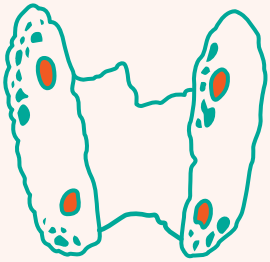
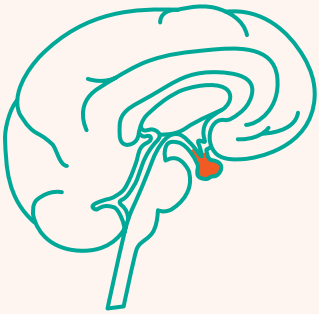
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE

Genomic
Medicine Centre

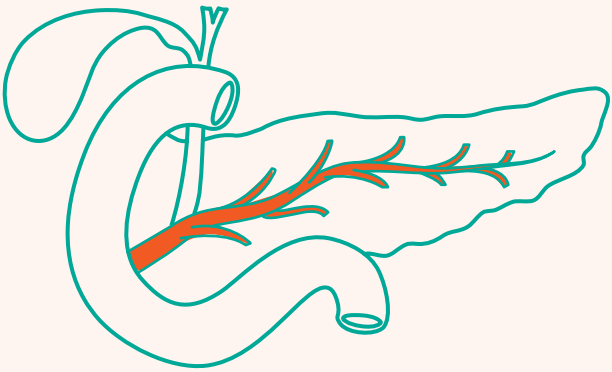
Multiple Endocrine Neoplasia Type 1 (MEN1)

Parathyroid





Pancreas



Pituitary

SingHealth

Multiple Endocrine Neoplasia Type 1 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 tumour/cancer growth. When they are not working well, it causes an increased risk for tumours/cancers to grow. 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/cancer that they may be at increased risk of 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 for 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/cancer.

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.

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 Multiple Endocrine Neoplasia Type 1?

Multiple Endocrine Neoplasia Type 1 (MEN1) is a hereditary condition associated with an increased risk of tumours of the endocrine (hormone-producing) glands.

These glands are located in different parts of the body and control the production of hormones that direct many body processes, including growth, digestion and sexual function.

MEN1 is caused by a fault (i.e., mutation) in the *MEN1* gene. The gene provides instructions for producing a protein called menin which is known to play a role in keeping cells from growing and dividing too fast.

How common is MEN1?

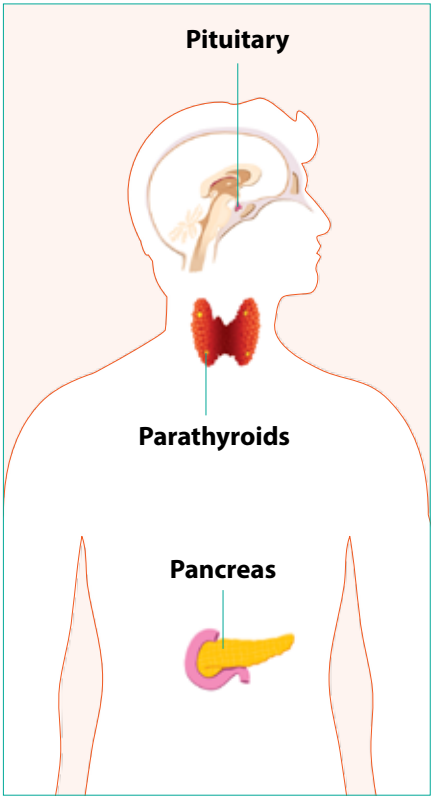
It is estimated that about **one in 30,000 people** have MEN1.

- The majority of individuals with MEN1 inherit the condition from a parent.
- About 10% of people with MEN1 do not have a family history of the condition. This is because they may have acquired a *de novo* (new) change or fault in the *MEN1* gene at birth.

What are the tumours associated with MEN1?

MEN1 is typically characterised by tumours in the following locations of the body:

- Glands of the endocrine system (i.e., parathyroid, pituitary, pancreas)
- Other parts of the digestive tract (e.g., duodenum and stomach)



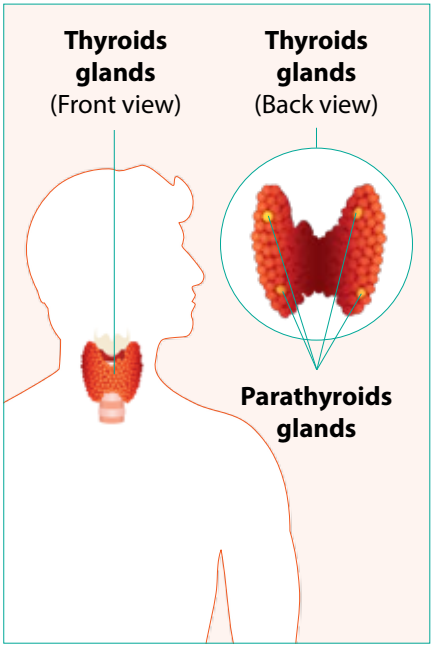
Glands of the endocrine system

1. Parathyroid glands

About 95% of people with MEN1 develop tumours in the parathyroid glands by age 50.

These four pea-sized glands produce the **parathyroid** hormone, which helps to maintain the right balance of calcium and phosphate in your body. Over time, MEN1 can affect all four glands.

MEN1-related tumours cause the parathyroid glands to become overactive, producing too much parathyroid hormone. This condition, called **hyperparathyroidism**, is the most common complication associated with MEN1.



The parathyroid glands are located near the thyroid gland in the neck

Excess parathyroid hormone can cause calcium levels in your blood to rise too high. Complications may include:

- Fractures
- Kidney stones
- Muscle weakness
- Tiredness or confusion
- Increased thirst and urination
- Depression
- Aches and pains in bones and joints
- Constipation or abdominal pain

2. Pancreas and digestive tract

About 40% of people with MEN1 develop tumours in the pancreas, duodenum (small intestine), or other parts of the digestive tract.

Many different types of tumours may develop at the same time. Many of these tumours produce hormones while others do not. Some tumours may be cancerous.

In people with MEN1, the two most common tumours of the digestive tract are:

- **Gastrinomas.** These tumours produce the hormone **gastrin**, which causes the stomach to release acid that helps it digest food. Too much gastrin can cause stomach ulcers and severe diarrhoea. Over time, some of these tumours may become cancerous.

- **Insulinomas.** These tumours form in the pancreas, where the cells produce the hormone **insulin**. Insulinomas make too much insulin, leading to low blood sugar. These tumours are almost always noncancerous and can usually be removed with surgery.

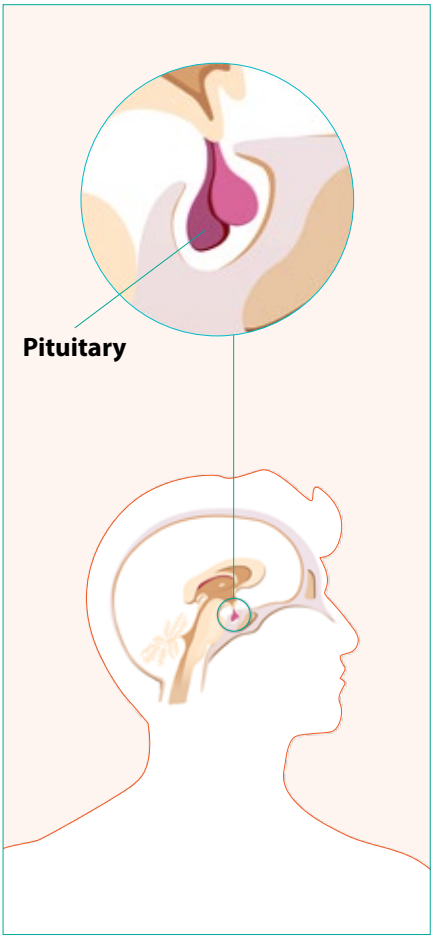
Other rare pancreatic tumours include:

- **Glucagonomas.** These tumours produce too much of the hormone **glucagon**, which raises blood sugar levels.

- **VIPomas.** These tumours may produce too much of a hormone called **vasoactive intestinal peptide (VIP)**, which may result in profuse watery diarrhoea.

3. Pituitary gland

Nearly one in three people with MEN1 develop tumours in the front part of the pituitary gland called the anterior lobe. Like other pituitary tumours, these growths are often small in size and are almost always noncancerous.



The pituitary gland sits at the base of the brain

In people with MEN1, the two most common pituitary tumours are:

a. **Prolactinomas.** These tumours are the most common, and produce the hormone **prolactin**. Normally, this hormone signals women's breasts to produce milk during pregnancy and breastfeeding. Women with a prolactinoma may notice milk discharge from their breast(s) (galactorrhea) when they are not pregnant or breastfeeding. In both men and women, high prolactin levels can lead to infertility and bone loss.

b. **Growth hormone (GH) tumours**. These tumours are the second most common, and produce excess GH which causes bones and other vital organs to grow larger in size. This condition is called acromegaly. Health problems caused by excessive GH include hypertension, diabetes, heart disease, stroke, arthritis, carpal tunnel syndrome and tumours of the colon or rectum.

   Pituitary tumours that grow large in size may prevent the pituitary gland from making enough hormones, leading to a condition called hypopituitarism. The tumours may also press against nearby brain tissues such as the eye nerve, causing vision problems and headaches.

   Hypopituitarism can usually be treated with oral hormone replacement pills.

4. Other tumours

MEN1 can also cause tumours to develop in other parts of the body. Examples include:

- **Tumours in other endocrine glands.** An example is the adrenal glands.
- **Carcinoid tumours.** Slow-growing tumours most often found in the stomach, thymus and lungs.
- **Skin tumours and tumours under the skin.** Common ones include angiofibromas, lipomas (benign tumours made of fat cells), and collagenomas (tumours involving a protein in the skin called collagen).
- **Meningiomas and ependymomas.** Tumours of cells that line the brain and spinal cord.

What are the tumour and cancer risks associated with MEN1?

Lifetime cancer and tumour risks for individuals with a faulty *MEN1* gene		
Tumour type	**MEN1 risk**	**General population risk**
Usually noncancerous		
Parathyroid glands (parathyroid adenomas or hyperplasia)	90 - 95%	Less than 1%
Pituitary gland (pituitary adenomas)	40%	5 - 10%
Adrenal glands (adrenocortical tumours)	26 - 40%	5 - 10%
Brain or spinal cord (meningiomas)	8%	Less than 0.01%
Lung airways (bronchopulmonary neuroendocrine tumours [NETs])	2 - 13%	Less than 1%
May become cancerous		
Stomach, duodenum and pancreas (gastroduodenpancreatic NETs)	30 - 70%	Less than 1%
Thymus (thymic NETs)	2 - 8%	Less than 1%

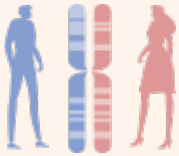
Note: The conditions associated with MEN1 and their risk estimates may change as more information is available.

While individuals with MEN1 have an increased risk of the tumours listed above, it does not mean that they will definitely develop tumours associated with MEN1.

How is MEN1 inherited?

MEN1 follows a **dominant inheritance pattern**. This means that having one faulty copy of the *MEN1* gene can result in an increased risk of tumours. It affects both males and females.

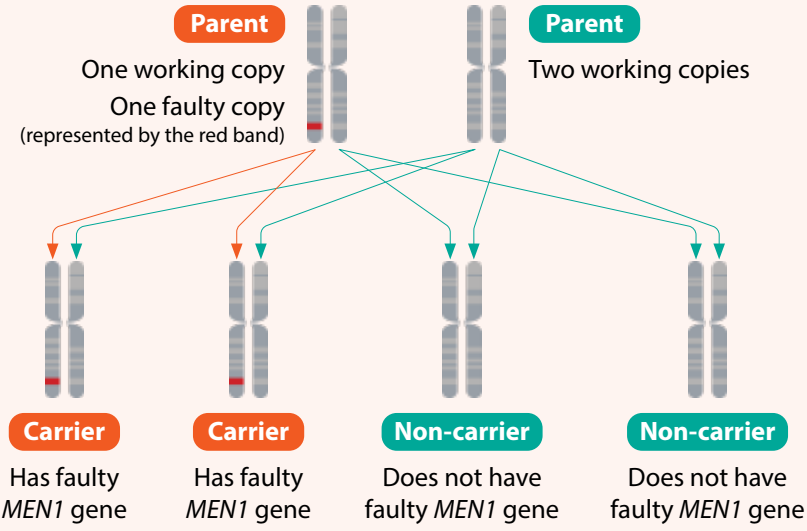
Everyone has 2 copies of each gene in their body's cells:



1 copy comes from our father

1 copy comes from our mother

Dominant inheritance pattern

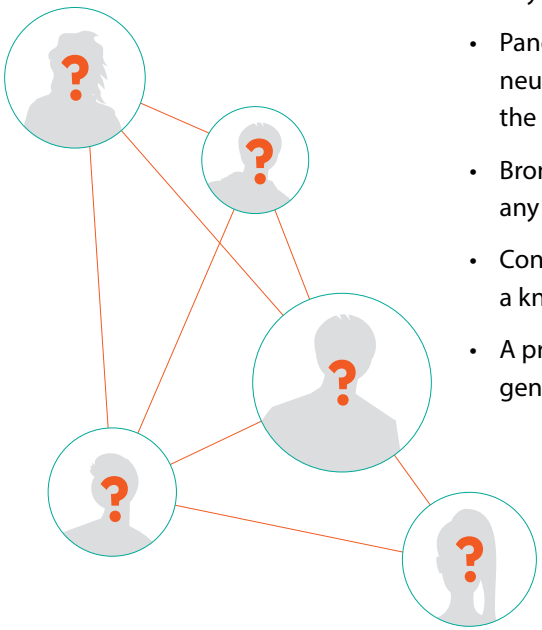


- A parent with a faulty gene(s) has a 50% chance of passing down their faulty gene(s) to their children.
- A child, sibling or parent of a family member with a faulty gene(s) has a 50% chance of also inheriting the same faulty gene(s).
- Extended relatives may also inherit the faulty gene(s).

How is MEN1 diagnosed by doctors?

You may be clinically diagnosed with MEN1 if you meet one of these three criteria:

- Two or more MEN1-related tumours (tumours in parathyroid glands, pituitary gland and pancreas, or other parts of the digestive tract)
- One MEN1-related tumour and a first-degree relative (a parent, sibling or child) who has been clinically diagnosed with MEN1
- A faulty *MEN1* gene, even if you have no signs or symptoms of MEN1



Who should undergo genetic testing for MEN1?

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

- Clinical diagnosis of MEN1
- Familial hyperparathyroidism (FIHPT)
- Parathyroid tumours diagnosed before the age of 40
- Recurrent or multiglandular primary hyperparathyroidism at any age
- Gastrinomas or multifocal pancreas/digestive tract neuroendocrine tumours at any age
- Pancreas and digestive tract neuroendocrine tumours before the age of 40
- Bronchial or thymic tumours at any age
- Consideration of pregnancy with a known family history of MEN1
- A previously identified faulty *MEN1* gene in the family

How can your genetic test result help you?

1. Personalised management

Your genetic test result may confirm whether your personal and/or family history is due to a hereditary condition like MEN1, and clarify what your lifetime tumour/cancer risks may be.

As MEN1 may present similarly to other conditions, undergoing genetic testing can help you confirm your diagnosis of MEN1, which can help to direct your medical management.

Understanding if you have MEN1 provides you with options for managing your increased risk of tumours/cancer. For example, screening options (blood tests/imaging) may be recommended to you which can help to detect tumours/cancer at its earliest, most treatable and manageable stage.

In some cases, you may choose to undergo surgery that can help to reduce your risk of developing tumours/cancer. For individuals planning a family, reproductive options may also be available.

2. Familial implications

Your genetic test result can also help you understand if other family members are at risk of MEN1. 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 *MEN1* 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 *MEN1* 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?

Screening

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

Parathyroid glands (parathyroid adenomas)

- Blood tests to measure calcium and parathyroid hormone levels

Pituitary gland (pituitary adenomas)

- Physical examination
- Brain/whole-body magnetic resonance imaging (MRI) scan*

Adrenal glands (adrenocortical tumours)

- Whole-body MRI with focus on adrenals*

Lung airways (bronchopulmonary NETs)

- Whole-body MRI with focus on chest *

Stomach, duodenum and pancreas (gastroduodenpancreatic NETs)

- Fasting blood test to measure gut hormones
- MRI of the pancreas and intestines*

Thymus (thymic NETs)

- Whole-body MRI with focus on chest*

* Computed tomography (CT) scans can be considered if MRI is unavailable

Your managing doctor(s) will discuss screening recommendations with you in greater detail. The onset and frequency of screening would be personalised according to your needs, personal and family history. Screening guidelines may change as more information is known.

Risk-reducing surgery

In some cases, risk-reducing surgery may be offered to help reduce the risk of tumours developing.

For example, in thymic NETs, concurrent surgery to remove the thymus can be considered along with surgery to remove the parathyroid.

However, do note that this is not standard management and this option will be discussed in detail with you by your managing doctor(s).

Lifestyle adjustments such as avoiding smoking can help manage this risk.

Frequently Asked Questions (FAQs)

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

A: In order to determine if a hereditary cause exists in the family, genetic testing is usually offered to **the family member whose personal history is most suggestive of MEN1** (e.g., someone with a personal history of tumours at a young age or clinical presentations suggestive of MEN1).

It is usually not advisable to test someone without a history of cancer / tumours / clinical features 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 not a hereditary cause of cancer/ tumours/clinical features in the family. The individual being tested may not have inherited it, but others in the family may have, or the faulty gene(s) 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 extended 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 and if so, tailor their management to manage or reduce their risks.

Common Myths & Misconceptions

If my genetic test result is positive, it means that I have or will have tumours, or my tumour will recur.

FALSE. The genetic test result cannot determine the likelihood of tumour recurrence or the presence of a tumour. A positive result only indicates an increased risk of developing tumours.

If I or my child tests positive, it means that my children/ grandchildren will also have MEN1.

FALSE. If you or your child has MEN1 and a positive genetic test result where a faulty *MEN1* gene(s) is identified, it means each of your children/grandchildren has a 50% (1 in 2) chance of inheriting the same faulty *MEN1* gene(s) and having the MEN1 condition.

My child looks a lot like me, so he/she must have inherited the faulty gene(s) since I have it.

FALSE. Genes that govern your appearance are different from the *MEN1* gene that causes the MEN1 condition. All first-degree relatives (siblings, children and parents) have a 50% (1 in 2) chance of inheriting the faulty *MEN1* 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 of the other sibling.

If you have any questions, please contact:

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Weekends and Public Holidays: Closed

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Acknowledgements

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Reg. No.: 200002698Z
Information correct as at February 2023

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