

Multiple Endocrine Neoplasia

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Multiple endocrine neoplasia is a group of disorders that affect the body's network of hormone-producing glands called the endocrine system. Hormones are chemical messengers that travel through the bloodstream and regulate the function of cells and tissues throughout the body. Multiple endocrine neoplasia typically involves tumors (neoplasia) in at least two endocrine glands; tumors can also develop in other organs and tissues. These growths can be noncancerous (benign) or cancerous (malignant). If the tumors become cancerous, the condition can be life-threatening.

Keywords: genetic conditions

1. Introduction

The major forms of multiple endocrine neoplasia are called type 1, type 2, and type 4. These types are distinguished by the genes involved, the types of hormones made, and the characteristic signs and symptoms.

Many different types of tumors are associated with multiple endocrine neoplasia. Type 1 frequently involves tumors of the parathyroid glands, the pituitary gland, and the pancreas. Tumors in these glands can lead to the overproduction of hormones. The most common sign of multiple endocrine neoplasia type 1 is overactivity of the parathyroid glands (hyperparathyroidism). Hyperparathyroidism disrupts the normal balance of calcium in the blood, which can lead to kidney stones, thinning of bones, nausea and vomiting, high blood pressure (hypertension), weakness, and fatigue.

The most common sign of multiple endocrine neoplasia type 2 is a form of thyroid cancer called medullary thyroid carcinoma. Some people with this disorder also develop a pheochromocytoma, which is an adrenal gland tumor that can cause dangerously high blood pressure. Multiple endocrine neoplasia type 2 is divided into three subtypes: type 2A, type 2B (formerly called type 3), and familial medullary thyroid carcinoma (FMTc). These subtypes differ in their characteristic signs and symptoms and risk of specific tumors; for example, hyperparathyroidism occurs only in type 2A, and medullary thyroid carcinoma is the only feature of FMTc. The signs and symptoms of multiple endocrine neoplasia type 2 are relatively consistent within any one family.

Multiple endocrine neoplasia type 4 appears to have signs and symptoms similar to those of type 1, although it is caused by mutations in a different gene. Hyperparathyroidism is the most common feature, followed by tumors of the pituitary gland, additional endocrine glands, and other organs.

2. Frequency

Multiple endocrine neoplasia type 1 affects about 1 in 30,000 people; multiple endocrine neoplasia type 2 affects an estimated 1 in 35,000 people. Among the subtypes of type 2, type 2A is the most common form, followed by FMTc. Type 2B is relatively uncommon, accounting for about 5 percent of all cases of type 2. The prevalence of multiple endocrine neoplasia type 4 is unknown, although the condition appears to be rare.

3. Causes

Mutations in the *MEN1*, *RET*, and *CDKN1B* genes can cause multiple endocrine neoplasia.

Mutations in the *MEN1* gene cause multiple endocrine neoplasia type 1. This gene provides instructions for producing a protein called menin. Menin acts as a tumor suppressor, which means it normally keeps cells from growing and dividing too rapidly or in an uncontrolled way. Although the exact function of menin is unknown, it is likely involved in cell functions such as copying and repairing DNA and regulating the activity of other genes. When mutations inactivate both copies of the *MEN1* gene, menin is no longer available to control cell growth and division. The loss of functional menin allows cells to divide too frequently, leading to the formation of tumors characteristic of multiple endocrine neoplasia type 1. It is unclear why these tumors preferentially affect endocrine tissues.

Mutations in the *RET* gene cause multiple endocrine neoplasia type 2. This gene provides instructions for producing a protein that is involved in signaling within cells. The RET protein triggers chemical reactions that instruct cells to respond to their environment, for example by dividing or maturing. Mutations in the *RET* gene overactivate the protein's signaling function, which can trigger cell growth and division in the absence of signals from outside the cell. This unchecked cell division can lead to the formation of tumors in endocrine glands and other tissues.

Mutations in the *CDKN1B* gene cause multiple endocrine neoplasia type 4. This gene provides instructions for making a protein called p27. Like the menin protein, p27 is a tumor suppressor that helps control the growth and division of cells. Mutations in the *CDKN1B* gene reduce the amount of functional p27, which allows cells to grow and divide unchecked. This unregulated cell division can lead to the development of tumors in endocrine glands and other tissues.

3.1. The Genes Associated with Multiple Endocrine Neoplasia

- CDKN1B
- MEN1
- RET

4. Inheritance

Multiple endocrine neoplasia type 1 usually has an autosomal dominant pattern of inheritance. People with this condition are born with one mutated copy of the *MEN1* gene in each cell. In most cases, the altered gene is inherited from an affected parent. The remaining cases are a result of new mutations in the *MEN1* gene and occur in people with no history of the disorder in their family.

Unlike most other autosomal dominant conditions, in which one altered copy of a gene in each cell is sufficient to cause the disorder, two copies of the *MEN1* gene must be altered to trigger tumor formation in multiple endocrine neoplasia type 1. A mutation in the second copy of the *MEN1* gene occurs in a small number of cells during a person's lifetime. Almost everyone who is born with one *MEN1* mutation acquires a second mutation in certain cells, which can then divide in an unregulated way to form tumors.

Multiple endocrine neoplasia type 2 and type 4 are also inherited in an autosomal dominant pattern. In these cases, one copy of the mutated gene is sufficient to cause the disorder. Affected individuals often inherit an altered *RET* or *CDKN1B* gene from one parent with the condition. Some cases, however, result from new mutations in the gene and occur in people without other affected family members.

5. Other Names for This Condition

- adenomatosis, familial endocrine
- endocrine neoplasia, multiple
- familial endocrine adenomatosis
- MEA
- MEN
- multiple endocrine adenomatosis
- multiple endocrine neoplasms

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