

What Is Genetic Pheochromocytoma & Paraganglioma?

Pheochromocytoma (pheo) and paraganglioma (para) are rare slow-growing neuroendocrine tumors arising from adrenal medulla and sympathetic or parasympathetic paraganglia respectively.

There is one adrenal gland above each kidney. Pheos develop in cells located in the adrenal medulla while paras develop outside the adrenal gland in the head, neck, chest, abdomen, or pelvis.

Up to 40% of pheos and paras are the result of an inherited genetic mutation. Genetic testing, which includes a blood or saliva test and speaking with a genetic professional, is recommended for all patients diagnosed with pheo or para. If a genetic mutation is found then other members of the family are recommended to have genetic testing because each of his or her children will have a 50% chance of inheriting the mutation, this is called autosomal dominant. This doesn't mean that someone with a genetic mutation will develop tumors, but life-long monitoring is important to catch tumors early.

Pheo and para can occur at any age, but most commonly affect people between the ages of 20 and 50. Younger patients are more likely to have an inherited genetic mutation. In addition, some mutations are more likely to develop metastatic disease than others.

Symptoms +/- associated syndromes

Pheos and paras can produce an excess amount of hormones called catecholamines, which may include norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine. The release of catecholamines can cause persistent or episodic:

- High blood pressure
- Headache
- Sweating
- Flushing
- Paleness of the face
- Weight loss
- Palpitations/tremors
- Severe anxiety and other symptoms

Most head and neck paras do not produce any catecholamines and consequently common symptoms do not appear. They are often found incidentally or due to local mass effect (e.g., pulsatile tinnitus, hearing loss, cervical mass).

Early diagnosis is important, because if left untreated, hormone-producing pheo or para can lead to severe or life-threatening conditions, including stroke and heart attack. Tumors can also metastasize, and ultimately, lead to death.

Approximately 20 genetic mutations are associated with an increased risk of developing pheo or para, and researchers believe more genes will be discovered in the near future. Some of the most common gene mutations are mentioned below. All are autosomal dominant, which means that children of a parent with a genetic mutation will have a 50% chance of inheriting the mutation. The risk of developing a tumor during life (disease penetrance) varies across genetic mutations.

Knowing your genetic mutation may guide your medical team on:

- how often follow up scans and tests should occur

- selecting a course of treatment if new tumors are discovered or tumors grow

SDHx syndrome

The SDHx syndrome is the result of mutations in the genes of subunits of the succinate dehydrogenase. Patients with mutations in any of the SDH genes are at increased risk for pheo and para and increased risk of tumors in the kidney and GI tract. The SDHx genes include four subunits (SDHB, SDHD, SDHC, and SDHA) and an assembly co-factor (SDHAF2).

SDHB: Mutations in SDHB are one of the most common causes of familial pheo and para. Mutations in SDHB are most often associated with pheo and para (mostly located in the abdomen). Pheos and paras that have an SDHB mutation are more likely to be metastatic, particularly in younger patients.

SDHD: The risk of developing a tumor from a mutation in this gene is increased almost exclusively when inherited from the father. This is known as paternal inheritance. If inherited from the mother, children can still carry the genetic mutation and pass on an increased risk to their children. Patients with SDHD mutations typically have head and neck paragangliomas and are more likely to have multiple tumors. The likelihood of metastasis is relatively low.

SDHC: SDHC is extremely rare, and much research still needs to be done. It is unlikely that someone who carries an SDHC mutation but does not currently have a tumor will develop one by the age of 60. Para are almost always located in the head and neck or chest and the risk for metastasis is exceptionally low.

SDHA: SDHA mutations are rarely found in pheo and para patients. These tumors may occur in the head and neck or abdomen and may behave aggressively.

SDHAF2: The risk of developing a tumor from a mutation in this gene is increased only when inherited from the father. This is known as paternal inheritance. If inherited from the mother, children can still carry the genetic mutation and pass on an increased risk to their children. The tumors associated with SDHAF2 tend to be primarily in the head and neck, and patients often have multiple tumors. This gene mutation is rare and metastases have not been reported so far.

VHL syndrome

Mutations in the VHL gene lead to Von Hippel-Lindau (VHL) syndrome, which affects approximately 1 in 36,000 people. Type 2, which is predominantly associated with *VHL* missense mutations, is defined by the occurrence of pheo, either alone (type 2C) or in combination with hemangioblastomas (type 2A) or with hemangioblastomas and RCCs (type 2B).

Over 90% of patients with this genetic mutation will develop VHL by the age of 65. With careful monitoring, early detection, and appropriate treatment, the most harmful consequences of this gene mutation can be greatly reduced, or in some cases, completely prevented. Approximately 20% of patients with VHL will develop pheo with a trend towards bilaterality. Malignant pheos in VHL patients are rare.

MEN2 syndrome

Multiple endocrine neoplasia type 2 (MEN2) is caused by mutations in the RET gene. It is estimated that about 1 in 30,000 people have MEN2. Among these cases, MEN2 can be divided in 2 main subgroups. The most frequent, MEN2A, represents 95% of all MEN2: it leads to MTC in almost 100% cases, pheo in 50% of cases, and hyperparathyroidism in approximately 10-20% cases. The second group, MEN2B represents 5% of cases: while penetrance of MTC and pheo are close to the ones of MEN2A, patients will not present

hyperparathyroidism, but a whole set of extra-endocrine features (marfanoid body habitus, mucosal and intestinal ganglioneuromatosis). Malignancy risk of pheo is very rare.

NF1

Neurofibromatosis type 1, or von Recklinghausen's disease, affects approximately 1 in 3,000 people. The disorder is characterized by multiple café au lait (light brown) skin spots and neurofibromas (small neoplasms) on or under the skin, and/or freckling in the armpits or groin. About 50% of people with NF1 also have learning challenges. Softening and curving of bones, and curvature of the spine (scoliosis) may also occur. NF1 children may develop optic pathway gliomas. NF1 is usually diagnosed in childhood. People who have NF1 are at moderate risk of developing pheo (approximately 5%-13% life-time risk) compared with the general population. The risk of metastases of the pheo is low.

Other genes

TMEM127, MAX, FH, PHD2 and KIF1B β , also have been associated with pheochromocytoma and paraganglioma but in extremely rare cases. Research is ongoing to learn more about these genes.

Causes and/or risk factors for pheo and para

We do not know exactly what causes pheo and para, but 40% of patients diagnosed have a genetic mutation. Everyone diagnosed should talk to their doctor about genetic testing. In addition, it is important to follow advice in leading a healthy lifestyle: eat healthy, exercise and avoid smoking and too much alcohol.

Common tests that may be used to help diagnose

Blood/Urine Tests

Blood and urine tests (24-hours urine collection) for measurement of metabolites of catecholamines are used for the diagnosis. These metabolites include normetanephrine (metabolite of norepinephrine), metanephrine (metabolite of epinephrine) and 3-methoxytyramine (metabolite of dopamine). The last metabolite is very useful for the diagnosis of head and neck para and may help in the diagnosis of metastases. All three metabolites are measured simultaneously in one blood sample although not all labs measure 3-methoxytyramine. Further, it is not readily available in the U.S. and may not be widely available.

Scans and other tests

Imaging will help to identify where, how many, and size of the tumor(s). CT and/or MRI are often used first, before functional imaging is used.

Functional imaging may include FDG PET/CT, 123I-MIBG or 68Ga-DOTATATE/DOTATOC. The choice between tracers depends on the underlying genetic mutation and tumor location.

Pathology

It is not recommended for patients suspected of having a pheo or para to have a biopsy because manipulation of the tumor can cause a release of catecholamines resulting in a hypertensive crisis.

Treatment

There is global consensus agreement that all neuroendocrine cancer patients should be reviewed by a specialist neuroendocrine cancer multidisciplinary team to ensure best care.

If detected early, pheo and para can be successfully treated and managed in the vast majority of cases. The treatment of choice for the condition is surgery to remove the tumor(s), but if surgery is not possible there are other treatment options.

Before surgery

Anesthesia and manipulation of the tumor during surgery can cause a massive release of catecholamines which can result in a hypertensive crisis. To avoid this, patients must be adequately “blocked” with medication before surgery.

Alpha and beta-blockers are prescribed to normalize blood pressure and heart rate, which protect the patient from the effects of high levels of catecholamines released during surgery. First, an alpha blocking medication is prescribed for at least 2 weeks before the surgery.

Phenoxybenzamine and doxazosin are the most commonly used alpha-blocking drugs. After some days on an alpha-blocker, in most patients a beta-blocker is additionally prescribed, sometimes in combination with calcium channel blockers. Adequate oral hydration and a high salt diet may be recommended, as well.

Non-surgical treatment:

Surgery may not be possible because of advanced or metastatic disease. In this case, one or more of the approaches below may be suggested:

- Active observation. An experienced doctor may suggest only regular monitoring of the tumor(s) if they are stable (not growing), and clinically controlled
- Targeted therapies, systemic chemotherapy
- External beam radiation, interventional radiology
- Targeted radiopharmaceutical (radionuclide) therapy such as ¹³¹I-MIBG (only available in the U.S.) or ¹⁷⁷Lu-DOTATATE (PRRT)
- Your pheo para specialist team may suggest consideration to participate in an appropriate clinical research study

Follow up

Long-term regular follow-up is recommended for all patients. Yearly urine or blood tests for pheo and para should be performed for life to detect remaining disease, return of the disease, or the development of metastases. Those with secretory pheo and para due to remaining disease or metastatic disease should let their care team know about any planned procedure so that a blocking regimen can be prescribed if needed, and they should wear a medic alert bracelet / necklace to aid in the event of an emergency. For those with a large primary tumor and/or with a genetic mutation, follow-up CT, MRI or functional imaging is recommended. Long term regular follow-up keeps those with pheo and para updated on new information, treatments and research in the field, as it becomes available.

Resources

Association for Multiple Endocrine Neoplasia Disorders

www.amend.org.uk

Pheo Para Alliance

www.pheopara.org

For the full list of INCA members: <https://incalliance.org/members/>