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## Medullary Thyroid Carcinoma Associated with *RET* Mutations Located in Exon 8

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### 1. Introduction

Medullary thyroid carcinoma is a neuroendocrine tumor which accounts for 5-10% of all thyroid cancers, with a various clinical course, being either an extremely benign tumor or an aggressive variant with a high mortality rate. Medullary thyroid carcinoma is sporadic in 80% of cases while in 20% of cases it follows a hereditary pattern, known as isolated familial MTC or multiple endocrine neoplasia type 2 syndromes, transmitted in an autosomal-dominant manner. Genetic analysis of the *RET* protooncogene constitutes an excellent powerful diagnostic tool for medullary thyroid carcinoma, especially for the hereditary form. Somatic, germline but also *de novo* mutations have all been associated with sporadic and hereditary forms of the disease and exons 10,11,13-16 of the *RET* gene locus are mainly involved. However, accumulating data support the association of other exons, including exon 8, with MTC but more studies need to be done, in order to provide more information about its role on the disease start, progression, potential and penetrance. At present, a “complete” germline *RET* testing should be performed in all MTC patients, independently of the family history and especially in the case of a negative testing, should include “non classical” exons, including exon 8.

### 2. Medullary thyroid carcinoma

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor which originates from the parafollicular C-cells of the thyroid gland, accounting for 5-10% of all thyroid cancers. (Pacini, 2010, Alevizaki 2006, Leboulleux 2004) Nowadays, the rate of MTC diagnosis gradually increases due to high awareness and thus careful investigation. MTC is a multifacet disease being either an extremely benign tumor or an aggressive variant which is associated with a high mortality rate because of lack of appropriate therapeutic regimens. (Pacini, 2010, Alevizaki 2006, Leboulleux 2004, Roman 2006)

MTC, is sporadic in 80% of cases (SMTC), presenting as an asymptomatic, accidentally found neck mass in the middle age, which spreads to regional lymph nodes in up to 50% of cases, as well as to distant sites (mediastinum, liver, lungs, bone). (Moo-Young 2009, Raue 2010, Alevizaki 2009) However, in 7% of individuals with apparently sporadic tumors, genetic screening revealed germline mutations of the RET (REarranged during Transfection) protooncogene (*RET*), indicating an overdiagnosis of SMTC in the absence of genetic screening. (Elisei 2007, Romei 2011).

In 20% of cases, MTC follows a hereditary pattern (HMTC), known as isolated familial (FMTC) or multiple endocrine neoplasia type 2 (MEN2) syndromes, transmitted in an autosomal-dominant manner. (Moo-Young 2009, Raue 2010, Alevizaki 2009) In opposite to the sporadic form, HMTC is characterized by small, frequently multifocal and bilateral nodules. (Moo-Young 2009, Raue 2010, Alevizaki 2009) The earlier identification of kindreds at risk of HMTC and the earlier selection of affected members for prophylactic thyroidectomy (14.9 versus 36.4 years), has resulted in a decrease in primary tumor size from 0.8 to 0.2 cm, a reduction in the percentage of bilateral neoplasms from 100% to 13%, a fall in the rate of lymph node metastases from 58% to 0%, all of them associated with less morbidity and mortality from HMTC. (Wells 1994, Graze 1978, Lips 1994)

FMTC, accounts for 35–40% of HMTC, exhibits variable expressivity and penetrance and follows a more indolent course compared to MEN syndromes, with a late onset or no clinically manifest disease and relative good prognosis. (Moo-Young 2009, Raue 2010, Alevizaki 2009) However, the diagnosis of MTC as FMTC is not sometimes correct. MTC is often the first manifestation of MEN2A, misclassified as FMTC with pheochromocytomas diagnosed later while a significant overlap in the genetic mutations between FMTC and MEN2A is observed. (Moo-Young 2009, Raue 2010, Alevizaki 2009) Thus, the definition of FMTC is strict and needs multiple members affected after the age of 50 years and the absence of either pheochromocytoma or hyperparathyroidism in more than 10 carriers. (Brandi 2001) Nowadays, FMTC is considered as a phenotypic mildest variant of MEN2A, in which there is a strong predisposition to MTC and decreased penetrance of pheochromocytoma and primary hyperparathyroidism. In practical terms, especially in smaller kindreds, it is suggested that it is safer to label a family as MEN2A than FMTC, which ensures that patients are screened and monitored for the development of pheochromocytomas. (Moo-Young 2009, Raue 2010, Alevizaki 2009, Brandi 2001)

MEN2, is a rare cancer syndrome, transmitted in an autosomal dominant manner. The estimated prevalence is 2.5 per 100,000 cases in the general population. More than 1,000 kindreds have been described while many others have never been reported. MEN2 syndromes, involve MTC, following by pheochromocytoma in 50% of cases, primary hyperparathyroidism in 30% of cases and less commonly other clinical manifestations such as cutaneous lichen amyloidosis or Hirschsprung's disease. (Moo-Young 2009, Raue 2010, Alevizaki 2009)

MEN2A, accounts for 55% of all cases with MEN2, consisting of MTC in 75% -90% of cases, in combination with pheochromocytoma and primary hyperparathyroidism. MTC is typically multifocal and bilateral, starts in early adulthood and is responsible for most of the mortality associated with MEN2A, indicating the need for early recognition and treatment. (Moo-Young 2009, Raue 2010, Alevizaki 2009)

MEN2B syndrome, accounts for 5-10% of cases with MEN2, consisting of MTC, pheochromocytoma (50%), ganglioneuromatosis, Marfanoid habitus and less often clinical

manifestations (megacolon, skeletal abnormalities, markedly enlarged peripheral nerves). MTC has its onset at a very young age (infancy), is most commonly aggressive and the patients are rarely cured of their disease, due to delayed diagnosis. (Moo-Young 2009, Raue 2010, Alevizaki 2009)

### 3. Diagnosis of medullary thyroid carcinoma

Since MTC is a multifacet thyroid cancer with a benign or aggressive course, the early recognition and treatment, even at the preclinical stage, is of crucial importance, leading in a higher cure rate of affected patients and a much better prognosis. (Roman 2006, Wells 1994, Graze 1978).

During the last decade, a great progress in the diagnostic identification of MTC has been made. Although questionable, calcitonin screening in patients with thyroid nodules has led to an increased rate of MTC diagnosis. Traditionally, calcitonin levels either basal or after provocative testing, constitute important diagnostic tools, in the identification of patients harbouring MTC. (Lips 1994) However, since the late 1990s, with the advent of molecular biology, genetic analysis of the *RET*, has been proved as a powerful diagnostic tool for MTC, especially HMTC. (Brandi 2001, Kouvaraki 2005)

### 4. Genetics of medullary thyroid carcinoma

MTC has been associated with mutations in the *RET*, a 21 exons gene, mapped to chromosome 10q11.2. (Brandi 2001, Kouvaraki 2005, Arighi 2005, Plaza-Menacho 2006) *RET* is a receptor tyrosine kinase, which exhibits trans-autophosphorylation of intracellular tyrosine residues and activation of downstream signaling pathways (Ras/ERK, phosphatidylinositol-3-kinase/AKT, beta-catenin/WNT, phospholipase, C gamma, Src), in tissues that express the receptor. The *RET* protein consists of a N terminal signal peptide, an extracellular region with 4 cadherin-like repeats, a calcium-binding site and a cysteine-rich domain, a transmembrane region, and an intracellular portion with two tyrosine kinase domains. (Kouvaraki 2005, Arighi 2005, Plaza-Menacho 2006) Activating point mutations in *RET* lead to constitutive activity of the receptor, C-cell hyperplasia (CCH) and MTC. The scenario of the "two hits" is now supported, including an inherited "first hit" leading to C-cell hyperplasia and a secondary somatic "second hit" in activated C cells, leading to HMTC. (Roman 2006) Genetic analysis of *RET* diagnoses MTC in about 98% of known families. (Brandi 2001) Since the distinction between sporadic and hereditary forms of MTC is not often clear, nowadays, *RET* molecular testing has solved a lot of diagnostic problems in patients with MTC, ensuring a better management of patients and their families and less MTC associated morbidity and mortality. (Wells 1994, Graze 1978, Lips 1994)

#### 4.1 *RET* mutations

Since 1993, that the first germline mutation of the *RET* was identified, an accumulating number of *RET* mutations has been isolated, linked to MTC. (Brandi 2001, Kouvaraki 2005, Arighi 2005, Plaza-Menacho 2006) Based on the *RET* molecular testing, 1-7% of cases with apparently sporadic tumors were found to have *RET* mutations. (Elisei 2007, Romei 2011, Wohllk 1996, Blaugrund 1994, Elisei 2008)

Genetic testing of the *RET* is performed by PCR amplification of the patient's germline DNA obtained from white blood cells or thyroid tissue. Initially, exons 10, 11, 13, 14, 15, and 16 are carefully screened and if no mutations are detected, the remaining 15 exons of the *RET* gene should be sequenced. It has been estimated that mutations are found in over 95% of cases of HMTc. Otherwords, the predicted risk of HMTc in a patient with a negative genetic testing is estimated to be only 0.18%. (Kouvaraki 2005)

The *RET* mutations might occur: in the substrate recognition pocket of the catalytic core (mutations in codon 918), leading to receptor dimerization and cross-phosphorylation; in the extracellular domain (exons 8, 10, 11) leading to ligand-independent homodimerization, cross-phosphorylation and receptor activation; in the intracellular domain (exons 13, 14, 15, 16), leading to alteration in the substrate recognition pocket of the catalytic core with constitutive activation of the *RET* kinase enzyme catalytic site and autophosphorylation. *RET* mutations in MEN2 are typically missense mutations that lead to ligand independent receptor activation, a model that is well known for a variety of human cancers, but is uncommon for a hereditary cancer gene. (Kouvaraki 2005, Arighi 2005, Plaza-Menacho2006) The identified *RET* mutations exhibit a strong genotype-phenotype correlation and they are classified into 3 groups with a 14-fold incremental increase from mutations in level 1 to level 3. (Kouvaraki 2005, Donis-Keller 1993, Eng 1996, Alevizaki 1997, Yip 2003, Marx 2005, Mulligan 1993, Machens 2003) Recent guidelines from the American Thyroid Association (ATA) propose a classification of *RET* mutations in 4 levels (A-D), with level D mutations denoting the highest risk for early onset or aggressive MTC and level A mutations carrying the lowest risk. (Kloos 2009).

#### **4.2 *RET* mutations and sporadic medullary thyroid cancer**

Approximately 50-60% of specimens from patients with SMTC, contain somatic but not germline *RET* mutations. (Wohllk 1996, Blaugrund 1994, Elisei 2008) The most common somatic mutations occur in codons 918 and 833 (exons 15 and 16) while less commonly somatic mutations in exons 10 and 11 are found which are associated with poor prognosis (Wohllk 1996, Blaugrund 1994, Elisei 2008) Murra et al, has demonstrated somatic mutations in 64.7% of MTC tumours. Exon 16 was the most frequently affected (60.6%), followed by exon 15, while exons 5,8,10-14, were less affected. Mutations in exons 15 and 16, were associated with higher prevalence of persistent, multifocal MTC with a spread in regional lymph nodes, while mutations in exons 5,8,10-14, were associated with the most indolent course of MTC. (Moura 2009) Schilling et al, examined multiple lymph nodes from patients with SMTC and demonstrated that 76% of patients with SMTC had concordant codon-918 mutation in all lymph nodes tested (43% all positive, 33% all negative). Moreover, patients with somatic codon-918 mutations had an increased rate of metastases to distant sites (lung, bone, liver) and an overall worst prognosis. (Schilling 2001 A single nucleotide polymorphism (SNP) of *RET*, G961S, has been shown to be more frequent in patients with SMTC compared with healthy subjects, associated with an earlier age of MTC, and with higher calcitonin levels. (Cardot-Bauters 2008, Robledo 2003, Elisei 2004). The real significance of the observed mutations is not clear. The coexistence of mutation positive and negative regions in MTC tumors, suggests that these mutations may not always be initiating or essential. (Eng 1996)

At present, genetic testing for tumor mutations of the *RET* is not part of the routine practice in patients with SMTC, as the clinical utility is still undefined. However, screening of individuals with apparently sporadic MTC may uncover germline *RET* mutations in approximately 7% of



cases, which in about 2-9% are *de novo* mutations, suggesting that these cases had actually HMTC and not SMTC. (Elisei 2007, Romei 2011, Wohllk 1996, Blaugrund 1994, Elisei 2008) In addition, the existing clinical data suggest a correlation of the *RET* mutations with the course of the disease and possibly the response to treatment which is going to be further evaluated by clinical trials which are in progress. Thus, it might be useful to perform *RET* genetic testing in all patients with MTC, even in those with apparently SMTC.

#### 4.3 *RET* mutations and hereditary medullary thyroid cancer

To date, 98% of affected families with HMTC apparently exhibit genetic linkage to the *RET* gene locus and only a small percentage of MEN2 families have had no *RET* mutation detected. (Kouvaraki 2005, Donis-Keller 1993, Eng 1996, Alevizaki 1997, Yip 2003, Marx 2005, Mulligan 1993 )

Isolated FMTC has been traditionally associated with germline-activating mutations of the extracellular region of *RET*, mainly at cysteine codons 609, 611, 618, 620, 630, 634 in exons 10 and 11, in the extracellular domain which is associated with the three-dimensional ligand-binding pocket. These mutations lead to ligand-independent dimerization and receptor activation. Noncysteine mutations of the intracellular region of *RET* in exons 13–16 are less commonly linked to FMTC while mutations in other exons have been rarely reported in isolated families. Some mutations (particularly codons 532, 533, 630, 769, V804M, 844, 912) are thought to be relatively specific for FMTC. However, codon 533 is also associated with MEN2A, indicating that only time and observation in large numbers of families can confirm this specificity. (Kouvaraki 2005, Peppia 2008, Kamakari 2008) Nowadays, FMTC constitutes a challenging form of MTC, which is considered as a phenotypic mildest variant of MEN2A. A number of FMTC patients finally have MEN2A while a significant overlap in the observed *RET* mutations, is commonly found.

Different *RET* mutations lead to the distinct clinical syndromes of MEN2A, MEN2B, and FMTC while a significant overlap exists between *RET* mutations associated with FMTC or MEN2A. The great majority of patients with MEN2A have mutations of *RET* in exons 10,11,13-16 while patients with MEN2B exhibit a single mutation at codon 918 of exon 16. (Kouvaraki 2005, Donis-Keller 1993, Eng 1996, Alevizaki 1997, Yip 2003, Marx 2005, Mulligan 1993, Hofstra 1994 )

Due to a strong genotype-phenotype correlation in MTC, the genetic analysis and the identification of specific germline *RET* mutations offer important information regarding the penetrance of MTC and associated lesions. For example, mutations at codon 634 in exon 11 accounts for approximately 60% of all MEN2 families rather than FMTC, with hyperparathyroidism occurring in 20% of patients, a manifestation which is uncommon with other *RET* mutations. (Schuffenecker 1998, Karga 1998) In addition, the same mutations are associated with significantly earlier progression from C-cell hyperplasia to MTC and earlier lymph node involvement than patients with most other mutations related to MEN2A and FMTC. (Peppia 2008, Hofstra 1994) According to the International *RET* Exon 10 Consortium, codon-associated penetrance by age 50, ranged from 60% (codon 611) to 86% (620) while more advanced stage and increasing risk of metastases correlated with mutation in codon position (609→620) near the juxtamembrane domain. (Frank-Raue 2011) A large European consortium study reported by Machens et al, offer detailed clinical penetrance data, analyzed according to individual mutations. (Machens 2003)

#### 4.4 *De novo* RET mutations and hereditary medullary thyroid carcinoma

A small percentage (3-6%), of patients with MTC, have a negative family history and germline *RET* mutations which arise *de novo*. Such *de novo* mutations are noted at a much higher frequency in the allele inherited from the patient's father. (Wohllk 1996, Donis-Keller 1993, Eng 1996, Alevizaki 1997, Carlson 1994) Unlike MEN2A, MEN2B is commonly associated with *de novo* germline mutations and the diagnosis is most often based on the characteristic clinical features (elongated facies, oral ganglioneuromas of the lips and tongue). Such *de novo* mutation at codon 883 in exon 15, has been found in a small number of MEN2B families. (Gimm 1997) Because of frequent *de novo* mutations, patients with MEN2B should be suspected on the basis of the characteristic features and not on the family history. *De novo* *RET* mutations, tend to be disproportionately clustered in the intracellular domain (exons 13-15), linked with reduced MTC penetrance, compared to the more classic familial patterns associated with extracellular mutations in exons 10 and 11.

#### 4.5 *RET* mutations in exon 8 and hereditary medullary thyroid carcinoma

In addition to the classical *RET* mutations observed in exons 10,11,13-16, accumulating data support the association of *RET* mutations in other exons associated with HMTC, including exon 8. The first report by Pigny et al. described a 9 bp duplication of exon 8 in a family with FMTC. (Pigny 1999) Da Silva et al, in a study of 76 patients with FMTC from a 6-generation Brazilian family with 229 subjects, demonstrated a new missense point *RET* mutation in exon 8 (1597G-->T) corresponding to a Gly(533)Cys substitution in the cysteine-rich domain. (Da Silva 2003) Kaldrymides et al, detected the same mutation in all seven FMTC Greek patients and in 13 heterozygotes and 1 homozygote asymptomatic relatives, with a wide clinical heterogeneity. (Kaldrymides 2006) Fazioli et al, found 4 novel *RET* variants, located in the extracellular domain (p.A510V, p.E511K and p.C531R) coded by exon 8 on the leukocyte DNA from apparently sporadic cases, in addition to the intracellular juxtamembrane region (p.K666N) coded by exon 11, suggesting that these variants are associated with FMTC. (Fazioli 2008) Peppia et al, found the same mutation, in 2 index patients with MEN2A, consisting of pheochromocytoma and MTC and in 6 out of 12 (50%) family members. Additionally, one of the index patients was asymptomatic, the pheochromocytoma being accidentally found, while the second patient had hypertension but negative testing for pheochromocytoma despite repeated measurements. Furthermore, the MTC was least aggressive as it was not clinically apparent, while none of the family members died from MTC-related causes. (Peppia 2008) Moreover, Kamakari et al, have identified the same G533C mutation in 11 unrelated families with FMTC and 4 with MEN2A, explaining the 'RET-negative' FMTC/MEN2A patients. (Kamakari 2008). The above observations are considered quite interesting points in the characterization of the MEN2A phenotype associated with the G533C point mutation in exon 8 of the *RET* which seems to be less aggressive. The existing data, reveal an oncogenic potential for all the novel germline *RET* variants, including exon 8 genomic variations, which seem to have a higher oncogenic potential than previously thought. (Muzza 2010)

The above findings indicate that patients with MTC should be screened for other components of MEN and also should be evaluated through a complete genetic screening including exon 8, especially if the classical *RET* screening is negative.

## 5. Conclusion

*RET* molecular testing has offered tremendous help on the early identification of patients with MTC, the distinction between the sporadic and hereditary forms of MTC, the prognosis of the natural course of the disease and the response to treatment. To date, the identified *RET* mutations exhibit a strong genotype-phenotype correlation, which has been the basis for establishing the clinical risk levels depending on the nature of the mutations. A “complete” germline *RET* testing should be performed in all MTC patients, independently of the family history, including 10, 11, 13–16 and other “non classical” exons including exon 8, especially in the case of a negative testing. At present, the risk profiles and the penetrance estimations cannot be done in patients with MTC of all causes, caused by *RET* mutations in exon 8, due to the deteriorated data. More studies need to be done, in order to provide more information about the role of exon 8 genomic variations, on the disease start, progression, potential and penetrance.

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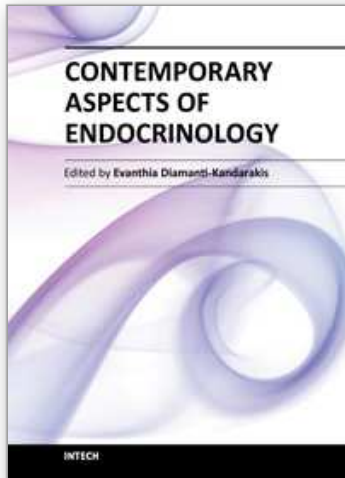
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## **Contemporary Aspects of Endocrinology**

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This book aims to provide readers with a general as well as an advanced overview of the key trends in endocrine disorders. While covering a variety of topics ranging from thyroid carcinogenesis and pituitary adenomas to adrenal tumors and metabolic bone disease, this book also focuses on more specific issues not yet fully elucidated (e.g. the molecular pathways involved in thyrotropin beta gene regulation or monogenic phosphate balance disorders). Readers of different fields and background will have the opportunity to update their knowledge and more importantly to clarify areas of uncertainty and controversies in several topics of endocrine disorders.

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