Multiple Endocrine Neoplasia Type 2 (MEN2): RET Mutation

*RET* gene mutations are associated with multiple endocrine neoplasia type 2 (MEN2). The clinical presentation varies by specific *RET* mutation. MEN2 is divided into three subtypes: MEN2A, MEN2B and Familial Medullary Thyroid Carcinoma. In all subtypes, there is a very high risk of developing medullary thyroid cancer (MTC).¹ The clinical presentation and cancer risks vary by specific *RET* mutation.

The *RET* gene mutation c.1900T>C (p.Cys634Arg, or codon C634) is classified as a high-risk mutation by The American Thyroid Association (ATA). Codon C634 mutations are associated with MEN2A.¹

**Codon 634 Cancer Risks and General Management Recommendations**

Below are recommendations for management based on the Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma (2015).¹

<table>
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<tr>
<th>Cancer Type/Clinical Feature</th>
<th>Codon 634 Mutation Carrier Risks</th>
<th>Surveillance/Management Recommendations¹</th>
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</table>
| Medullary Thyroid Cancer (typically multifocal) | 95% (MTC often develops in first years of life) | **Pre-Thyroidectomy Screening**  
  • Annual physical examination, neck ultrasounds, and serum calcitonin levels beginning at age 3  
**Surgery**  
  • Prophylactic thyroidectomy should be considered at or before age 5 based upon on serum calcitonin levels  
  • If there is elevated calcitonin, the minimum surgical procedure should be total thyroidectomy with central lymph node dissection  
  • A more aggressive neck dissection should be performed if there is evidence of involved lymph nodes in the lateral neck  
**Post-Thyroidectomy Screening**  
  • Approximately 50% of individuals diagnosed with MTC who have undergone total thyroidectomy and neck nodal dissections have recurrent disease  
  • Thyroid glands removed from individuals who had normal plasma calcitonin concentrations have been found to contain MTC²  
  • Physical exam, neck ultrasound, and measurements of calcitonin and CEA every six months for one year, then annually after that  
**Chemotherapy**  
  • Tyrosine kinase inhibitors (TKIs) targeting RET and VEGFR tyrosine kinases have been shown to be effect therapy for metastatic MTC  
  • These drugs can be used as single-agent, first-line systemic therapies  
| Pheochromocytoma (typically benign, often bilateral) | 35% by age 3⁰  
  52% by age 50  
  88% by age 77 | **Screening**  
  • Annual measurement of plasma or 24 hour-urinary fractionated metanephrines beginning at age 11 |
Additional Findings: Rarely, patients with mutations in codon 634 mutations have been reported to develop cutaneous lichen amyloidosis. This skin condition presents with lesions, particularly on the back and scapular area that improves with sun exposure and worsens with stress. These lesions can present at an early age. Consideration of a dermatological exam can be given.

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial RET mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References


