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What is New in Multiple Endocrine Neoplasia Type 2?

INVITED REVIEW
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ABSTRACT

Multiple endocrine neoplasias (MENs) are rare inherited endocrine tumor syndromes that occur due to an underlying constitutional *RET* mutation. After the phenotypic description in 1903 by Erdheim, Wermer described cases of endocrine gland tumors from the same family and proposed a genetic basis for the syndrome. The term MEN was coined by Steiner in 1968. Later, in 1990s MEN type 1 (MEN 1) and MEN type 2 (MEN 2) were described. Currently, MEN syndromes are defined as MEN 1, MEN 2A, MEN 2B, MEN 4, and MEN 5. Recent years have witnessed several advancements in genetic characteristics and associated clinical features of MEN 2 syndromes. The aim of this review is to summarize current information, novel genotype–phenotype associations, and future recommendations about MEN 2.

Keywords: Multiple endocrine neoplasia, MEN 2, medullary thyroid cancer, pheochromocytoma, primary hyperparathyroidism

Introduction

RET(*REarranged in Transfection*) proto-oncogene was discovered as an oncogene in 1985.[1] *RET* oncogene which is located on chromosome 10 (10q.11.2) encodes for a receptor of the tyrosine kinase family, which is important in the development of the nervous system, and the development of organs and tissues originating from the neural crest. Each of the 3 *RET* isoforms are encoded by 3 distinct transcripts. The 3 transcripts all have *RET* exon 19; however, with variable splicing of the 3′ end of exon 19, they form unspliced exon 19, exon 20, and exon 21. *RET* isoforms with 9 (*RET9*), 51 *(RET51)*, and 43 (*RET43*) amino acid C-terminal ends are encoded by these transcripts. The predominant isoforms in vivo are *RET9* and *RET51*, composed of 1072 and 1114 amino acids, respectively. Although co-expressed in the majority of tissues, these 2 isoforms have differential developmental roles and gene expression profiles, implying possible discrepancies in cell-cell contact pathway regulation.[2,3]

RET protein is formed of an extracellular cysteine-rich domain (exon 8, 10, 11), transmembrane domain, and intracellular tyrosine kinase domain part 1 (exons 13 and 14) and part 2 (exon 15 and 16).[4] The major 4 ligands of the *RET* receptor are glial cell line-derived neurotrophic factor (GDNF), artemin, neurturin, and persephin, which are all from the GDNF family. Additionally, the binding of growth differentiation factor-15 to GFRα-like has been shown to activate *RET*. As a stress response cytokine, elevated serum levels of GDF15 affect metabolism and regulate body weight.[3] *RET* tyrosine kinase activation necessitates the binding of each ligand with its specific glycosylphosphatidylinositol bound co-receptor, GDNF family receptor α (GFRα 1–4), as a complex. When the ligand binds to the extracellular domain, the receptors dimerize, triggering the activation of the tyrosine kinase modules in the cytoplasmic domain. The signal that is transmitted into the cell plays a role in migration, cell differentiation, growth, and survival. A range of loss-of-function mutations in the *RET* gene may end up with absence of enteric ganglia in the bowel and cause of Hirschsprung disease (OMIM #142623). On the other hand, constitutively active receptors that dimerize even in the absence of a ligand or react excessively to a ligand are seen in the case of gain-of-function receptor mutations. Germline activating variants (single/multiple, missense, duplications, insertions, deletions, chromosomal rearrangements, etc.) in *RET* proto-oncogene cause multiple endocrine neoplasia (MEN) syndrome type 2, which has an autosomal dominant pattern of inheritance.[5] The behavior of a pathogenic variant depends on the organ. In this way, the same variant can end up with a gain-of-function in the thyroid C-cells and a loss-of-function in the colon and result in MEN 2A co-existing with Hirschsprung's disease.[5]

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Figure 1 shows principal pathogenic *RET* variants and associated risk levels as moderate, high, and highest according to the 2015 American Thyroid Association medullary thyroid cancer management guidelines.[6] This risk particularly denotes medullary thyroid cancer (MTC) aggressiveness, which is a component of nearly all MEN 2 cases. Medullary thyroid carcinoma needs to be managed appropriately according to the risk level, which necessitates timely prophylactic thyroidectomy according to *RET* mutation types. This risk classification, based on the mutated codon, forms the basis of international recommendations not only for management but also for monitoring of pathogenic *RET* carriers.[6]

RET Variant Classification

When a pathogenic *RET* variant causes MEN 2, there will be at least 2 affected individuals in the family.[5] Affected individuals of the family are expected to have at least 1 MEN 2 clinical feature; MTC, pheochromocytoma, primary hyperparathyroidism (PHPT), or MEN 2B specific features. Medullary thyroid cancer must be seen in at least 1 affected family member. Detection of C-cell hyperplasia or finding an elevated level of calcitonin is not considered as affected. If the family information is not available, the variant will be accepted as pathogenic under the following circumstances:

- if the patient has MTC with another clinical feature of MEN 2, or,
- if MTC is diagnosed in more than 2 subjects who have the same *RET* variant but are not related.[5]

A variant can be accepted as benign when it does not cause MEN 2, which is by definition, 5 family members >60 years of age carrying the variant but having no evidence of MEN 2 on screening.[5]

In the absence of clinical information to classify as benign, pathogenic, or causing Hirschsprung's disease, a variant should be classified as uncertain.[5]

In case a family or even a patient has only Hirschsprung's disease without evidence of MEN 2 disease on screening, a Hirschsprung's disease variant will be established.[7]

MAIN POINTS

- Regardless of family history, all patients with medullary thyroid cancer, spontaneous pheochromocytoma, cutaneous lichen amyloidosis, and Hirschsprung's disease should undergo a germline RET mutation study.
- Despite high-risk RET variant individuals developing medullary thyroid cancer (MTC) earlier than intermediate-risk subjects, studies indicate comparable disease progression and survival rates.
- Since the Exome Aggregation Consortium database found a lifetime risk of MTC of only 4% for V804M carriers, they may be withdrawn from the preventative thyroidectomy group and managed with a more flexible approach.
- Personalization of screening for MEN 2A-associated cancers may be influenced by paternal inheritance.
- European Association of Nuclear Medicine recommends 18F-FDOPA positron emission tomography/computed tomography for detecting recurrent MTC in patients with increasing tumor markers, serum calcitonin above 150 pg/mL, or a shorter calcitonin doubling time (<24 months).

Several novel pathogenic, benign, uncertain, or Hirschsprung's disease germline variants of the *RET* proto-oncogene have been reported in recent years.[5]

Some of the *RET* proto-oncogene mutations, corresponding exons and associated hereditary disease forms are shown in Figure 2.[8]

Multiple Endocrine Neoplasia 2A and Multiple Endocrine Neoplasia 2B

Multiple Endocrine Neoplasia 2A: Multiple endocrine neoplasia 2A constitutes approximately 95% of the MEN 2 syndromes (OMIM #171400) (d). Multiple endocrine neoplasia 2A occurs with a prevalence of 13-24 per million and an incidence of 8-28 per million live births per year.[5] Most prevalent mutations in MEN 2A are seen in codon 634 (American Thyroid Association [ATA] high risk).[9] De novo variants are known to be uncommon in MEN 2A with a reported rate of 6%-9%.[5]

There are 4 MEN 2A phenotypes (Figure 3).[10] Classical MEN 2A, which is the most frequent form; either MTC and pheochromocytoma and/or PHPT is seen in an individual patient or, 2 or more of the tumors occur in multiple members within the same family.[5] Classical MEN 2A is due to high risk (codon 634) and moderate risk category (codons 609, 611, 618, 620) *RET* mutations in 95% of cases.[5] The other MEN 2A phenotypes are MEN 2A with cutaneous lichen amyloidosis, MEN 2A with Hirschsprung's disease, and familial MTC.[5]

Classical Multiple Endocrine Neoplasia 2A

Medullary thyroid cancer, which is generally the first manifestation of the syndrome, occurs in nearly all MEN 2A patients. Around 25% of MTCs develop as a component of MEN 2 syndromes, and since there is no family history in nearly 50% of cases, germline *RET* mutation analysis is required in all patients with MTC.[4] Sporadic MTCs are usually seen in the fourth and sixth decades, while hereditary MTC may be seen even in the first decade of life. C-cell hyperplasia precedes MTC. Importantly, when occurring as a component of MEN 2, MTC is typically bilateral, multifocal, and is frequently localized in the upper regions of the thyroid lobes.[11] It should be kept in mind that cytological diagnosis of MTC is possible in around 56% of cases.[12] Preoperative calcitonin measurement in serum and aspiration needle washout fluids may increase the diagnostic accuracy.[13] For MTC, the age of diagnosis, clinical presentation, metastatic potential, and treatment response changes in a wide spectrum in accordance with the mutated codon of the *RET* proto-oncogene. For this reason, the ATA published a guideline for the management of MTC in 2015 to standardize the approach to these patients.[6]

Pheochromocytoma

Pheochromocytoma is seen in around 20%-50% of MEN 2A cases, but in the majority of cases, it is diagnosed concurrently with or after MTC.[14] Patients are symptomatic in roughly 50% of cases. Adrenomedullary hyperplasia precedes pheochromocytoma, and it can be multifocal in the same gland.[14,15] Pheochromocytoma occurs bilaterally in 50%-73% of the patients.[16] In patients with unilateral disease, pheochromocytoma in the contralateral adrenal generally develops within a 5-10 years period of time.[14] Most MEN 2-associated pheochromocytomas produce metanephrine predominantly.[16] Even in the adrenal medullary hyperplasia phase, patients may present with symptoms due to catecholamine excess. Both extra-adrenal and/or malignant pheochromocytomas are reported to be rare (0%-3%).[5]

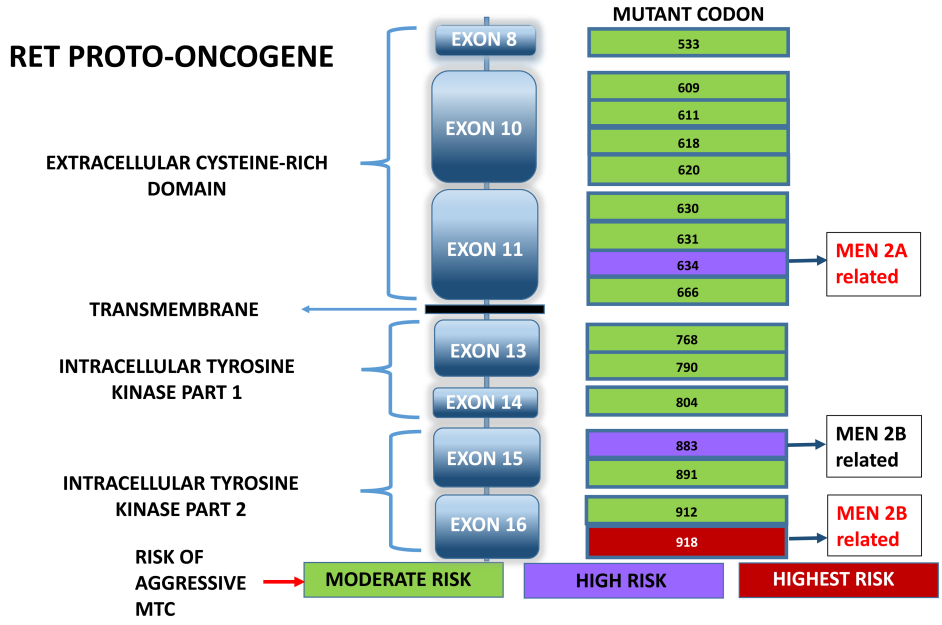

Figure 1. Principal pathogenic *RET* variants, corresponding MEN 2 subtypes, and risk level of MTC.[4]

Primary Hyperparathyroidism

The prevalence of PHPT in MEN 2A is reported to be much lower when compared to previous publications (3%-11%).[17] This difference may be attributed to the late recognition of MEN 2A in previous decades, previous studies including more ATA high-risk variants, or the choice of different definitions for PHPT (biochemically or histologically). Primary hyperparathyroidism is usually mild and can be both uni- and multiglandular.[18] Around 50% of PHPT cases are due to adenoma, and parathyroid carcinoma is exceedingly uncommon.[5] In an international study that included 1085 index MEN 2A cases, PHPT was the first manifestation in less than 1% of cases.[19] Codon 634 was the most commonly mutated variant, seen in 52% of cases.[19] In a 2023 Danish MEN 2A 1930-2021 cohort, retrospective study; 62% of PHPT cases were seen in ATA moderate-risk (most commonly Cys611Tyr) and 38% in ATA high-risk mutation patients.[18] This difference was attributed to a Danish Cys611Tyr founder effect.

Multiple Endocrine Neoplasia 2A with Cutaneous Lichen Amyloidosis

Cutaneous lichen amyloidosis is an intensely pruritic dermatological lesion associated with upper dermis amyloid deposits, which generally occurs in the scapular area. It is, for the most part, associated with germline codon 634 mutations, but cases with 611 and 804 mutations have been reported as well.[20,21] It can be the presenting symptom of MEN 2A and has a female preponderance. In a systematic literature review, the prevalence of MTC, cutaneous lichen amyloidosis, pheochromocytoma, and PHPT were reported as 94%, 51%, 30%, and 16%, respectively.[22]

Multiple Endocrine Neoplasia 2A with Hirschsprung's Disease

Although loss-of-function type *RET* mutations are related to Hirschsprung disease, paradoxically, the disease can occur with MEN 2A. This binary occurrence is explained to be due to constitutive *RET* activation being enough to trigger neoplastic transformation in C-cells and adrenal medullary tissue but not in the precursor neurons due to a lack of expression of the *RET* protein at the cell surface.[23] Hirschsprung disease in MEN 2A is regarded to be generated exclusively by exon 10 located in codon 620 (48%), 618 (32%), 609 (18%), and 611 (2%) mutations.[24] There also is a report of the V804L mutation however without a clear description.[25] The mean age of diagnosis is 1 year, which may enable early diagnosis in *de novo* cases or undiagnosed families, but early childhood complications, including death, have been reported in up to 38%.[26] According to a report from The International RET Exon 10 Consortium, which includes 27 centers from 15 countries, in which *RET* exon 10-mutated patients were analyzed, the prevalence of MTC, pheochromocytoma, and PHPT was 77%, 17% and 3%, respectively.[27]

Familial Medullary Thyroid Cancer

Originally, familial MTC was defined by Farndon and colleagues as: MTC diagnosed in more than 10 family members, multiple members over 50 years of age who are either affected or carriers, and an adequate medical history for exclusion of pheochromocytoma and PHPT, particularly in older family members.[6] Later, 2 families were reported as familial MTC with *RET* codon G533C mutation in exon 8. The first family was from Brazil, including 76 gene carriers (29 with MTC and none with PHPT or pheochromocytoma)[6] and the other from Greece[28] which included 20 carriers, 6 with MTC and none with pheochromocytoma or PHPT. However, in time, a kindred from the Brazilian family developed pheochromocytoma, and reports from Greece and the United States clarified *RET* codon G533C mutation causing MEN 2A.[6] Therefore, in the 2015 ATA guidelines, familial MTC was rather accepted as a variant along the spectrum of disease expression of MEN 2A, not to cause a missed diagnosis of pheochromocytoma.[6] The latest definition was: families with only MTC but fulfillling the original strict criteria for the familial form, small families of at least 2 generations, with at least 2 but less than 10 subjects with germline *RET* mutations, small families in which 2 or fewer members in a single generation have *RET* germline mutations, and single individuals with a RET germline mutation.[6]

Multiple Endocrine Neoplasia 2B

Multiple endocrine neoplasia 2B (OMIM #162300) has a prevalence of 1-2 per million and an incidence of 1-3 per million live births per

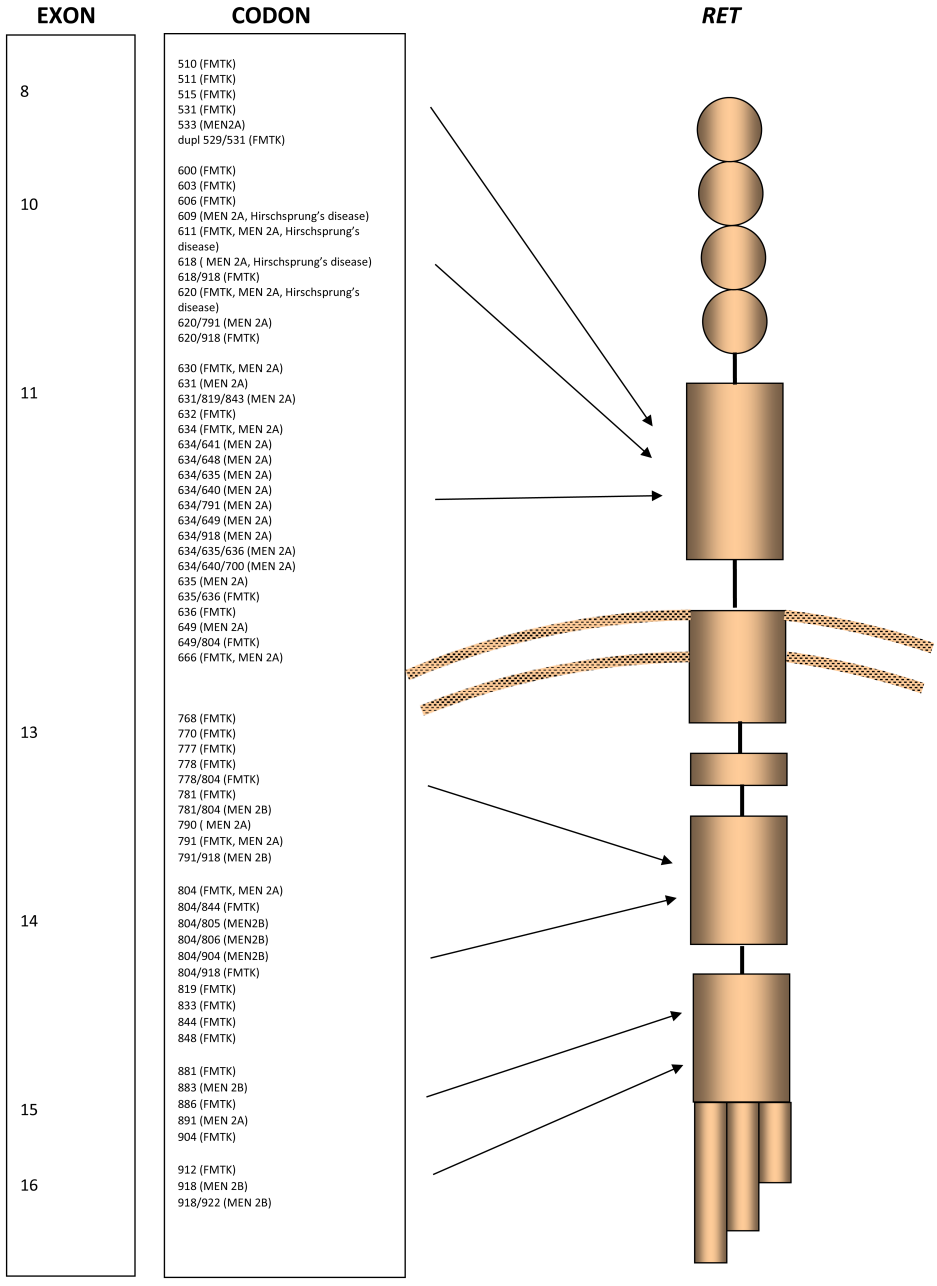

Figure 2. Some of the *RET* proto-oncogene mutations, corresponding exons and associated hereditary disease forms (modified from "Cakir M, Grossman AB. Medullary thyroid cancer: molecular biology and novel molecular therapies. Neuroendocrinology 2009;90(4):323-348," Courtesy of Ashley Grossman and S. Karger AG).[6,8]

year.[5] The syndrome, in >95% of cases, is due to Met918Thr *RET* mutation (ATA highest risk),[9] <5% are caused by Ala883Phe *RET* mutations, and on very rare occasions, the reason is tandem *RET* mutations.[29]

The most common constituent of the syndrome is MTC, followed by pheochromocytoma (Figure 3). Typical specific clinical aspects of MEN 2B are as follows: narrow long face with thickened lips, mucosal neuromas on conjunctiva, tongue, lips, and musculoskeletal abnormalities.[30] Ganglioneuromas of the gastrointestinal tract and resultant abnormalities in gastrointestinal motility may cause diarrhea or constipation. These patients may be seen in gastroenterology units at a young age with colonic dilatation (megacolon).[30]

The largest international, multicenter, retrospective study about natural history, management, and follow-up of subjects with MEN 2B was published in 2019.[29] The penetrance of pheochromocytoma was reported as 50% in this study.[29] By the age of 28, 50% already had bilateral disease. The median time to develop contralateral pheochromocytoma was 4 years.[29] Overall, 73% of patients (synchronous or metachronous) had bilateral pheochromocytoma. Pheochromocytoma diagnosis was either concurrent with (26%) or after (69%) MTC.[5] Malignant pheochromocytoma has been seen in 3%, and extra-adrenal pheochromocytoma is even less.[29]

As nearly all MEN 2B mutations occur de novo,[4,29] the diagnosis of MEN 2B is a challenge. At an early age, the endocrine symptoms are

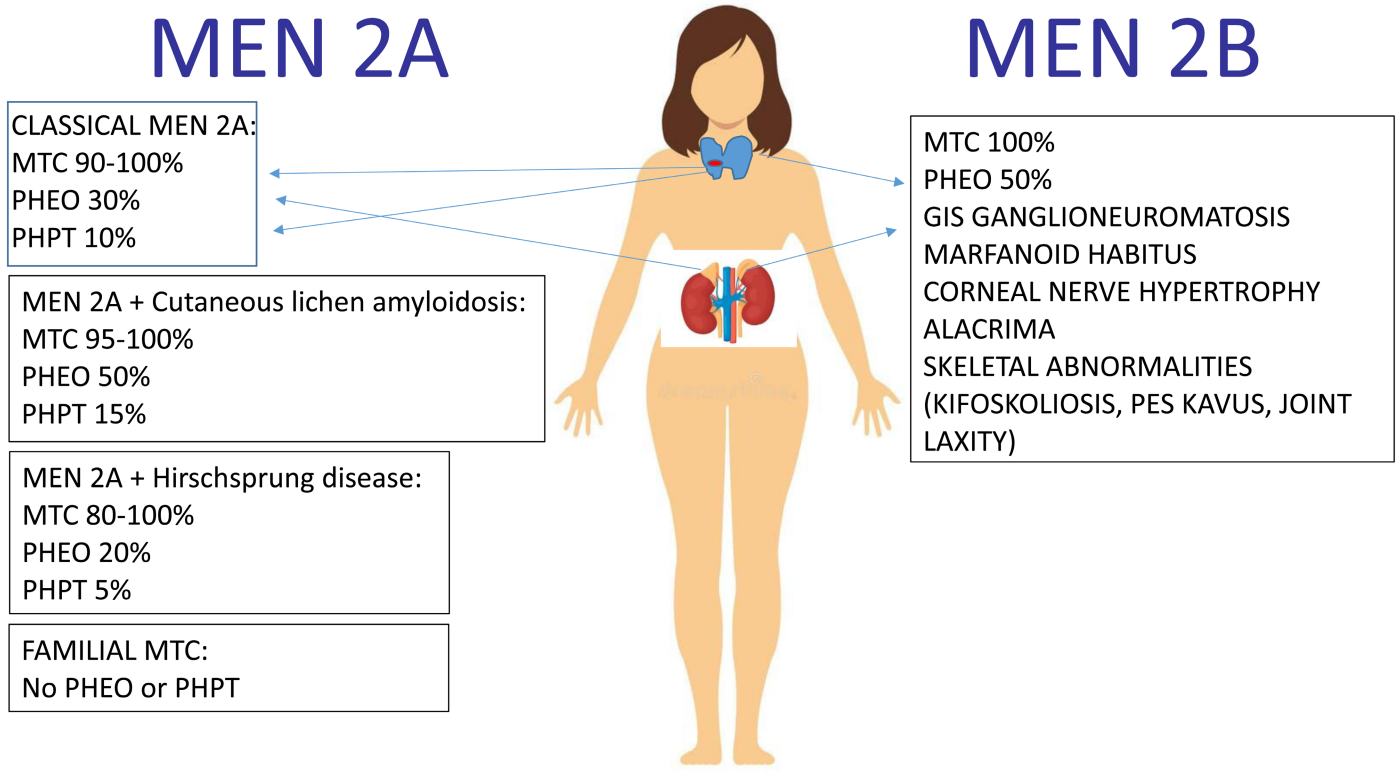

Figure 3. Classical clinical features of MEN 2 syndromes.[5,10]

absent, and marfanoid body features and mucosal neuromas are seen after the age of 1 year.[29] On the other hand, the first year of life is the most critical time window in these patients for early prophylactic thyroidectomy. However, gastrointestinal signs and symptoms such as feeding difficulties, pseudo-obstruction, constipation, and alacrima are early signs that can alert the physician to further evaluation.[29] For that reason, health care providers who deal with children need to be aware of several non-endocrine clinical features of MEN 2B. The frequency of extra-endocrine features of MEN 2B patients is shown in Table 1.[29]

Table 1. Extra-Endocrine Features of MEN 2B (Modified from Castinetti and Colleagues).[29]

Feature	%
Ganglioneuromatosis	97
Tongue	62
Lips	53
Eyelid or conjuctival	19
Marfanoid habitus	73
Pseudo Hirschsprung's disease or severe constipation	65
Achalasia or gastroparesis	4
Pes cavus	38
Pectus excavatum	26
Motor or muscle weakness (hypotonia)	27
Scoliosis	9
Corneal hypertrophy	45
Alacrima	40
Kidney anomalies (kidney atrophy, kidney cysts, hydronephrosis, and ureteral atonia)	13

Admittedly, it has been difficult to make recommendations for the high-risk group of MEN 2B patients with the *RET* A883F mutation because of the scarcity of the variant. In the largest case series, which included 13 patients, the median age of diagnosis for C-cell hyperplasia and MTC was 7.5 years and 19 years, respectively.[31] The median age for pheochromocytoma diagnosis was 34 years, which occurred in 38% of cases bilaterally. The earliest diagnosis of MTC was at age 10 years, while the development of regional lymph node or distant metastases was at age 20 years. Penetrance of MTC and pheochromocytoma was 50% by the age of 19 and 34 years, respectively. Both overall and disease-specific, 5- and 10-year survival rates of the cohort were similar and 88%. The median age for the diagnosis of pheochromocytoma was 8 years earlier than exon 10 mutation carriers and 12 years later in comparison to M918T carriers.[31] Based on these data, authors have concluded that the A883F mutation has an indolent course and it is justifiable to classify it as ATA high-risk level.

Current Approach to Medullary Thyroid Cancer According to American Thyroid Association Risk Groups

As MTC has a high metastatic potential, 70% of subjects who are seen with a palpable nodule already have cervical lymph node involvement, while 10% have distant metastases.[4] According to the 2015 ATA recommendations, children with the M918T mutation in the highest risk category should have a thyroidectomy in the first year, or even in the first months of life. Thyroidectomy at age 5 years or earlier, depending on the detection of serum calcitonin levels, should be performed in children in the high-risk category with mutations in codon 883 (MEN 2B) and codon 634 (MEN 2A).[6] Children whose serum calcitonin levels are above 40 pg/ml, or who have evidence on imaging or direct observation of lymph node metastases, are

recommended to have a central neck dissection. In the moderate risk category, screening needs to start around 5 years of age, with physical examination, ultrasonography of the neck, and measurement of serum calcitonin levels. As the detection of an elevated serum calcitonin level marks the timing of thyroidectomy, the family should be informed that evaluations, either 6 months or annually, may last several years or decades.[32] In accordance, if the parents have concerns about such a long-term follow-up schedule, thyroidectomy may be planned around 5 years of age.

What Is New in Multiple Endocrine Neoplasia 2?

There is clinical variability in several Mendelian conditions even between affected members of the same family. Intra-familial variability is due to some combinations of the impact of other unlinked genes (modifier genes) and environmental effects. Although a certain genotype–phenotype correlation depending on the identified *RET* variant exists for MEN 2 syndromes, there is both inter- and intrafamilial variability in patients having the same mutation. Despite the fact that studies of several families with the same *RET* mutation have expanded our knowledge of MEN 2 syndromes, there still may be substantial variability in the age of diagnosis and clinical spectrum of presentation, which makes the standardization of approach to these patients complex and difficult. Although the variability of presentation is often observed among carriers of moderate-risk variants, it is also seen among highest and high risk groups.[29,33] Several studies have investigated the potential genetic modifiers behind phenotypic variability, including single nucleotide polymorphisms in *RET*,[34,35] copy number variations,[36] somatic variants, epigenetic,[37] and geographical factors.[38] Unfortunately, none of these exceptional studies were clearly able to delineate the reasons for differences in presentation and enable a prediction profile at the individual level. However, remarkable studies aimed at revealing different aspects of MEN 2 syndromes have been published in recent years, trying to refine the clinical approach to these subjects. The following part of the manuscript will sum up the recommendations and results of these studies.

Is It Time for a Four Level Risk Classification?

Development of the MEN 2 associated signs and symptoms largely depends on the carrier's age and, to a much lesser extent, on index status.[39,40] In 2018, Machens and co-workers evaluated genetic and clinical data of 567 consecutive carriers of missense unique *RET* variants in a retrospective cohort study with the aim of refining the ATA risk categories of MTC patients.[33] As a result, the authors proposed that the moderate risk category could be further separated into 2 groups: low–moderate risk category (p.Glu768Asp, p.Leu790Phe, p.Val804Leu, p.Val804Met, and p.Ser891Ala) and moderate–high risk category (p.Cys609, p.Cys611, p.Cys618, p.Cys620, and p.Cys630). Later, in their subsequent publications, the authors slightly changed the terminology to highest, high, intermediate, and low risk, but preserved their 4-level *RET* mutation risk approach.[39,41]

Is Current Approach to American Thyroid Association Highest Risk Group Still Valid?

The most comprehensive and largest study on the genotype-specific occurrence of all constituents of MEN 2 was reported by Machens and colleagues in 2024.[41] This study included 683 carriers of heterogeneous *RET* germline mutations: 53 carriers with 1 highest-risk mutation (codon 918); 240 carriers with 8 different high-risk mutations (codon 634); 176 carriers with 16 different intermediate-risk mutations (codon 609, 611, 618, 620, or 630); and 214 carriers with 6 different low-risk mutations (codon 768, 790, 804, or 891). Median age for MEN 2-related interventions was 12 years vs. 17-38 years for thyroidectomy; 23 years vs. 34-39 years at first adrenalectomy; and 27 years vs. 35-41 years at contralateral adrenalectomy; and not observed vs. at a median age of 37-61 years at parathyroidectomy, for highest risk vs. high, intermediate, and low-risk mutations. As clearly noted, carriers of highest-risk mutations had undergone MEN 2-related interventions earlier than carriers of high-risk, intermediate-risk, or low-risk mutations. The highest risk group, the majority of which were index patients (83.0% vs. 20.8%-35.5%), had developed more often MTC (96.2% vs. 75.3%-63.4%), node-positive MTC (72.5% vs. 39.9%-52.0%), pheochromocytoma (32.1% vs. 32.1%-3.3%) in the first, and 20.8% vs. 19.6%-1.4% in the contralateral adrenal, and PHPT (not observed vs. 11.3%-0.1%), respectively, by the time of surgery than the latter groups. Owing to more advanced disease at thyroidectomy, carriers of highest-risk mutations were less often biochemically cured than carriers of high-risk, intermediate-risk, or low-risk mutations.[41] This study also reported important evidence regarding a strong genotype-specific age-related development of MEN 2 constituents with well-defined age gradients: from C cell hyperplasia to node-negative MTC, from node-negative to node-positive MTC, from node-positive MTC to pheochromocytoma.[41]

The second study that needs mentioning is the one by Castinetti and colleagues, which included 345 MEN 2B Met918Thr mutant subjects.[29] Thyroidectomy was performed in 98% of these subjects; however, surgery was performed in the first year of life in only 20 subjects. Except for the 2 patients who died of reasons not related to MTC, early surgery yielded long-term remission (i.e., undetectable calcitonin level) in 83% of 18 patients. Although there was no significant difference between MTC-specific survival curves, the remission status between patients who underwent thyroidectomy before and after the age of 1 year was significantly different. Biochemical and structural remission was provided in 15% of 318 patients who underwent thyroidectomy after 1 year of age. Among 31 patients who had adrenal-sparing surgery, normal adrenal function was obtained in 62% and 10% had long-term recurrence.

These 2 elegant studies clearly demonstrate the importance of early intervention for the ATA highest risk group and support 2015 ATA MTC guidelines' recommendations.[6]

A Paradigm Shift for High Risk Variants?

In 2014, Machens and colleagues reported annual primary tumor growth rates among the different risk groups and stages of MTC.[42] The moderate and high-risk subjects did not have significantly different primary tumor growth rates. Additionally, independent of the ATA risk group, an annual rate of 0.6 to 0.7 lymph node development was calculated. In 2017, Voss and colleagues compared data of 135 high- and 127 moderate-risk patients retrospectively, with reference to time to distant metastatic disease and overall survival.[43] In terms of diagnosis, median age was 23.0 years (range, 3.7-66.8 years) for high-risk and 42.3 years (range, 6.4-86.4 years) for moderate-risk subjects, which was significantly different. Although at diagnosis moderate-risk subjects had more T3/T4 tumors ($P = .03$), there was no significant difference for lymph node or distant metastases. On the other hand, after MTC diagnosis, similar overall survival and development

of distant metastatic disease were noted in subjects with moderate- and high-risk *RET* mutations which demonstrated a similarly aggressive clinical course of the disease in both groups. The authors concluded that the pathogenic *RET* variant predicts age at MTC onset; therefore, in future guidelines, instead of risk (high vs. moderate), a *RET* mutation classification by disease onset (early vs. late) should be considered. Because of the mean age difference at follow-up (34.5 years for the high- and 48.5 years for the moderate-risk group), comparisons for survival and mortality in this study may be difficult after a median follow-up of 11.5 years and 6.5 years, respectively. In 2018, Machens and colleagues analyzed patients with hereditary MTC classified according to the risk of *RET* mutations.[33] When patients were grouped according to histopathology (normal/C-cell hyperplasia, lymph node negative, and lymph node-positive MTC), the progression of MTC was considerably age-related within the groups. However, in all risk groups, the progress of status from lymph node-negative to lymph node-positive MTC took place at comparable time intervals (8-12 years). In a similar study, Raue and colleagues retrospectively analyzed data of 122 moderate-risk, 120 high-risk, and 21 highest-risk MEN 2 subjects.[44] The mean follow-up period was 12.9 ± 9.8 years. The age of MTC onset was clearly different (14.9, 23, and 35.3 years, respectively) with an interval of 8.1-12.3 years among the highest-, high-, and moderate-risk groups. However, not for high-risk, only for the highest-risk group, increasing age and stage III/IV disease at diagnosis were significantly associated with worse disease-specific survival. From stage I (lymph node negative) to stage III (lymph node positive), tumor growth had a similar interval of 12 years in the moderate- and high-risk groups. Although there was no significant difference in the disease-specific survival rates and outcomes between the moderate- and high-risk groups, in the highest-risk group both were significantly inferior. In 2021, Machens and colleagues investigated the relationship of the pathogenic *RET* variant with progression from local disease without lymph node involvement (n = 201) to locally advanced disease (node positive, n = 186).[45] In moderate risk *RET* variant patients, the time to progression was around 9 years, while in those with a high-risk *RET* variant, the period was 13 years.

As a result, all these data imply that although diagnosed later in life, the progress of MTC seems similarly aggressive in the moderate-risk group compared to high-risk individuals. In other words, high-risk subjects develop MTC maybe more than 1 decade earlier, but once MTC develops, the clinical course may be statistically similar between the 2 groups in terms of the time to the development of lymph node-positive or distant metastatic disease and survival.

What About Low Risk Variants?

In 2005, Lesueur and colleagues reported 3 unrelated cases of individuals homozygous for codon 804 mutations (V804M and V804L).[46] Although the cases had homozygous mutations at codon 804, when compared with 6 heterozygous cases from the same population, the age at diagnosis and clinical features were not significantly different.[46] To date the largest analysis, which includes 160 individuals identified with p.Val804Met via familial cascade genetic screening, has been published by Rich and colleagues.[47] The median age of MTC diagnosis was 54 years, and the cumulative probability of *RET* p.Val804Met for MTC at age 70 was 87% (95% CI, 71%-94%). The exclusion of index cases minimized bias and rendered the methodology robust. The study emphasized that, although *RET* p.Val804Met seemed to be associated with a later onset of MTC compared to other pathogenic germline *RET* mutations, notwithstanding the later onset, penetrance for the disease was near complete.[47] Yet, later in 2018, prophylactic thyroidectomy as a standard recommendation for all carriers of the variant V804M was questioned by a study.[48] The analysis was based on a subset of the Exome Aggregation Consortium database and reported a lifetime risk of MTC of just 4% in V804 M carriers.[48] This was in great contrast to the previous MTC numeric penetrance estimate of 87% at 70 years by Rich and colleagues reported in 2014.[47] C-cell hyperplasia in prophylactically removed thyroid glands from "unaffected" carriers of p.Val804Met has been reported as a ubiquitous finding in a number of studies.[49-51] It is a possibility that all these differences are due to codon 804 mutations occurring in combination with another unnoticed *RET* mutation at that time. Also, in rare patients with MEN 2A, double, triple, or even quadruple *RET* mutations occur that target residues other than codon V804.[52] In case of several *RET* mutations, an extraordinary clinical phenotype compared to that seen with the corresponding single *RET* mutations may occur. Such variants need to be approached with great caution, as misclassification may give rise to major consequences for the patients. Therefore, it is plausible that the V804M variant may be removed from the early age prophylactic thyroidectomy group in the future.

Does Homozygosity of RET Mutations Effect the Clinical Course in Multiple Endocrine Neoplasia 2A?

In 2024, Machens and Dralle analyzed the differences between homozygote and heterozygote *RET* mutation carriers to enlighten the impact of homozygosity on different features of the disease like onset, course, magnitude, and extent.[53] Five *RET* families with more than 1 homozygous carrier and more than 3 heterozygous carriers per family were included in the study. As a result, in consanguineous families with first-degree cousins, homozygotes presented with node-positive MTC and pheochromocytoma earlier in their mid-teens, whereas heterozygotes presented at the end of their 30s and early 40s. In homozygotes, pheochromocytoma occurred 23 years and lymph node metastatic MTC 27.4 years earlier than heterozygotes. Importantly, in the 15 families carrying the founder mutation p.Leu666delinsAsnSer, these age differences were smaller, in which homozygotes developed lymph node metastatic MTC in their mid-40s, 6 years earlier than heterozygotes in their early 50s. Briefly, this study genuinely has revealed a moderate dose–response effect and acceleration of MEN 2A development due to homozygosity in *RET* carriers.

When it comes to homozygous carriers of weakly activating *RET* mutations, 2 case studies have reported different results. As mentioned above, a pronounced effect due to biallelic impact was not reported in the case study of Lesueur and colleagues.[46] In p.Val804Met mutation carriers, no clear differences were noted in terms of age at diagnosis and clinical features between heterozygote and homozygote subjects.[46] Lecube and colleagues analyzed 53 members from 4 successive generations of a family with a high level of consanguinity.[54] Twenty-six gene carriers (4 homozygous and 22 heterozygous) for the V804M mutation were identified. Total thyroidectomy was performed in 3 homozygous patients. In 1 patient, even C-cell hyperplasia was not detected, and in another patient, only 3 small foci of C-cell hyperplasia were found on the pathological examination. In all the heterozygous gene carriers, the pentagastrin stimulation test results were negative and as a result, thyroidectomy was not indicated. These diverse results support the

notion of heterogeneity in disease manifestation, even for weakly activating *RET* mutations.

Paternally Derived vs. Maternally Derived Multiple Endocrine Neoplasia 2 Disease

A possible impact of parental inheritance was among the many factors analyzed with the aim of determining the different expression patterns of MEN 2A.[55] Machens and colleagues examined parental inheritance information of 405 heterozygous MEN 2A patients. Subjects who inherited the disease from their father developed node metastases, pheochromocytoma, bilateral pheochromocytoma, and PHPT at a considerably earlier age compared to the offspring who inherited the disease maternally.

Positron Emission Tomography Scan in Medullary Thyroid Cancer

In the 2015 ATA MTC Guidelines for the detection of the presence of distant metastases, neither fludeoxyglucose-positron emission tomography (PET)/computed tomography (CT) nor F-DOPA-PET/CT was recommended (recommendation 23).[6] In cases with a postoperative serum calcitonin level higher than 150 pg/mL, imaging procedures such as neck ultrasonography, bone scintigraphy, magnetic resonance imaging (MRI) of the pelvis and axial skeleton, chest CT, contrast-enhanced MRI, or 3-phase contrast-enhanced CT of the liver were recommended (recommendation 48).[6] In 2016, the European Association of Nuclear Medicine (EANM) disputed these recommendations with an editorial providing evidence-based explanations[56] and 3 years later EANM published a practice guideline for PET/CT imaging in MTC.[57] In this guideline, for MTC patients with rising tumor markers when serum calcitonin exceeded 150 pg/mL or calcitonin doubling time was shortened (i.e., <24 months), fluorodopa F18 (^{18}F-FDOPA) PET/CT was recommended as the first-line imaging modality because of its higher diagnostic performance in comparison to other PET tracers. In cases where ^{18}F-FDOPA PET/CT is negative or unavailable, ^{18}F-FDG PET/CT was recommended, especially if calcitonin and carcinoembryonic antigen levels are rising rapidly (i.e., doubling time <1 year) or an aggressive clinical course of the disease is suspected (e.g., carcinoembryonic antigen (CEA) levels disproportionately high compared with calcitonin levels). When ^{18}F-FDOPA and ^{18}F-FDG PET/CT imaging results are not conclusive or to assess the usefulness of peptide receptor radionuclide therapy, ^{68}Ga-SSA PET/CT (^{68}Gallium-somatostatin analog) could be considered in highly selected patients.

In 2020, a large network meta-analysis of 14 direct comparison studies, which in total included 306 patients using 5 different PET radiopharmaceuticals (^{18}F-DOPA, ^{18}F-FDG, ^{68}Ga-somatostatin analogs, 3-O-methyl-6-[^{18}F]fluoro-DOPA, and ^{11}C-methionine) for the detection of recurrent MTC, was published.[58] The results of this analysis indicated that irrespective of serum calcitonin and CEA levels or calcitonin doubling time, in both patient- and lesion-based analyses, ^{18}F-DOPA PET undeniably exhibited the best performance for the detection of recurrent MTC.

Adult Endocrinologists Need to Be Vigilant for Atypical Multiple Endocrine Neoplasia 2B Presentations

As MEN 2B tumors develop in childhood, these patients are generally diagnosed by pediatricians. However, on some occasions this is not the case. There are rare double *RET* germline variants, E768D/L790F, V804M/Q781R, V804M/E805K, V804M/Y806C causing MEN 2B.[59-61] These patients all were reported to develop mucosal neuromas and MTC, but median age among the index cases was 33 years, which is higher than both M918T and A883F carriers. Again, in a case series, a MEN 2B patient presenting with hypertensive episodes due to pheochromocytoma at the age of 56 and another case presenting at the age of 38 with volvulus were presented.[62] These data once again emphasize that genetic analysis of all MEN 2B-related tumor patients is indispensable regardless of the age of presentation.

Multiple Endocrine Neoplasia 2B Phenotype Without RET Mutations

There are rare case reports about patients presenting with typical physical features of MEN 2B but without associated endocrine tumors (MTC or pheochromocytoma) or a *RET* gene mutation.[63,64] This elusive clinical presentation is a distinct condition named "pure mucosal neuroma syndrome." These patients have marfanoid body features, mucosal neuromas, and thickened corneal nerves. Genetic analysis has discerned a heterozygous *SOS1* gene frameshift mutation.[63]

A patient with MEN 1 and MEN 2B features without any mutations in *RET* has been reported.[65] The patient presented with typical MEN1 features (PHPT, Cushing's syndrome, pheochromocytoma, Zollinger–Ellison syndrome, pituitary adenoma, bronchial carcinoid) in addition to thickened corneal nerves and pheochromocytoma. She did not have a *CDKN1B* (*p27*) or *RET* mutation, but had *RET* polymorphisms in Gly691Ser and Arg982Cys and a germline 1132delG frameshift mutation in *MEN 1*.

It seems that recent advances in understanding MEN 2 syndromes may offer changes for some of the classical approaches to hereditary tumor syndromes in the future. A delicate balance between prophylactic surgery and overtreatment needs to be preserved in these patients. As the number of families diagnosed with the less common *RET* variant mutations increases, management strategies may better shape up for these patient groups as well. A good number of studies published after the 2015 ATA MTC guidelines favor a shift in risk classification and management of MEN 2 patients. In their elegant study evaluating birth cohorts with 10-year increments within a time frame between ≤1950 and 2011-2020, Machens and co-workers beautifully demonstrated the shift from "reactive to preventative medicine" in MEN management over the years.[39] Still, anticipating when a patient with a certain *RET* mutation is going to develop the components of the disease is not always straightforward, even when there is a positive family history. For this reason, biochemical screening and regular follow-up carry utmost importance in these individuals. Regarding our country, somehow multicenter studies are still are consistent with both late diagnosis and surgical intervention in MEN 2 subjects.[66] As endocrinologists, it is our responsibility to specify and overcome the setbacks in diagnosis and follow-up to provide a more standardized healthcare for MEN 2 patients and their families.

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