CURRENT ONCOLOGY
A Canadian Cancer Research Journal

REVIEW ARTICLE

RARE CANCER SERIES

A primer on the genetics of medullary thyroid cancer

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ABSTRACT

Medullary thyroid cancer is a rare type of neuroendocrine tumour that arises from the parafollicular cells (C cells) of the thyroid gland. It accounts for 3%–5% of thyroid cancer cases. Close to 25% of cases are familial, and 75% are considered sporadic. Familial cases are associated with a germline *RET* mutation; 43%–65% of sporadic cases harbour a somatic event in the gene. Germline *RET* mutations are associated with the autosomal-dominant inherited multiple endocrine neoplasia (MEN) 2A and 2B syndromes and the isolated familial medullary thyroid cancer syndrome. More than 100 *RET* codon mutations have been reported to date, with genotype–phenotype correlations that include the extent and aggressiveness of the medullary thyroid cancer and the presence of other features of the MEN2 syndromes. The latter include pheochromocytoma–paraganglioma, hyperparathyroidism, cutaneous lichen amyloidosis, and Hirschsprung disease.

In this narrative review, we focus on *RET* proto-oncogene physiology and pathogenesis induced by germline and somatic *RET* mutations, the genotype–phenotype correlation, and the management and follow-up of patients with germline-mutated medullary thyroid cancer.

Key Words Medullary thyroid cancer, multiple endocrine neoplasia type 2, *RET,* vandetanib

***Curr Oncol.* 2019 December;26(6):389-394** **www.current-oncology.com**

INTRODUCTION

Medullary thyroid cancer (MTC) is a rare type of neuroendocrine tumour arising from parafollicular cells (C cells) of the thyroid gland. It accounts for 3%–5% of thyroid cancer cases[1]. The most common clinical presentation of MTC is a solitary thyroid nodule, and investigations typically include biochemistry—more specifically, measurement of calcitonin and carcinoembryonic antigen (CEA), ultrasonography, and fine-needle aspiration. Calcitonin and CEA are secreted by the C cells of the thyroid and serve as tumour markers in MTC. Close to 25% of cases are familial, and 75% are considered sporadic[2]. Familial cases are caused by a germline *RET* proto-oncogene mutation on chromosomal band 10q11.2. Consistent with the prominent role of *RET,* sporadic cases of MTC harbour a somatic *RET* mutation in a significant 43%–65% of cases[3]. Somatic *RAS* mutations are also present in 20%–25% of sporadic cases. Germline *RET* mutations give rise to autosomal-dominant inherited multiple endocrine neoplasia (MEN) 2A and 2B syndromes and isolated familial medullary thyroid cancer (FMTC) syndrome[4]. More than 100 *RET* mutations have been reported to date, and there is a direct genotype–phenotype correlation between *RET* mutations and the extent and aggressiveness of MTC and the other features of MEN2 syndromes, including pheochromocytoma–paraganglioma, hyperparathyroidism, cutaneous lichen amyloidosis, and Hirschsprung disease[5].

In this narrative review, we discuss *RET* proto-oncogene physiology and pathogenesis induced by germline and somatic *RET* mutations, the genotype–phenotype correlations, and the management and follow-up of patients with germline-mutated MTC.

REVIEW

RET Proto-oncogene Physiology and Mutational Pathogenesis

The RET protein is a tyrosine kinase receptor known to drive growth and differentiation in tissues arising from the neural crest. The RET protein comprises an extracellular ligand-binding domain, with cadherin-like and cysteine-rich domains; a single transmembrane domain; and intracellularly, two tyrosine kinase subdomains, TK1 and TK2[6]. For RET to be activated, 1 of its 4 ligands—namely, artemin,

Sanofi Genzyme supported the publication of this article with an unrestricted educational grant. They had no influence over the content.

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persephin, neurturin, or glial cell line–derived neutrophic factor—requires binding to a specific co-receptor (glial cell line–derived neutrophic factor receptor family α-1, α-2, α-3, or α-4). In turn, binding results in RET dimerization, cross-autophosphorylation, and intracellular substrate phosphorylation[7–11].

Although most of the known inherited predispositions to neoplasia are caused by loss-of-function mutations in tumour suppressor genes, *RET* mutations represent gain-of-function mutations[12]. Most germline mutations in MEN2A syndrome are attributable to extracellular domain mutations in the cysteine-rich domain. Common examples include *RET* mutations in exons 10 and 11, with a codon 634 mutation in exon 11 being the most common gene variant in MEN2A[13]. Such mutations lead to ligand-independent dimerization of receptor molecules and activation of the intracellular signalling pathway.

Germline mutations in intracellular TK domains such as exon 13 (codon 768), exon 14 (codon 804), and exon 15 (codon 891) give rise to FMTC, even though they represent a small proportion of causal mutations for that syndrome. Exon 13 mutations (codons 790 and 791) are relatively uncommon and give rise to MEN2A or FMTC[14]. An intracellular TK2 domain mutation on exon 16 (codon 918) is responsible for more than 95% of cases of MEN2B and is associated with aggressive behaviour and poor prognosis[15]. A codon 883 mutation in exon 15 has been associated with a small proportion of MEN2B cases[16–18]. Interestingly, although *RET* mutations cause gain of function in thyroid C cells, some can also cause a loss of function in the colon, giving rise to congenital megacolon and Hirschsprung disease[19–22]. Furthermore, as already mentioned, 75% of MTC cases are sporadic, but 43%–65% of those cases harbour a somatic *RET* mutation, typically in exon 16 (codon 918)[23–29]. In addition, *RAS* mutations are detected in 20%–25% of sporadic *RET* wild-type MTC cases[30], highlighting a potential mechanism for lack of sensitivity to *RET* inhibitors.

Genotype–Phenotype Correlation

Clinically, MEN2A syndrome has been classified into 3 subtypes: classical MEN2A, which includes MTC, pheochromocytoma, and parathyroid hyperplasia; MEN2A with Hirschsprung disease; and MEN2A with cutaneous lichen amyloidosis[31]. The distinct MEN2B syndrome is accompanied by MTC and pheochromocytomas, but parathyroid hyperplasia is generally not part of the syndrome. Patients with MEN2B also have distinctive features, including mucosal neuromas, intestinal ganglioneuromas, chronic constipation, megacolon, a Marfanoid habitus, and myelinated corneal nerves. A variant of MEN2A, FMTC refers to familial cases of MTC with a germline mutation, but without associated parathyroid or adrenal disease. It was initially defined using these strict criteria: more than 10 family members who carry the germline mutation, multiple carriers more than 50 years of age, and an adequate history, particularly in older family members[32]. A more recent and less rigid definition states that a diagnosis of FMTC requires only 4 affected family members with germline-mutated *RET* and without hyperparathyroidism or pheochromocytoma[33].

Genotype–phenotype correlations between various *RET* mutations and clinical manifestations are well-established, as detailed in Figure 1. Codon 918 mutation on exon 16 is responsible for 95% of cases of MEN2B, and codon 883 mutation on exon 15 is responsible for fewer than 5%. Of all MEN2 cases, MEN2B accounts for 5%, and in affected patients, MTC has been reported to occur earlier (as early as 9 months of age in codon 918 mutation) and to have a tendency toward more aggressive behaviour. Codon 918 mutation on exon 16 has therefore been assigned the highest risk category, and codon 883 mutation on exon 15, the high-risk category, in the 2015 American Thyroid Association (ATA) guideline. In such cases of MEN2B, prophylactic thyroidectomy is recommended before a known carrier infant reaches 1 year of age[31].

Codon 634 mutation on exon 11 is the most common germline mutation in MEN2A and exemplifies the classical MEN2A syndrome[13]. In carriers of that mutation, MTC has been detected as early as 15 months, and the penetrance of pheochromocytoma increases with age up to 88% at 77 years of age[34]. Moreover, with the mutation, the penetrance of hyperparathyroidism is approximately 20%[35]. The codon 634 mutation has also been associated with cutaneous lichen amyloidosis. It was therefore also assigned a high-risk category in the 2015 ATA guideline, and prophylactic thyroidectomy is recommended at or before the age of 5 years in children who harbour the mutation[31].

Exon 10 (codons 609, 611, 618, 620), exon 8 (codon 533), exon 11 (codons 630, 631, 666), exon 13 (codon 790), exon 14 (codon 804), and exon 15 (codon 891) mutations are assigned to a moderate risk of MTC and a varying risk of pheochromocytoma–paraganglioma in the 2015 ATA guideline[31]. Exon 13 (codon 768) and exon 16 (codon 912) mutations are associated with a moderate risk of MTC, but not with pheochromocytoma–paraganglioma. Exon 10 (codons 609, 611, 618, 620, 630), exon 11 (codon 634), exon 14 (codon 804), and exon 15 (codon 891) mutations have been associated with hyperparathyroidism. Together with exon 11 (codon 634) mutation, exon 14 (codon V804M) mutation is associated with cutaneous lichen amyloidosis. All exon 10 mutations are associated with Hirschsprung disease (Figure 1). For all ATA moderate-risk disease, prophylactic total thyroidectomy is recommended when serum calcitonin becomes elevated or before the individual reaches adulthood, depending on patient and parent preference[31].

Genetic Screening

Current guidelines recommend germline *RET* testing in all patients with a new diagnosis of MTC or C cell hyperplasia[31]. Initial testing should include next-generation sequencing of exons 10, 11, 13, 14, 15, and 16; the remaining exons should be sequenced if the initial screen is negative, but clinical suspicion of a hereditary MTC syndrome remains high. That approach is particularly relevant in cases in which surgical pathology identifies C cell hyperplasia. Infants or young children with a MEN2B phenotype should be tested for exon 16 (codon 918) mutation first, and if negative, they should be tested for exon 15 (codon 883) mutation. Similarly, parents of infants and young children with a MEN2B phenotype should undergo *RET* mutation testing. Patients with cutaneous lichen amyloidosis and infants or young children with Hirschsprung disease should receive *RET*

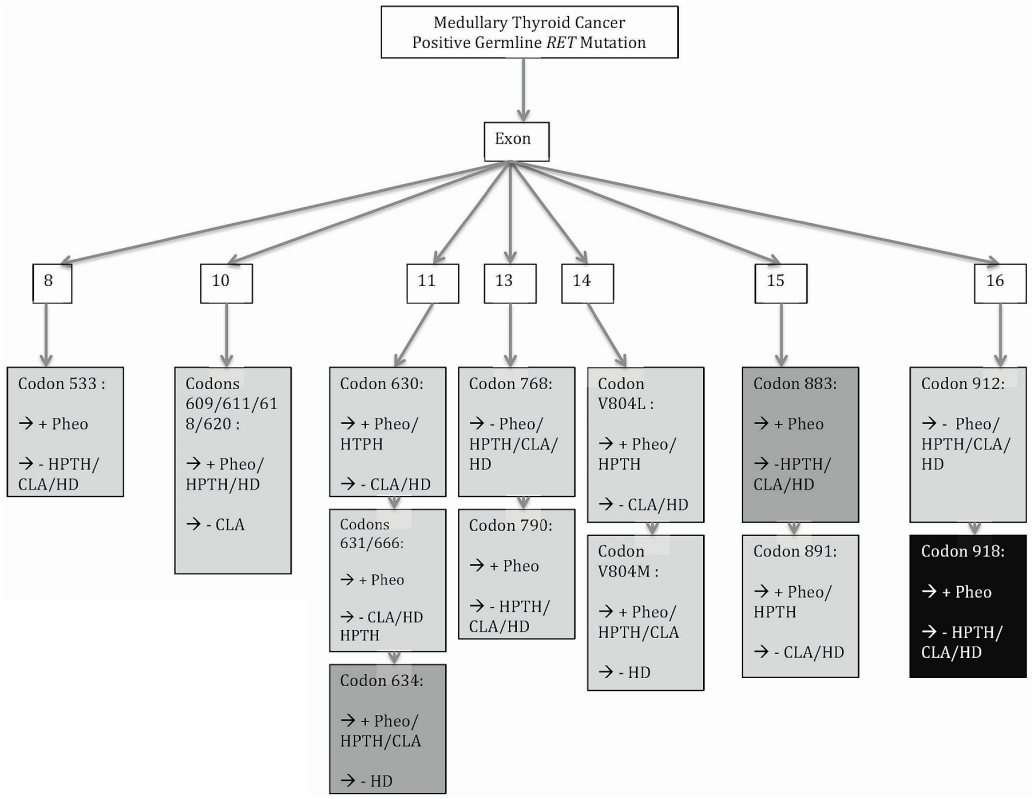

FIGURE 1 Genotype–phenotype correlation in medullary thyroid cancer (MTC). Pale grey boxes = moderate MTC risk; dark grey boxes = high MTC risk; black box = highest MTC risk; Pheo = pheochromocytoma; HPTH = hyperparathyroidism; CLA = cutaneous lichen amyloidosis; HD = Hirschsprung disease.

testing and genetic counselling. Genetic counsellors who are familiar with the MEN2 syndromes should be involved early as consultants. Once an index patient is found to be positive for a *RET* germline mutation, first-degree relatives should be offered genetic screening and appropriate counselling. That approach is essential, because MTC can be a life-threatening disease that is preventable with early prophylactic thyroidectomy. Although 43%–65% of sporadic MTC cases have somatic mutations in the *RET* gene within tumour cells, and one study showed that somatic mutations in exons 15 and 16 were associated with worse prognosis, tumour testing is not recommended or routinely performed.

Management and Follow-up of Germline *RET*-Positive Patients

As already mentioned, the current ATA guideline[31] concerning MTC recommends that patients who harbour mutations in the highest risk category (MEN2B) should undergo prophylactic thyroidectomy before the age of 1 year. Those who harbour mutations in the high-risk category (codon 634 mutations) should undergo thyroidectomy before reaching the age of 5 years. Those who harbour a moderate-risk mutation should be assessed by physical examination, thyroid ultrasonography, and serum calcitonin and CEA levels at age 5 and then every 6–12 months. The timing of thyroidectomy could be as early as age 5 or when reaching adulthood, depending on patient and parent preference.

Screening for pheochromocytoma should begin at the age of 11 years for children in the high- and highest-risk categories and by the age of 16 years for those in the moderate-risk category. These individuals should undergo screening (by plasma free metanephrines, or by 24-hour urine collection for metanephrines and catecholamines) annually, and adrenal imaging with computed tomography or magnetic resonance imaging is recommended if the biochemical screening is positive. The 24-hour urine metanephrines and catecholamines test is considered positive if those compounds are twice the upper limit of normal; a plasma free metanephrines level higher than the upper limit of normal is considered positive[31]. Individuals with a diagnosis of MTC should be screened for a pheochromocytoma before thyroidectomy, and adrenalectomy should precede thyroid surgery if a pheochromocytoma is diagnosed. Women with MEN2 who are planning a pregnancy or who are pregnant should be screened for a pheochromocytoma, and if one is detected, they should be treated before the third trimester.

Depending on the patient's risk category, screening for hyperparathyroidism should start at the same time as screening for pheochromocytoma. Bloodwork, including albumin-corrected calcium or ionized calcium, with an intact parathyroid hormone level, should be undertaken at least annually, and if positive, should be followed with localization studies such as sestamibi imaging and neck

ultrasonography or computed tomography. In patients with hyperparathyroidism, only visibly enlarged glands should be resected. If all glands are enlarged, surgical options include subtotal parathyroidectomy and total parathyroidectomy with a heterotopic autograft.

Once a diagnosis of MTC is suggested in a fine-needle aspiration cytology specimen from a patient with a thyroid nodule, next steps include a physical examination, CEA and calcitonin measurement, testing for *RET* genetic mutation, and exclusion of pheochromocytoma or hyperparathyroidism. All patients with biopsy-proven MTC (both sporadic and germline-mutated) should undergo neck ultrasonography. In the context of extensive neck disease, signs and symptoms of regional or distant metastases or calcitonin greater than 500 ng/L should lead to imaging studies (structural imaging of head and neck, chest, and liver, and bone scintigraphy). If there is no evidence of distant metastases, the patient should then undergo total thyroidectomy with central-compartment lymph node dissection. If there are positive cervical lymph nodes or if the patient's calcitonin level is greater than 200 ng/L, then lateral-compartment neck dissection should be also performed[31].

Postoperatively, in all cases of MTC, serum calcitonin and CEA should be measured after 3 months. If levels are undetectable or within the normal range, they should be measured again every 6 months for 1 year, then annually thereafter indefinitely. If the postoperative serum calcitonin is less than 150 ng/L, a physical examination and neck ultrasonography should be performed. If those tests are negative, the patient should undergo physical examination and biochemical testing every 6 months. If postoperative serum calcitonin is greater than 150 ng/L, then more extensive imaging—including neck, chest, abdomen, and pelvis, with bone scintigraphy—should be performed. If persistent or recurrent locoregional disease without distant metastases is identified on imaging, then compartmental dissection of image-positive or biopsy-positive disease in the central or lateral compartments should be performed.

Postoperative adjuvant external-beam radiation therapy (EBRT) is indicated in patients at high risk of recurrence as indicated by microscopic or macroscopic residual MTC, extrathyroidal extension, extensive lymph node metastases, and risk of airway obstruction. Isolated brain metastases might be amenable to surgical resection or EBRT. Spinal cord compression can be treated with urgent glucocorticoid therapy, surgical decompression, or EBRT if the individual is not a surgical candidate. Denosumab or bisphosphonates can be considered for treating painful bone metastases. Evidence about management of painful bone metastases of MTC is scarce, but one small study showed improvement in the quality of life of patients with bone metastases from thyroid cancer treated with pamidronate[36]; use of denosumab is extrapolated from evidence for other solid tumours. Solitary lung metastases can be treated with surgical resection or radiofrequency ablation. Similarly, hepatic metastases that are large and isolated could be considered for surgical resection or embolization (or a combination)[37–40]. In patients who show disease progression despite total thyroidectomy and EBRT, with a significant MTC tumour burden and symptomatic or progressive metastases, systemic therapy with tyrosine kinase inhibitors such as vandetanib or cabozantinib should be used in the first line. Those two compounds have been associated with a significant increase in progression-free survival in prospective randomized double-blind phase III clinical trials when compared with placebo[41–45]. Future perspectives for the management of advanced and metastatic MTC include the anticipated results of phase I and II trials of RET inhibitor molecules, namely LOXO-292 (LIBRETTO trial, NCT03157128 at https://ClinicalTrials.gov/) and BLU-667 (ARROW trial, NCT03037385).

Finally, for the management of diarrhea induced by peptides (such as calcitonin) secreted by MTC, milder cases can be managed with anti-motility agents (loperamide or codeine); more severe cases can be treated with somatostatin analogs or local therapies such as metastases resection or embolization, and treatment of the primary tumour. Another possible complication of MTC is ectopic Cushing syndrome because of secretion of adrenocorticotropic hormone or corticotropin-releasing hormone. Patients should be treated promptly with medical therapy including ketoconazole, mifepristone, aminoglutethimide, metyrapone, or mitotane; in refractory cases, bilateral surgical adrenalectomy is often necessary.

SUMMARY

Medullary thyroid cancer accounts for 3%–5% of thyroid cancer cases, and 25% of those cases are attributable to a germline *RET* proto-oncogene mutation. There is a reasonably direct genotype–phenotype correlation between the various mutations and the extent and aggressiveness of the medullary thyroid cancer and the presence of other features of the MEN2 syndrome. Early genetic screening of patients with a new diagnosis of MTC, first-degree relatives of index patients with *RET*-positive disease, and children with MEN2B phenotypes (cutaneous lichen amyloidosis or Hirschsprung disease) is paramount because prophylactic thyroidectomy can prevent MTC, which can develop into a life-threatening disease. Close follow-up of *RET* mutation carriers is also imperative to detect pheochromocytoma and parathyroid hyperplasia early. Treatment of MTC, whether positive or negative for germline *RET* mutation, is primarily surgical, including total thyroidectomy and neck dissection. Adjuvant therapy includes EBRT and, when distant metastases are detected, surgical resection, EBRT, or systemic therapies (including tyrosine kinase inhibitors) are the mainstay of treatment. Further studies are needed to clarify the optimal management of locally advanced and metastatic MTC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: MKK has received fees as consultant from Eisai and Bayer and has also received research support from Ipsen. SE has received fees as consultant from Eisai, Bayer, Pfizer, Ipsen, and Novartis. The remaining authors have no conflicts to disclose.

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