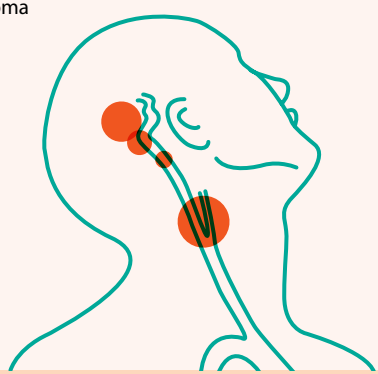
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE

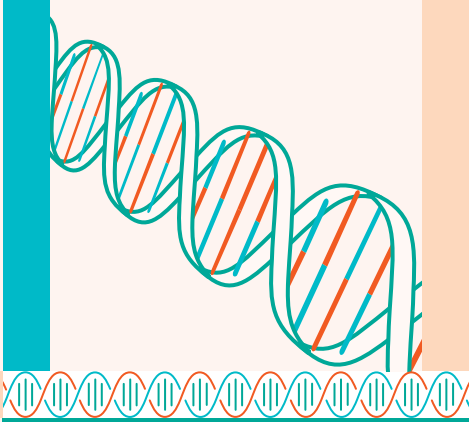
Genomic
Medicine Centre

Hereditary Paraganglioma-Phaeochromocytoma Syndrome

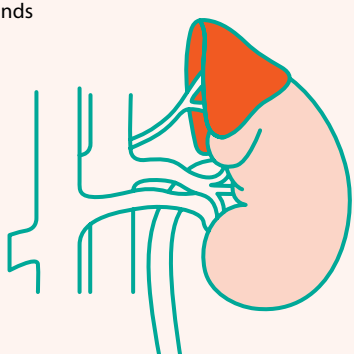
Head & neck
paraganglioma



DNA strand



Adrenal glands



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Hereditary paraganglioma-phaeochromocytoma syndrome is a hereditary tumour/cancer syndrome.

What are hereditary tumours and cancers?

Hereditary tumours and cancers develop because of the presence of a faulty gene. Some genes function to protect us from cancer/tumour growth. When they are not working well, it causes an increased risk of tumours/cancer developing. We refer to genes that are not working well as faulty genes.

Individuals who carry a faulty tumour/cancer gene(s) have a higher chance of developing certain tumours/cancers over their lifetime compared to the general population. The types of tumours/cancers that they may be at increased risk for will depend on the gene(s) involved.

If you have a faulty tumour/cancer gene, you may be at increased risk of developing certain tumours/cancers. As genes are shared among family, other family members may have inherited the faulty gene and may be at increased risk of tumours/cancer too.

What is genetic testing?

Genetic testing is offered to individuals where a hereditary cause of their personal and/or family history of tumours/cancer is suspected.

Genes contain the instructions that our body reads to carry out different functions. Genetic testing involves analysing your genes to understand if there are faults (i.e., mutations) that may increase the risk of tumours/cancers.

How is genetic testing done?

- Genetic testing is typically a one-time blood test.
- If a blood sample cannot be taken, other sample sources (e.g., skin or saliva) may be used.

Hereditary tumours account for up to  **of all paraganglioma and phaeochromocytoma cases.**

What are the possible results of genetic testing?

There are 3 types of results you may receive:

Positive

Faulty gene(s) identified

General Population Risk — Elevated Risk

Increased risk of developing certain tumours and cancers (depends on faulty gene(s) involved)

Your family (parents, siblings, children and extended relatives) may have inherited the faulty gene(s) and should consider genetic testing to clarify this

Uncertain

Variant of Uncertain Significance (VUS)

Uncertain gene change(s) identified, unclear if these change(s) increase risk for tumours and cancers

General Population Risk — Elevated Risk

May be clarified by testing other family members

May be reclassified over time as 'positive' or 'negative' when more information is known

Negative

No faulty gene(s) identified

General Population Risk — Elevated Risk

Tumour and cancer risk is similar to that of general population

Test limitations will be explained in the context of your personal and family history of tumours and cancers

What is hereditary paraganglioma-phaeochromocytoma syndrome?

Hereditary paraganglioma-phaeochromocytoma (PGL/PCC) syndrome is an inherited condition associated with an increased risk of noncancerous tumours (called paragangliomas and phaeochromocytomas) developing in certain parts of the body.

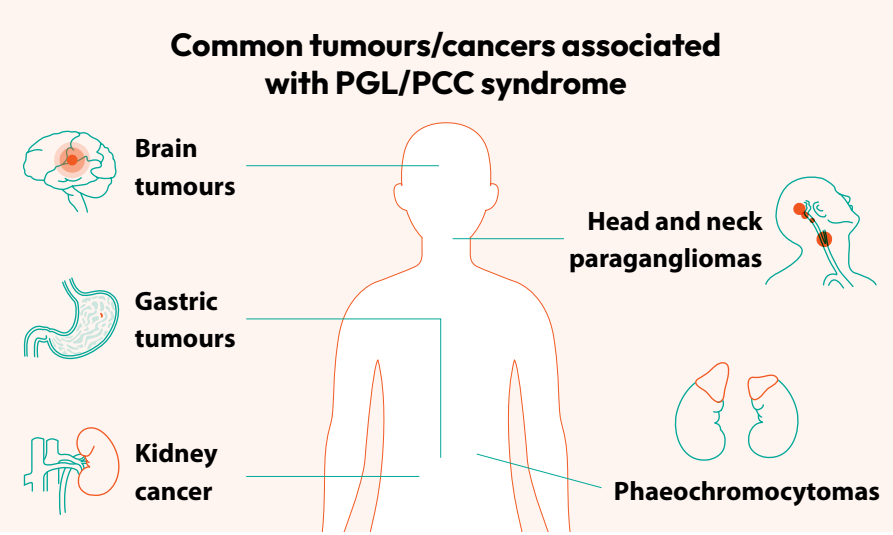
While these tumours are generally noncancerous, some can become cancerous (malignant) and spread (metastasise) to other parts of the body.

Other noncancerous tumours can also cause medical problems. There may also be a small increased risk of kidney cancer, gastric tumours and pituitary gland tumours in individuals who have this condition.

What are paragangliomas and phaeochromocytomas?

Paragangliomas (PGL) are rare tumours, usually noncancerous, and found near nerve cells. These tumours can develop in various parts of the body, such as the base of the skull, neck, chest, abdomen and pelvis. PGL tumours can also develop in other areas of the body.

Phaeochromocytomas (PCC) are tumours that develop in the adrenal glands, which are located on top of our kidneys.



Signs of PGL and/or PCC

Depending on where these tumours develop in the body, they may cause different symptoms (see figure below). The symptoms vary among individuals while some may even be asymptomatic.

Head and neck PGL

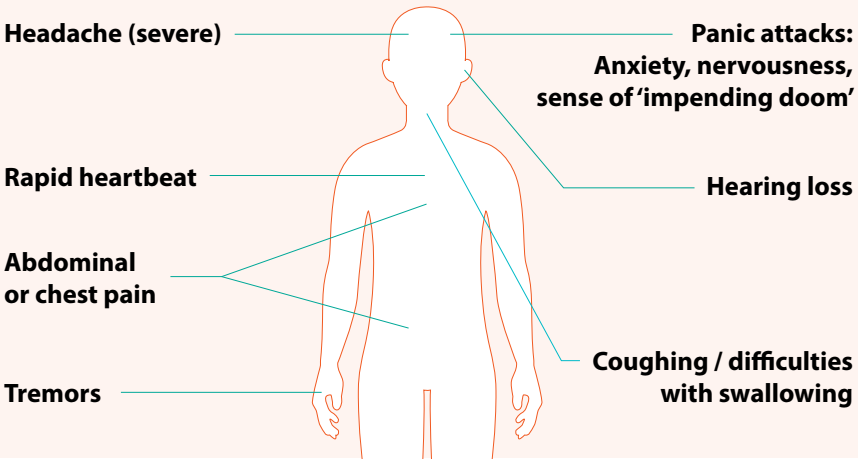
Most head and neck PGL tend not to overproduce hormones, and thus individuals do not show the signs associated with abnormal hormonal regulation.

PCC

PCC, which are tumours in the adrenal gland, can release excess hormones that can lead to symptoms such as high blood pressure, a fast heartbeat and excessive sweating.

If these tumours are ununtedected or untreated, more serious risks such as heart attacks, stroke or sudden death may occur.

Common signs and symptoms caused by PGL and PCC



Other symptoms associated with PGLs/PCCs include:

- Excessive sweating
- New onset diabetes
- Weight loss
- Pale appearance
- High blood pressure

What other tumours and cancers can be associated with hereditary PGL/PCC syndrome?

There may be an increased risk of kidney or thyroid cancer, and stomach or pituitary tumours developing in individuals with PGL/PCC syndrome. However, these risks are small.

1. Kidney cancer

Individuals with PGL/PCC syndrome may have an increased risk of developing a certain type of kidney cancer.

2. Thyroid cancer

Some individuals with PGL/PCC syndrome may have an increased risk of developing thyroid cancer.

3. Gastric tumours

Individuals with PGL/PCC syndrome may also be at increased risk of developing a type of stomach tumour called gastrointestinal stromal tumours (GISTs). GISTs develop within the walls of the stomach or small intestine.

Small GISTs may not cause any symptoms and are usually detected through bleeding in the gastrointestinal tract.

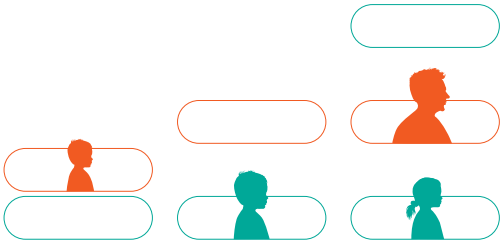
Some symptoms that an individual with GISTs might experience include:

- Vomiting blood which looks like coffee grounds
- Stools which are black or bloody
- Abdominal pain
- Loss of appetite and weight loss
- Feeling tired and weak

4. Pituitary tumours

The pituitary gland is a pea-sized gland found at the base of the brain and produces hormones which regulate growth and sexual function, and controls other glands such as the thyroid and adrenal glands.

Pituitary tumours are almost always benign but can cause problems, as a tumour can result in the pituitary gland making too little or too much hormones. Occasionally, pituitary tumours can cause headaches, or press on the eye nerves causing loss of vision.



What causes PGL/PCC?

There are two causes of PGL/PCC:

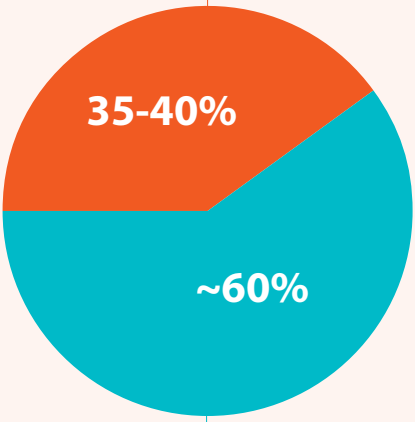
Hereditary

Mainly caused by a faulty *SDHx* gene (hereditary PGL/PCC syndrome)

Approximately 35-40% of individuals who are diagnosed with PGL/PCC may have a hereditary cause. This means that they may have inherited the condition from a parent and can pass it on to their children. Other family members may also be at risk.

Hereditary PGL/PCC syndrome is caused by the presence of a faulty (i.e., disease-causing) gene in any of the following genes: *SDHA*, *SDHB*, *SDHC*, *SDHD* and *SDHAF2* – collectively termed *the* ***SDH*** **family of genes** ***(SDHx)***.

However, the development of PGL and PCC can also occur in other genetic syndromes like von Hippel-Lindau (VHL), Neurofibromatosis type 1 (NF1) and multiple endocrine neoplasia type 2 (MEN2).



Sporadic

Caused by age, chance events and/or environmental factors

Most PGL/PCC happen sporadically (by chance) and are driven by factors such as age or lifestyle/environmental exposures (i.e. not hereditary/inherited).

Genetic testing can help to clarify if a personal or family history of PGL/PCC is due to a hereditary or sporadic cause.

What are the tumour and cancer risks associated with hereditary PGL/PCC syndrome?

The risk of tumours/cancers depends on which *SDHx* gene is faulty.

Lifetime tumour and cancer risks for individuals with PGL/PCC syndrome

Tumour/ cancer type	Specific risks associated with hereditary PGL/PCC syndrome				General population risk
	SDHA carrier	***SDHB*** carrier	***SDHC*** carrier	***SDHD*** carrier	
Benign PGL/PCC (noncancerous)	< 5%	Up to 30%	Up to 18%	Up to 60%	Rare
Malignant PGL/PCC (cancerous)	Un-common	5 - 10%	Un-common	Un-common	Rare
Kidney cancer (renal cell carcinoma)	< 2%	3 - 5%	< 2%	< 2%	1.4%
Gastric tumours (GISTs)	Increased				< 1%
Pituitary tumours (pituitary adenoma)	Increased				Unavailable

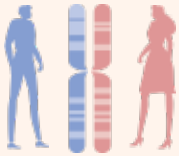
Note: The conditions associated with different faulty SDHx genes and their risk estimates may change as more information is available. Insufficient information is known about the risk of SDHAF2 carriers, thus it is not included in the table.

While individuals carrying a faulty *SDHx* gene face an increased risk of the tumours/cancers listed above, it does not mean that they will definitely develop them.

How is hereditary PGL/PCC syndrome inherited?

Hereditary PGL/PCC syndrome follows a **dominant inheritance pattern**. This means that having one faulty copy of any *SDHx* gene (i.e., *SDHA, SDHB, SDHC, SDHD and/or SDHAF2*) gene can cause the condition. It affects both males and females.

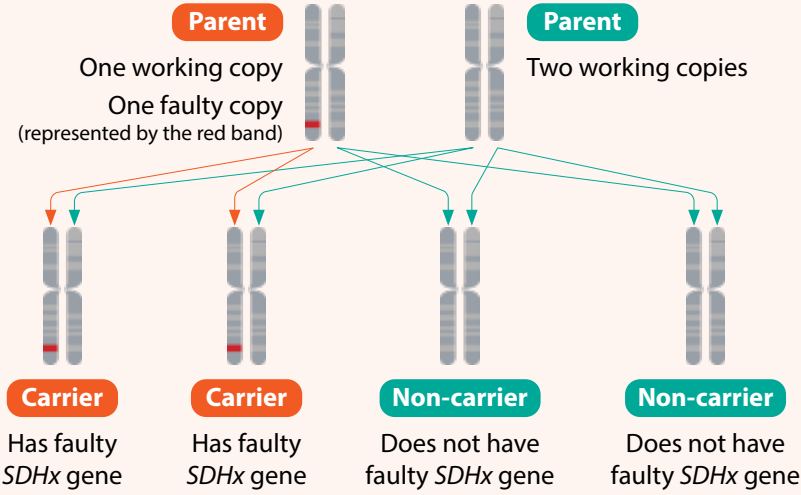
Everyone has 2 copies of each gene in their body's cells:



1 copy comes from our father

1 copy comes from our mother

Dominant inheritance pattern



- A parent with a faulty gene(s) has a 50% chance of passing down their faulty gene(s) to their children.
- A child, sibling or parent of a family member with a faulty gene(s) has a 50% chance of also inheriting the same faulty gene(s).
- Extended relatives may also inherit the faulty gene(s).

A maternally or paternally inherited faulty *SDHx* gene can determine the risk of tumour/cancer development in an individual.

Genes associated with hereditary PGL/PCC syndrome	Inheritance
SDHA, SDHB and ***SDHC***	Inheriting the faulty gene ***from your mother or father*** will result in hereditary PGL/PCC syndrome and its associated tumour/cancer risks.
SDHD and ***SDHAF2***	Inheriting the faulty gene ***from your father*** will result in hereditary PGL/PCC syndrome and its associated tumour/cancer risks. Individuals who inherit the faulty *SDHD/SDHAF2* gene ***from their mother*** almost never develop tumours/cancer (few cases have been reported to present with tumours/cancer).

Individuals who inherit a faulty *SDHx* gene, regardless of whether they have symptoms or not, still have a 50% chance of passing the faulty gene onto their children.

Who should undergo genetic testing for PGL/PCC syndrome?

You should consider genetic testing if you or your family members meet one or more of the following criteria:

- One or more PGL and/or PCC at any age
- Gastric GIST at any age
- Renal cell carcinoma at any age
- Pituitary adenoma at any age
- Individuals suspected to have hereditary PGL/PCC syndrome
- Consideration of pregnancy with a family history of PGL/PCCs
- A previously identified faulty *SDHx* gene in the family

How can your genetic test result help you?

1. Personalised management

Confirming a diagnosis of hereditary PGL/PCC syndrome would be beneficial for early diagnosis and timely surveillance. This helps to detect tumours/cancers at their earliest and most treatable stage, avoiding irreversible or serious medical complications. For individuals planning a family, reproductive options may also be available.

It is also important to identify which faulty *SDHx* gene you may have inherited, as the different genes are associated with different tumour/cancer risks which would influence how doctors plan for your medical management.

2. Familial implications

Your genetic test result can also help you understand if other family members are at risk of hereditary PGL/PCC syndrome. They can subsequently consider their own testing (predictive testing) to clarify their carrier status to determine tumour and cancer risks.

Family members who ***have inherited*** the same faulty *SDHx* gene may be at increased risk of tumours and cancer and can benefit from management options such as screening (to detect tumours and cancer at an early and manageable stage) or surgery (to reduce their risk of cancer).

Family members who ***did not inherit*** the faulty *SDHx* gene can avoid unnecessary screening and worry. Their children will also not be at risk.

What can I do to manage my increased risk of tumours and cancer?

Screening

Screening helps to detect (and in some cases treat) tumours and/or cancer at an early and manageable stage.

Paraganglioma-phaeochromocytoma

- Blood pressure and blood or urine tests to monitor for signs which may suggest the presence of a tumour.
- Imaging scans may be recommended to check for the presence of a tumour.

Kidney cancer (renal cell carcinoma)

- Regular imaging (e.g., MRI or ultrasounds) can help to detect if any tumours have formed in the kidney.

Gastric GIST / pituitary tumours

- An endoscopy can be considered if symptoms like gastrointestinal problems or anaemia are present.

Thyroid cancer / parathyroid tumours

- Imaging (e.g., thyroid ultrasounds) can be considered to screen for tumours/cancer. Further blood tests can be considered if needed.

Your managing doctor(s) will discuss these options with you in greater detail. The age, onset and frequency for screening may change according to the faulty *SDHx* gene that you have, and your personal and/or family history of tumours/cancer. Screening guidelines may change as more information is known.

Lifestyle adjustments/ considerations

- Avoid smoking
- Pregnant women with this condition should be closely monitored
- Avoid long-term exposure to high-altitude areas
- Encouraged to seek medical attention if experiencing unusual symptoms like headaches, heart palpitations and excessive sweating

Frequently Asked Questions (FAQs)

Q: Who is the best person in the family to undergo genetic testing?

A: In order to identify if a hereditary condition exists in a family, genetic testing is usually offered to **the family member whose personal history is most suggestive of hereditary PGL/ PCC syndrome** (e.g., someone who presents with PGL/PCC symptoms at a young age).

It is usually not advisable to test someone without a history of cancer/ tumours unless the condition has already been identified in the family.

The genetic test results of an asymptomatic individual may have limitations:

- If they were to receive a negative result, it may not mean that there is no hereditary cause of cancer/tumours in the family. The individual being tested may not have inherited it, but others in the family may have, or the faulty gene may not have been identified yet.
- The result is only useful to the asymptomatic person being tested and their children, but not to their parents, siblings and other second-degree family members.

Once the faulty gene in the family is identified, genetic testing can be offered to other family members including those who do not have a tumour/cancer. This will help them understand if they have inherited the faulty gene change and if so, tailor their management to manage or reduce their risks.

Common Myths & Misconceptions

If test positive, it means that the cancer/tumour will recur.

FALSE. The genetic test result cannot determine the likelihood of tumour/cancer recurrence or the presence of tumour/cancer. A positive result only confirms the diagnosis of hereditary PGL-PCC syndrome, which indicates an increased risk of getting tumour/cancer or a new tumour/cancer developing.

If I or my child tests positive, it means that my children/grandchildren will have it too.

FALSE. If you or your child have a positive genetic test result for hereditary PGL/PCC where a faulty *SDHx* gene(s) is identified, it means each of your children/grandchildren has a 50% (1 in 2) chance of inheriting the same faulty gene(s).

If I have hereditary PGL/PCC, and my daughter looks a lot like me, she must have inherited the faulty gene(s) since I have it.

FALSE. Genes that govern your appearance are different from the genes that determine the risk of hereditary PGL/PCC syndrome like any *SDHx* genes. All first-degree relatives (siblings, children and parents) have a 50% (1 in 2) chance of inheriting the faulty *SDHx* gene, regardless of whether they look like you or not.

I have two brothers, so one will inherit the faulty gene(s) and one will not, because there is a 50% chance.

FALSE. Each first-degree relative (parents, siblings and children) has a 50% (1 in 2) chance of inheriting the faulty gene(s). The genetic test result of one sibling does not impact the chances for the other sibling.

If you have any questions, please contact:

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Weekends and Public Holidays: Closed

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