Published on *My46* (https://www.my46.org) 01/23/2022

My46 Trait Profile

Multiple Endocrine Neoplasia type 2

Other Names: Sipple syndrome (MEN2A); Mucosal Neuroma syndrome (MEN2B)

Multiple Endocrine Neoplasia type 2 is a group of genetic conditions in which individuals have a higher chance to have certain cancerous and noncancerous tumors. It is caused by mutations in the RET gene which makes the proto-oncogene Ret protein.

Characteristics of Multiple Endocrine Neoplasia type 2

Multiple Endocrine Neoplasia (MEN2) is a group of inherited conditions that increase the chance of developing tumors (overgrowth of cells) in certain endocrine (hormone-producing) tissues. There are three main subtypes of MEN2: MEN2A, MEN2B and Familial Medullary Thyroid Cancer (FMTC; see trait profile). A certain form of thyroid cancer called medullary thyroid cancer is the most common feature of MEN2. Almost all people with MEN2 will develop this cancer at some point during their lives. Other features are very variable between families.

MEN2A is the most common form of MEN2. In MEN2A, tumors in organs other than the thyroid can occur. These are usually benign (noncancerous) but can cause medical problems due to the high levels of hormones produced. These tumors include pheochromocytoma (a tumor of the adrenal gland an organ that sits on top of the kidney) and parathyroid adenoma (a tumor of the parathyroid glands an organ located in the neck on the thyroid gland). Pheochromocytomas produce hormones that can increase blood pressure and heart rate, and cause sweating and anxiety symptoms. Parathyroid adenomas cause high parathyroid hormone (PTH) and increased calcium (i.e., hyperparathyroidism). The high calcium can cause problems including kidney stones and osteoporosis. In MEN2A, medullary thyroid cancer typically occurs in early adulthood.

In MEN2B, individuals often develop pheochromocytomas, however parathyroid adenomas are less commonly seen. There are often additional features seen in MEN2B such as growths of the tongue, digestive tract, and a distinctive shape of the face and body. In MEN2B, medullary thyroid cancer typically occurs in early childhood and is more aggressive than in the other types of MEN2.

Diagnosis/Testing

Individuals with MEN2 have a change or mutation in a gene called RET. The RET gene is a proto-oncogene that gives instructions to make a protein that is involved in signaling within cells. When growth factors attach to the RET protein, cells divide, mature, and take on other functions. Individuals with MEN2 have a change or mutation that over-activate the RET proto-oncogene, making it a cancer-promoting gene. Mutations in different parts of this gene are associated with specific characteristics, such as the subtype of MEN2 and the age of thyroid cancer onset.

Management/Surveillance

Because almost every person with MEN2 will develop medullary thyroid cancer, many at young ages, preventive removal of the thyroid (i.e., prophylactic thyroidectomy) is recommended. The recommended age for thyroidectomy varies depending on the subtype of MEN2 and exact mutation identified. Regular testing for parathyroid and adrenal tumors is recommended for individuals with MEN2A or MEN2B. This is done through blood and urine tests. If there is any increase in parathyroid or adrenal hormones, additional tests or treatment could be needed.

The high blood pressure caused by pheochromocytoma can worsen suddenly during pregnancy or during surgery. Therefore, it is especially important for individuals with MEN2 to be tested for pheochromocytoma before pregnancy or surgery.

Mode of inheritance

MEN2 is inherited in an autosomal dominant pattern. This means inheriting one RET mutation is enough for an individual to be affected and show signs of MEN2. Most mutations causing MEN2A or FMTC are inherited from an affected parent or it can occur brand new (de novo) in an affected child.

Risk to family members

The risk to family members depends on whether or not the individual with MEN2 has a parent affected with MEN2. If a parent also has MEN2, the risk of having a child with MEN2 is 50% with each pregnancy. If a parent does not have MEN2, the risk of other siblings being affected is very low.

Special considerations

Mutations in the RET gene may also cause Hirschsprung disease (see trait profile), a condition in which a part of the large intestine does not work because it has not developed proper nerve stimulation. Hirschsprung disease can occur in some families with MEN2A or as a separate isolated condition. If Hirschsprung disease is present, surgery to remove the affected part of the large intestine is often needed.

Resources

Association for Multiple Endocrine Neoplasia Disorders
http://www.amend.org.uk
Genetics Home Reference: Multiple endocrine neoplasia
http://ghr.nlm.nih.gov/condition/multiple-endocrine-neoplasia

References

American Thyroid Association Guidelines Taskforce. (2009)."Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association." Thyroid 19(6): 565-612.
Moline J, Eng C. (Updated 10 January 2013). Multiple Endocrine Neoplasia Type 2. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1257/. Accessed [05/27/2013].
Raue, F. et al. (2012)."Clinical utility gene card for: multiple endocrine neoplasia type 2." European Journal of Human Genetics 20(1).

Created: 05/2013 **Created by:** Julie Mak, MS, MSc, LCGC
Updated: mm/yyyy **Edited by:** Seema Jamal, MSc, LCGC