoma (<https://rarediseases.org/rare-diseases/pheochromocytoma>)

More resources:

- Making Sense of Your Genes: A Guide to Genetic Counseling (www.ncbi.nlm.nih.gov/books/NBK115508/)
 - Young People with Cancer: A Parent's Guide (www.cancer.gov/publications/patient-education/young-people)
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Sources:

1. Genetics Home Reference - Hereditary paraganglioma-pheochromocytoma syndrome
ghr.nlm.nih.gov/condition/hereditary-paraganglioma-pheochromocytoma#synonyms

2. Gene Reviews – Hereditary paraganglioma-pheochromocytoma syndrome
www.ncbi.nlm.nih.gov/books/NBK1548/

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