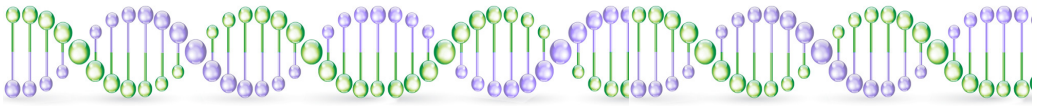
Information Sheet



Multiple Endocrine Neoplasia syndrome Type 2 (MEN2) and the RET gene

Multiple Endocrine Neoplasia syndrome Type 2 is rare, affecting 1 in 30,000 people. It is caused by a mutation in the RET gene.

There are 2 subtypes: MEN2A, describing 90% of cases, and MEN2B. The difference relates to the location of the specific mutation (pathogenic variant) in the DNA code of the RET gene.

How is MEN2B diagnosed?
MEN2B is associated with a very early onset of medullary thyroid cancer as well as physical changes. Almost all people with MEN2B are diagnosed in childhood or early adulthood.

Clinical features of MEN2B include:

- characteristic lumps on their lips and tongue (called mucosal neuromata)
- a long thin body shape (called a marfanoid body habitus)
- changes that can be detected on an eye exam called medullated corneal nerve fibres
- a pheochromocytoma
- tearless crying (occurs in >85% but is very rare in the general population)

How is MEN2B treated?
Without surgery to remove the thyroid, almost all individuals with MEN2B will develop a medullary thyroid cancer and almost all will die before age 20.

Surgery is preventative and is performed in the first year of life, usually around one month of age, as soon as the baby is strong enough for the surgery.

How is MEN2A diagnosed?
MEN2A is diagnosed clinically, with genetic testing to confirm the RET mutation and allow predictive testing of blood relatives. A clinical diagnosis of MEN2A is made when an individual patient has 2 of the 3 following types of endocrine tumours or cancers:

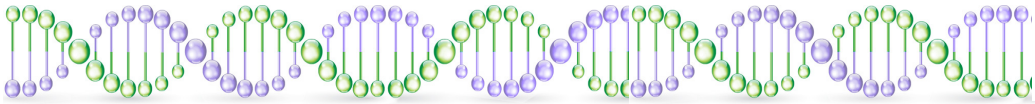
- medullary thyroid carcinoma
- phaeochromocytoma, a rare tumour affecting the adrenal gland
- a parathyroid adenoma or hyperplasia, usually associated with hyperparathyroidism

In individuals who carry a RET mutation, 50% will meet these criteria by age 50 and 70% by age 70.

…./2

Clinics in Sydney. Telehealth throughout Australia including to rural and regional areas
All Correspondence: PO Box 845, Broadway, NSW, 2007
All appointments: (+61 2) 9304 0438 Fax: (+61 2) 9304 0468 E:info@SydneyCancerGenetics.com.au
www.SydneyCancerGenetics.com.au
Hereditary Health and Hope

Multiple Endocrine Neoplasia syndrome Type 2 (MEN2) and the RET gene



How does a RET mutation cause cancer?
The RET gene is a growth gene. It effects tissues derived from the neural crest cells. These tissues include:

- the C cells in the thyroid gland (hence medullary thyroid cancer)
- the parathyroid cells (hence hyperparathyroidism)
- the chromaffin cells of the adrenal medulla (hence pheochromocytoma)
- the enteric autonomic plexus (may be associated with Hirschsprung disease)

When the RET gene is mutated, these cells grow when they shouldn't. This causes problems because of unregulated hormonal production and the cells can become cancerous and spread. In the case of the enteric autonomic plexus there is a loss of the normal function of these cells, which are located in the bowel, and can cause severe constipation that is diagnosed in childhood.

What is Medullary thyroid cancer?
Medullary thyroid cancers arise in the C cells of the thyroid. (These cells were previously known as parafollicular cells).

Medullary thyroid cancer is rare, accounting for less than 5% of all thyroid cancer. However, medullary thyroid cancers are much more likely to be aggressive (grow rapidly or spread even metastasise (spread) when very small). While nearly all thyroid cancer is found early and cured, if it is a medullary thyroid cancer, 20% are already metastatic at diagnosis and are very hard to treat.

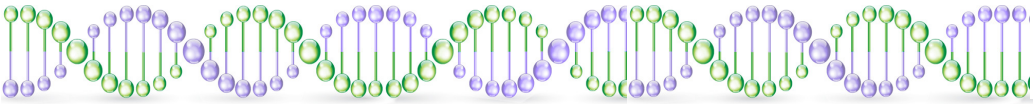
Medullary thyroid cancer occurs in around 50% of individuals with MEN2A by age 30 and >90% to 100% by age 70. For MEN2B, medullary thyroid cancer can occur very young, with almost 100% affected by age 10. The risk is related to the location of the specific RET mutation.

What is a pheochromocytoma?
A pheochromocytoma is a growth occurring in the adrenal medulla, a small gland that sits above each kidney. They are very rare. Pheochromocytoma cause problems by secreting the "flight or fight" hormones such as adrenalin. Symptoms include flushing, headaches, very high blood pressure and a racing heart. Pheochromocytoma can become cancerous, spreading (metastasising) to distant sites.

What is Primary Hyperparathyroidism?
There are 4 small parathyroid glands, that sit 2 on each side of the thyroid. They are important for keeping the calcium in the blood under steady control. Primary hyperparathyroidism occurs due to a growth within the gland itself while secondary hyperparathyroidism is simply the gland getting bigger in response to a calcium problem caused by another disease in the body (most commonly kidney disease).

..../3

Multiple Endocrine Neoplasia syndrome Type 2 (MEN2) and the RET gene



Management of Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
Screening for medullary thyroid cancer is not effective. Fortunately, surgery, called thyroidectomy, is preventative. Thyroidectomy is recommended by age 5 if it is a high risk mutation (as classified by the American Thyroid Association) and usually by age 10. The timing depends on the location of the mutation in the RET gene.

- Thyroidectomy is strongly recommended in first months of life for MEN2B, usually as soon as the baby is fit.
- Screening to detect a pheochromocytoma starts between ages 11 and 16. Screening includes annual blood pressure measurement and fasting free plasma metanephrines (the breakdown products of adrenalin).
- Primary hyperparathyroidism results in raised serum calcium and also high levels of parathyroid hormone (PTH) in the blood. Blood tests, starting between ages 11 and 16, are performed each year for MEN2A (but are not needed for MEN2B).

Is Multiple Endocrine Neoplasia syndrome type 2 (MEN2) inherited?
Yes. Multiple Endocrine Neoplasia syndrome type 2 is a hereditary cancer syndrome. There is a 50% chance of a person who carries a germline RET mutation, whether male or female, passing the mutation to their son or daughter. If a mutation is identified, then predictive testing is available for blood relatives. This testing is Medicare funded.

95% of people who meet the clinical criteria for MEN2A or MEN2B will be found to carry a RET mutation. In an individual with an isolated medullary thyroid cancer, the likelihood is around 30%.

The likelihood of a RET mutation in someone with a pheochromocytoma and no other features of MEN2 is around 5%. Generally, testing in this case is done via a panel of genes associated with a high risk of a pheochromocytoma including VHL, NF1, the SDH genes and the TMEM127 and MAX genes. Follow the links for more information on these genes and the hereditary cancer syndromes associated with them.

What are De Novo RET mutations?
In individuals with MEN2a, 5% of the time, they are the first person in their family to carry a RET mutation. For MEN2B it is the majority - 75%. This is called a “de novo” mutation, meaning "from new". That is, the mutation occurred either in the making of that particular sperm or egg or the first few cell divisions after fertilisation. In this situation, the parents are not affected but the mutation can be passed on to the next generation.

Does this sound like you or your family?
Has a medullary thyroid cancer been detected in you or has a RET mutation been detected in a blood relative? Medicare funded testing is available.
Make an appointment with Dr Hilda High at Sydney Cancer Genetics. It is a confidential opportunity to discuss your personal and family history of cancer and genetic testing can be organised, if needed.

More information is available on our website, including links to the following:

- The AMEN, the American Multiple Endocrine Neoplasia Support Organisation has details of support groups is for individuals and families affected by MEN2. They are based in the USA but have members worldwide.
- The Pheo Para Troopers support group is for individuals and families affected by pheochromocytoma. They are based in the USA but have members around the world.
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines
- The US National Library of Medicine website has more information about this syndrome.

Clinics in Sydney. Telehealth throughout Australia including to rural and regional areas
All Correspondence: PO Box 845, Broadway, NSW, 2007
All appointments: (+61 2) 9304 0438 Fax: (+61 2) 9304 0468 E:info@SydneyCancerGenetics.com.au