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Multiple Endocrine Neoplasia Type 2 (MEN2): *RET* Mutation

RET gene mutations are associated with multiple endocrine neoplasia type 2 (MEN2). 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.2410G>A (p.Val804Met or codon V804M) is classified as a **moderate-risk mutation** by The American Thyroid Association (ATA). This means that risk for aggressive medullary thyroid cancer may be reduced in comparison with other mutations in the *RET* gene. *RET* V804M mutations are associated with MEN2A.[1]

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]

Cancer Type/Clinical Feature	***RET* V804M Mutation Carrier Risks**	**Surveillance/Management Recommendations[1]**
Medullary Thyroid Cancer (typically multifocal)	Up to 95% (MTC often develops in young adulthood)	*Pre-Thyroidectomy Screening* • Annual physical examination, neck ultrasounds, and serum calcitonin levels beginning at age 5 *Surgery* • The timing of prophylactic thyroidectomy should be based on the detection of an elevated serum calcitonin level; however, 6-month or annual evaluations may extend to several years or decades. Parents who are concerned about a long-term evaluation program may opt to have their child's thyroid gland removed around 5 years of age. The surgeon and pediatrician caring for the patient, in consultation with the child's parents, should decide the timing of thyroidectomy. • 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 MTC[2] • Follow-up with evaluation every 6 months for 1 year, then annually if serum calcitonin remains undetectable or within normal range *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)	~10%[1]	*Screening* • Annual measurement of plasma or 24 hour-urinary fractionated metanephrines and normetanephrines beginning at age 16 • MRI and/or CT should be performed with biochemical evidence or symptoms consistent with a pheochromocytoma (i.e. hypertension, heavy sweating, tachycardia, pallor, dyspnea) • Other screening studies, such as scintigraphy or positron emission tomography, may be warranted in some individuals • Prior to any surgery, the presence of a functioning pheochromocytoma should be excluded • Females should be screened prior to or early in pregnancy *Surgery* • For unilateral pheochromocytoma, laparoscopic adrenalectomy or retroperitoneoscopic adrenalectomy is preferred treatment • Subtotal cortical-sparing adrenalectomy (open or laparoscopic) is advocated for bilateral pheochromocytoma • Adrenalectomy should be performed before thyroidectomy to avoid intraoperative catecholamine crisis • If a pheochromocytoma is identified during pregnancy, it should be treated prior to the third trimester • Individuals with bilateral adrenalectomy should be educated on administration of corticosteroids and should wear an emergency bracelet indicating the possibility of adrenal insufficiency
Hyperparathyroidism	~10% Average age of onset is 33 years[1]	*Screening* • Annual biochemical screening of albumin-corrected calcium or ionized serum calcium measurements (with or without serum intact-parathyroid hormone) beginning at age 16 *Surgery* • Visibly enlarged glands should be resected • If all four glands are enlarged, consider a subtotal parathyroidectomy or a total parathyroidectomy with autograft to the forearm

Other Findings: Rarely, patients have been reported to develop cutaneous lichen amyloidosis.[3] 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.

Additional Considerations: A rare subset of individuals with *RET* codon V804M mutations also carry additional mutations on the same allele involving both *RET* codon V804M and either *RET* codon Y806C, S904C, E805K, or Q781R mutations.[4-7] The occurrence of multiple *RET* mutations may cause an unusual clinical presentation compared to that seen with the corresponding single *RET* mutations, including more aggressive MTC. The patient's test did NOT indicate an additional mutation on the same allele.

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

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