Cleveland Clinic
Genomic Medicine Institute

Multiple Endocrine Neoplasia Type 2 (RET gene)

Multiple Endocrine Neoplasia Type 2 (MEN 2) is a hereditary condition that predisposes individuals to certain endocrine malignancies and tumors. There are three subtypes of MEN 2 – MEN 2A, FMTC, and MEN 2B.

MEN 2A, the most common subtype, causes medullary thyroid cancer (MTC) in almost all individuals (>95%), adrenal pheochromoctyoma in about 50%, and hyperparathyroidism in 20-30%. Typically, individuals with MEN 2A first present with medullary thyroid cancer in the second or third decade of life. However, up to 27% can have a pheochromocytoma as their first symptom. Hyperparathyroidism is usually diagnosed several years after MTC.

In families with Familial Medullary Thyroid Cancer (FMTC), medullary thyroid cancer is the only manifestation of MEN 2.

MEN 2B makes up about 5% of all cases of MEN 2. This subtype is characterized by medullary thyroid cancer very early in childhood, a 50% risk of adrenal pheochromocytoma, and no increased risk of hyperparathyroidism. Individuals with MEN 2B have characteristic physical features, including neuromas (small benign tumors on the lips, tongue, eyelid), ganglioneuromatosis of the gastrointestinal tract, and a Marfanoid body habitus (tall and thin, flexible).

All subtypes of MEN 2 are caused by errors, or mutations, in the *RET* gene. The gene is passed on in families by autosomal dominant transmission, whereby each child of a carrier has a 50% (1 in 2) chance of inheriting the abnormal copy from the carrier parent. In some rare instances, an individual with MEN 2 may be the first in their family to have a *RET* mutation. This is referred to as a *de novo* mutation. Five percent of individuals with MEN 2A have a *de novo* mutation. Fifty percent of those with MEN 2B have a *de novo* mutation.

The Center for Personalized Genetic Healthcare