

Phenotype Specific RET Oncogene Mutations and Multiple Endocrine Neoplasia Syndromes

Multiple endocrine neoplasia (MEN) syndromes constitute a family of disorders characterized by neoplasias of 2 or more endocrine tissues. Medullary thyroid carcinoma (MTC) is a tumor of the thyroid C cells that can occur sporadically or as part of the inherited cancer syndromes MEN IIA, MEN IIB, and familial MTC (FMTC).

Individuals with MEN IIA are predisposed to C-cell hyperplasia or MTC, pheochromocytoma, and hyperparathyroidism. Individuals with MEN IIB are predisposed to mucosal neuromas and marfanoid habitus.

The loci for MEN IIA, MEN IIB, and FMTC have been mapped to an interval on chromosome 10q11.2. The RET proto-oncogene is also located in this region. The RET proto-oncogene is a receptor tyrosine kinase gene expressed in MTC and pheochromocytoma and in normal thyroid and adrenal tissue.

Mulligan et al reviewed 118 unrelated families with inherited MTC for mutations of the RET proto-oncogene. They found mutations in 1 of the 5 cysteines of the proto-oncogene in 97% of patients with MEN IIA and in 86% of the patients with FMTC, but not in the MEN IIB patients. Eighty-four percent of the MEN IIA mutations affected codon 634, and patients with a Cys634 to

Arg substitution had a greater risk of developing parathyroid tumors than those with other codon 634 mutations.

They concluded that the precise location of the mutation corresponds with the clinical phenotype and that mutations in the 634 codon may be predictive in families predisposed to adrenal or parathyroid disease. The basis of the tissue specificity of these RET mutations is unclear, but the authors suggested the possibility of tissue-specific differences in RET expression or in RET protein interactions.

Mulligan LM, et al. *Nat Genet* 1994;6:70-75.

Editor's comment: *It is not absolutely clear that there is just 1 mutation for MEN. The identification of a mutation for phenotype-specific RET mutations is important for early screening in individuals known to be at risk. Prenatal screening for the RET mutation, however, may prove to be controversial and cause serious ethical and moral dilemmas, since the decision to terminate a pregnancy is always difficult. This is especially true in adult-onset diseases.*

Judith G. Hall, MD