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THE IMPACT OF FAMILY HISTORY ON MEDULLARY THYROID CANCER IN MEN2A PATIENTS

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MEN2A PATIENTS

A

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THE IMPACT OF FAMILY HISTORY ON MEDULLARY THYROID CANCER IN MEN2A PATIENTS

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The American Thyroid Association recently classified all MEN2A-associated codons into increasing risk levels A-C and stated that some patients may delay prophylactic thyroidectomy if certain criteria are met. One criterion is a less aggressive family history of MTC but whether families with the same mutated codon have variable MTC aggressiveness is not well described. We developed several novel measures of MTC aggressiveness and compared families with the same mutated codon to determine if there is significant inter-familial variability. Pedigrees of families with MEN2A were reviewed for codon mutated and proportion of *RET* mutation carriers with MTC. Individuals with MTC were classified as having local or distant MTC and whether they had progressive MTC. MTC status and age were assessed at diagnosis and most advanced MTC stage. For those without MTC, age was recorded at prophylactic thyroidectomy or last follow-up if the patient did not have a thyroidectomy. For each pedigree, the mean age of members without MTC, with MTC, and the proportion of *RET* mutation carriers with local or distant and progressive MTC were calculated. We assessed differences in these variables using ANOVA and the Fisher's exact test. Sufficient data for analysis were available for families with mutated codons 609 (92 patients from 13 families), 618 (41 patients from 7 families), and 634 (152 patients from 13 families). The only significant differences found were the mean age of patients without MTC between families with codon 609 and 618 mutations even after accounting for prophylactic thyroidectomy (p=0.006 and 0.001, respectively), and in the mean age of MTC

diagnosis between families with codon 618 and 634 mutations even after accounting for symptomatic presentation (*p*=0.023 and 0.014, respectively). However, these differences may be explained by generational differences in ascertainment of *RET* carriers and the availability of genetic testing when the proband initially presented.

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ABBREVIATIONS

ATA: American Thyroid Association

CCH: C-cell hyperplasia

MDACC: MD Anderson Cancer Center

MEN2: Multiple Endocrine Neoplasia Type 2

MTC: Medullary Thyroid Cancer

N0MTC: Medullary Thyroid Cancer with No Lymph Node Metastases

N1MTC: Medullary Thyroid Cancer with Lymph Node Metastses

M1MTC: Medullary Thyroid Cancer with Distant Metastases

NED: No Evidence of Disease by Family Report

NEDP: No Evidence of Disease (MTC) on Prophylactic Thyroidectomy

NEDTI: No Evidence of Disease (MTC) with Thyroid Intact

PHEO: Pheochromocytoma

PHPT: Primary Hyperparathyroidism

RET: Rearranged During Transfection Proto-oncogene

TICt: Thyroid Intact with Elevated Calcitonin

Background

       Multiple Endocrine Neoplasia 2A (MEN2A) is an autosomal dominant cancer

predisposition syndrome affecting approximately 1/30,000 people worldwide [1]. It is

characterized by a high risk for medullary thyroid cancer (MTC) as well as risk for

pheochromocytoma (PHEO) and primary hyperparathyroidism (PHPT). The first

presentation and most common cause of morbidity and mortality in MEN2A is MTC, which

affects approximately 90% of patients [2,3]. MTC is a malignant neuroendocrine tumor

comprising approximately 5% of all thyroid cancers but accounting for a disproportionate

number of thyroid cancer-related mortality [4]. It is derived from the parafollicular

calcitonin-producing C-cells of the thyroid and starts as C-cell hyperplasia (CCH) and over

time leads to MTC, which may then metastasize to cervical lymph nodes and distant organs

such as the liver, lungs, and bone [3,5]. The treatment for MTC typically includes a total

thyroidectomy with central neck dissection; additional lymph node dissection may be

performed if metastases are suspected. When local lymph node metastases are present,

treatment is less likely to result in cure, and is typically incurable once spread to distant sites

[2]. Progression of MTC is typically monitored with the aid of serum calcitonin levels,

which increase with volume of MTC and may also be elevated in patients with CCH.

       MEN2A is associated with a limited number of recurring germline missense

mutations in the Rearranged During Transfection proto-oncogene (*RET*). Strong genotype-

phenotype correlations are well documented, though significant intra- and inter-familial

variability exists [2,6]. The American Thyroid Association (ATA) has categorized all known

MEN2A-causing mutations into three risk levels based on the aggressiveness of MTC

associated with each mutation [2]. These risk levels are used to guide the timing of

thyroidectomy in pre-symptomatic MEN2A patients, which greatly reduces the risk for an advanced thyroid cancer [7,8]. Patients in risk levels A and B may delay surgery beyond five years of age if the following criteria are met: a normal neck ultrasound, a normal calcitonin measurement, a less aggressive family history of MTC, and if the family would prefer to wait. Patients in risk level C are recommended to have a thyroidectomy by age 5 years, with the specific timing dependent upon the findings of ultrasound and calcitonin levels [2].

While the potential benefits of a prophylactic thyroidectomy are clear, delaying surgery may be beneficial for children with less-aggressive *RET* mutations, although this is controversial [9]. In these patients, MTC before the second decade of life is rare and children with normal annual calcitonin levels and thyroid ultrasounds are not likely to develop metastases [2,10]. Children undergoing thyroid surgery have more complications such as vocal cord paresis and hypocalcemia than adults, especially when they do not have access to a high-volume surgeon at a multidisciplinary center [9,11]. After surgery, the management of hormone therapy may be challenging for both the patient and family [9]. These considerations suggest that delaying prophylactic thyroidectomy may be a valid option for some patients, though the ideal timing of thyroidectomy and safety of delayed thyroidectomy is still unclear [3].

Most of the criteria proposed by the ATA for delaying thyroidectomy have been evaluated with regard to effectiveness of predicting the presence of MTC. Annual serum calcitonin screening is a powerful method used to screen for MTC and has been validated in many studies [12,13,14,15]. A serum calcitonin level of less than 40 pg/ml strongly indicates metastases are not present [8,16]. Limitations of calcitonin screening are also well studied, and this method may miss early MTCs [17]. Recently, a study evaluating ultrasound in

pediatric patients with MEN2A concluded it is not a useful method to detect microscopic

MTC and performs with a sensitivity of only 13% [18].

The criterion of a "less aggressive family history" is not well defined. To our

knowledge, no studies have established the relationship between family history of MTC and

MTC outcomes in MEN2 patients independent of genotype. The aim of this study is to

examine intra- and inter-familial variability of MTC within families with the same germline

RET codon mutation.

Methods

Approval from both the University of Texas MD Anderson Cancer Center (MDACC)

and Graduate School of Biomedical Sciences (GSBS) institutional review boards were

obtained for this retrospective chart review.

Participants

Pedigrees of families with MEN2A were acquired through institutional surgical and

genetic counseling databases. Almost all pedigrees were taken by one of three certified

genetic counselors with expertise in MEN2A. According to standard cancer pedigree

nomenclature, information obtained in each pedigree included a minimum of two generations

above the family member interviewed. Targeted questions were asked about each family

member's history of MTC including the stage, and treatment, genetic testing status, and

whether prophylactic thyroidectomy was performed. Each family member's age of cancer

diagnosis and current age or age of death was recorded [19].

Pedigrees had at least one MDACC patient and were not separated for related patients

and are updated as patients follow-up. If the pedigree had not been updated within the past

two years, ages were calculated to reflect what was known at last follow-up. We reviewed

each pedigree for *RET* mutation positive family members. Any family member with a diagnosis of MTC, pheochromocytoma, or primary hyperparathyroidism was presumed to be a *RET* mutation carrier. Obligate carriers were also recorded as *RET* mutation carriers. The proband was defined as the first person diagnosed with MTC.

Each *RET* mutation carrier was classified by MTC status (figure 1).

Figure 1: *RET* Mutation Carrier Classification

RET mutation carriers were classified into the above groups. Information for MDACC patients was obtained from the medical record and information about outside patients was recorded based on family report.
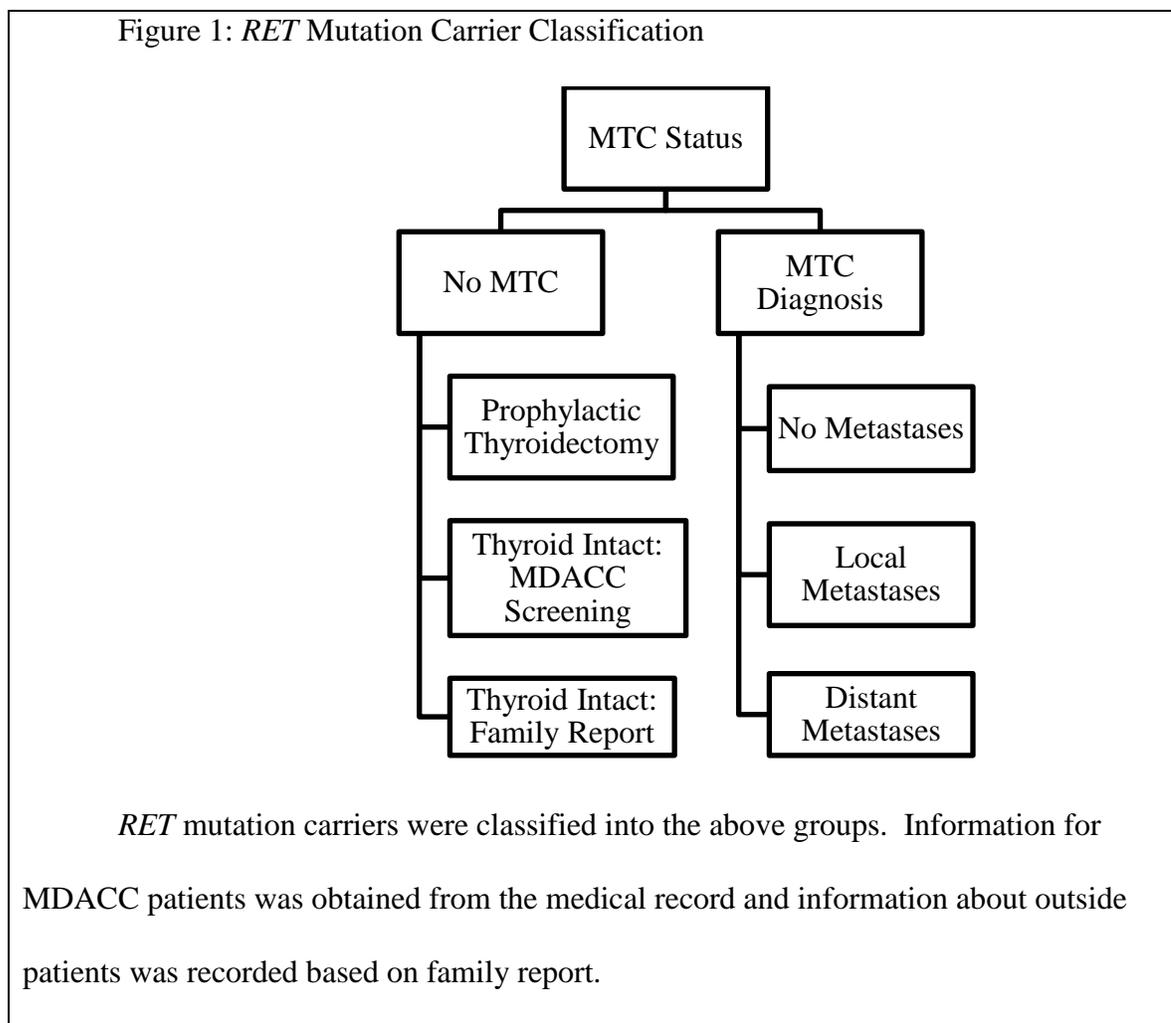
For patients with MTC, MTC status was recorded both at the time of diagnosis and at the patient's most advanced MTC stage. Those with an MTC diagnosis were also recorded as having progressive or non-progressive MTC. Progression was defined as clear

radiographic growth of MTC, a calcitonin doubling time of less than two years, development of new metastases, or MTC-related death.

Ages were recorded at the time of prophylactic thyroidectomy or last follow-up if the patient did not have a thyroidectomy for those without MTC and at the time of MTC diagnosis and most advanced MTC stage for those with MTC. We also recorded how patients came to clinical attention and whether they presented due to symptoms of MTC or through screening due to family history or a positive *RET* test.

Pedigrees with fewer than four *RET* mutation carriers, an unknown mutated codon or variant of uncertain significance (VUS) were excluded. Individuals who tested negative for the familial *RET* mutation, whose *RET* status was unclear, and those who had an intact thyroid with elevated calcitonin but no clear diagnosis of MTC were excluded from the study.

Statistical Analysis

The following calculations were performed for each pedigree: (1) mean age and standard error of *RET* carriers with no MTC (2) mean age and standard error of MTC diagnosis (3) proportion of carriers with MTC who had metastases at diagnosis (4) proportion of carriers with MTC who had metastases at most advanced MTC stage (5) proportion of carriers with MTC who had disease progression (figure 2).

Figure 2: Pedigree calculations
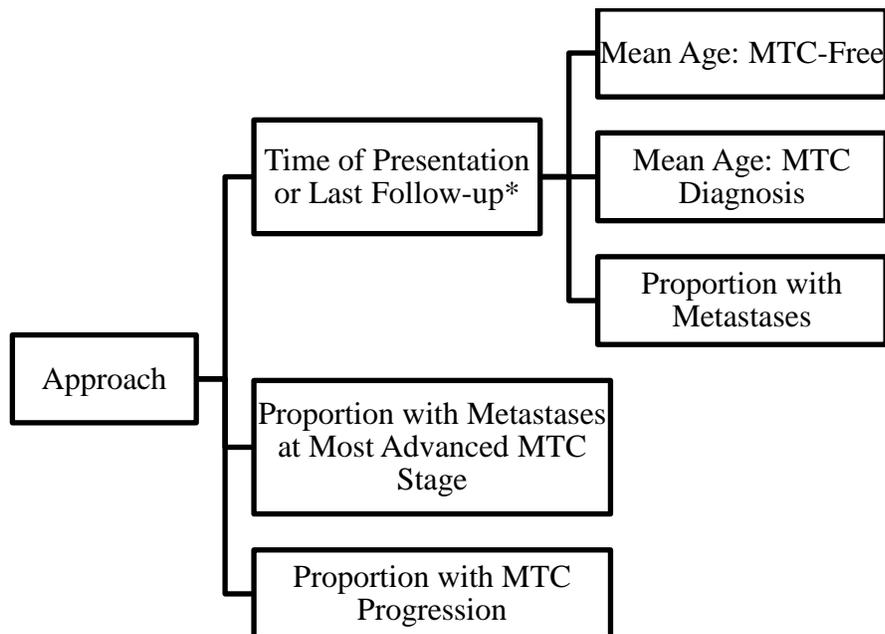
* Last follow-up applies only to MTC-free patients who have not had a thyroidectomy. The above calculations were performed for each pedigree. Differences in each variable were compared between families with the same mutated codon.

Calculations performed at the time of most advanced MTC stage included only patients seen at MDACC to confirm the diagnosis.

Differences in the mean age of individuals with and without MTC between families with mutations in the same codon were compared to each other using one-way analysis of variance (ANOVA) with SPSS21. If the resulting p-value from the ANOVA omnibus test was <0.05, Tukey's post-hoc test was used to evaluate all two-way differences. Differences in proportion of MTC metastases and MTC progression between families with mutations in the same codon were assessed using Fisher's exact test using STATA10 software. Significant differences were achieved if $p<0.05$.

Results

A total of 175 pedigrees were reviewed with mutations identified in 11 codons (table 1).

Table 1: Pedigrees Arranged by Mutated Codon and ATA Risk Level				
Mutated Codon	Number of Pedigrees Reviewed (Number Included)	Number of *RET* Mutation Carriers	Number of *RET* Mutation Carriers with MTC (%)	Number of Affected Family Members Included
804	12	--	--	--
891	5	--	--	--
666	3	--	--	--
791*	3	--	--	--
790	1	--	--	--
912	1	--	--	--
891+791*	1	--	--	--
Total Pedigrees Risk Level A: 26				
620	8	--	--	--
611	2	--	--	--
609	21 (13)	92	46 (50)	92
618	20 (7)	41	22 (54)	41
Total Pedigrees Risk Level B: 51				
634	34 (13)	152	113 (74)	152
Total Pedigrees Risk Level C: 34				
Unknown Codon Mutated/ Risk Level: 9				
*Patient had bi-allelic *RET* mutations. Pedigrees with fewer than four affected family members were excluded from the study.				

Due to limitations in the number of families and affected members, comparisons of mean ages were restricted to codons 609 (92 individuals from 13 families), 618 (41 individuals from 7 families), and 634 (152 individuals from 13 families) and comparisons of proportions were limited to codon 634. The median age of all family members, the percent of patients seen at MDACC, the percent of patients with symptomatic presentation, and the range of years of first MTC diagnosis representing each codon were recorded (table 2).

| Table 2: Each Codon Represented by Age, Patient Ascertainment, Patient Presentation and Year of First MTC Diagnosis			
	Codon 634	Codon 609	Codon 618
Patient Ascertainment			
MDACC	94 (62%)	30 (33%)	9 (22%)
Family Report	58 (38%)	62 (67%)	32 (78%)
Patient Presentation			
Symptomatic	39 (26%)	17 (18%)	8 (20%)
Screened	113 (74%)	75 (82%)	33 (80%)
Range of First MTC Diagnosis	1944-1992	1970-2011	1969-2001
Range of Ages	2-68	2-79	2-91
Median Age MTC Diagnosis	26	44	37
Median Age MTC-Free	25	28	30
The range and median age in years of family members representing each codon was recorded.			

Patient MTC Status

Overall, 133 patients were MTC-free with 50 having no evidence of MTC upon prophylactic thyroidectomy, 11 having no evidence of MTC upon screening at MDACC, and 72 having no evidence of MTC based on family report. There were 211 patients with an MTC diagnosis. Among these patients, 178 had no metastases, 28 had local metastases, and 5 had distant metastases.

Statistical Analyses

Mean Ages

Among families with a mutation in codon 634, differences in mean age of MTC diagnosis was observed after excluding individuals with symptomatic presentation (p=0.014). Pedigree 4 had an older age of MTC diagnosis (35.6 years) than pedigree 12 (12.5 years) and pedigree 68 has an older age of MTC diagnosis (40.6 years) than pedigrees 12 and 102 (5 years, figure 3).

Figure 3: Mean age of MTC Diagnosis Excluding Individuals With Symptomatic Presentation for Families with Mutations in Codon 634
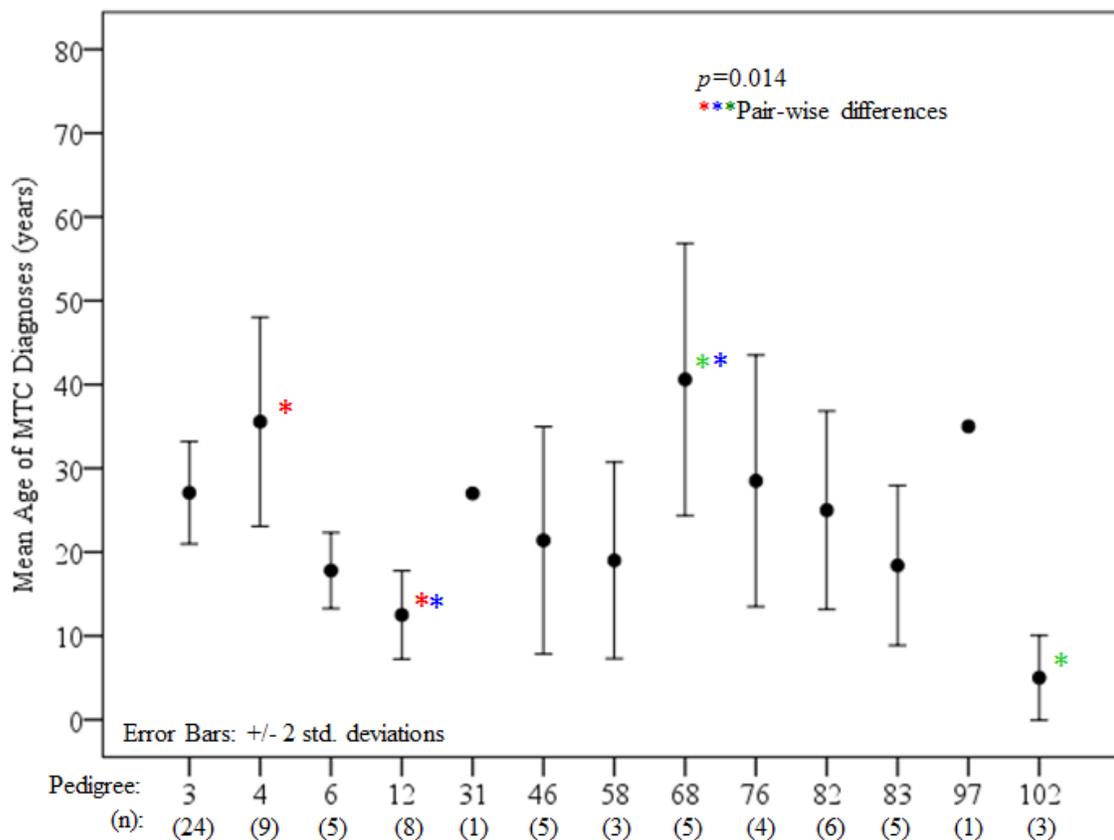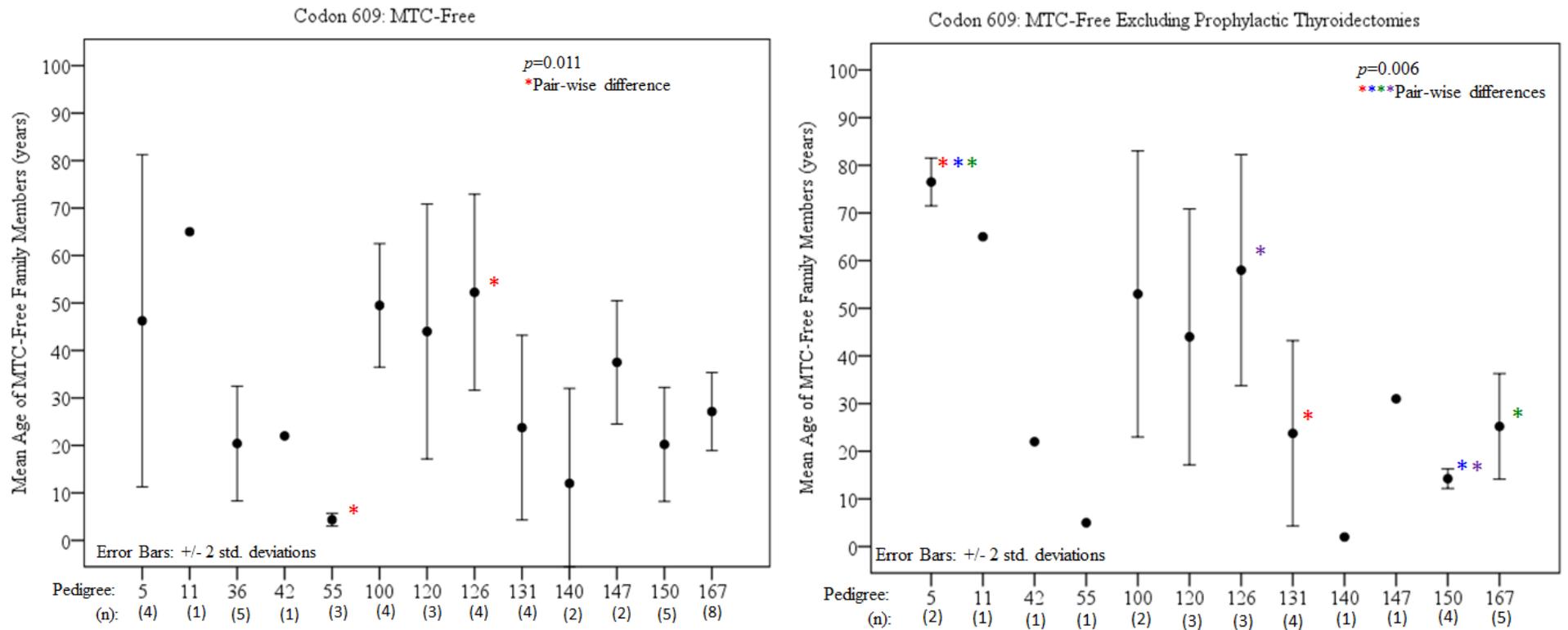

Significant differences were found among the average age of MTC diagnosis after excluding individuals with symptomatic presentation for families with a mutation in codon 634. Pair-wise differences are indicated by colored astrices.

Among pedigrees with an older mean age of MTC diagnosis, pedigree 4 is represented by 9 family members with 6 being in the same generation or a generation above the proband. Pedigree 68 is represented by family members in the same generation or a generation above the proband. Among pedigrees with a younger mean age of MTC diagnosis, both pedigrees 12 and 102 were represented by family members in the same generation or generations below the proband.

Significant differences in mean age were found among MTC-free family members with a mutation in codon 609 (p=0.011) with pedigree 126 having an older mean age (52 years) than pedigree 55 (4 years, figure 4). The difference was maintained after excluding individuals with prophylactic thyroidectomies (p=0.006). In this analysis, pedigree 5 has an older mean age (76 years) than pedigrees 131 (23 years), 150 (14 years), and 167 (25 years) and pedigree 126 has an older mean age (58 years) than pedigree 150 (14 years, figure 4).

Figure 4: Mean Age of MTC-Free Family Members for Families with Mutations in Codon 609
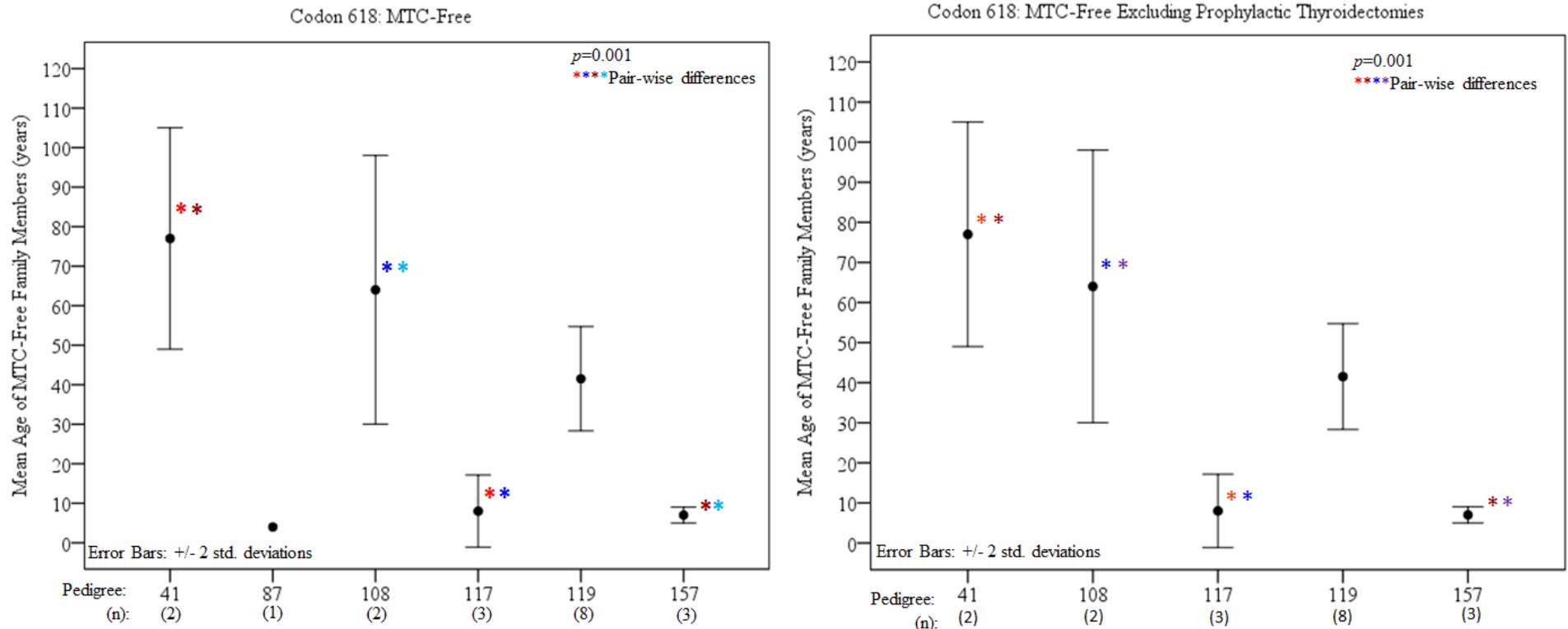

Significant differences were found among the mean age of MTC-free individuals even after excluding those with prophylactic thyroidectomies for families with a mutation in codon 609.

Among pedigrees with an older mean age of MTC-free family members, pedigree 126 is represented by primarily by family members in generations below the proband, but the familial *RET* mutation was known in 2008 when the proband's niece pursued genetic testing at 64 years of age. Subsequent *RET* testing and medical intervention identified mutation carriers who had not yet developed MTC. Pedigree 5 also has an older mean age of MTC-free family members and is represented by family members in the generation above the proband. All pedigrees with younger mean age of MTC-free family members (55, 131. 150, and 167) are represented by members in the same generation or generations below the proband.

Among families with a mutation in codon 618, differences were found among the mean age of MTC-free family members (p=0.001). None of these individuals had prophylactic thyroidectomy. Pedigrees 41 and 108 had older mean ages (77 and 64 years, respectively) than pedigrees 117 and 157 (8 and 7 years, respectively, figure 5).

Figure 5: Mean Age of MTC-Free Family Members for Families with Mutations in Codon 618

Significant differences were found among the mean age of MTC-free individuals even after excluding those with prophylactic thyroidectomies for families with a mutation in codon 618.

A significant difference was found when comparing mean ages of MTC diagnosis (p=0.036) with pedigree 41 having an older mean age (55 years) than pedigree 119 (20 years). There was still a difference after excluding individuals with symptomatic presentation (p=0.004) with pedigree 41 having an older mean age (63 years) than pedigrees 117 and 119 (34 and 16 years, respectively, figure 6).
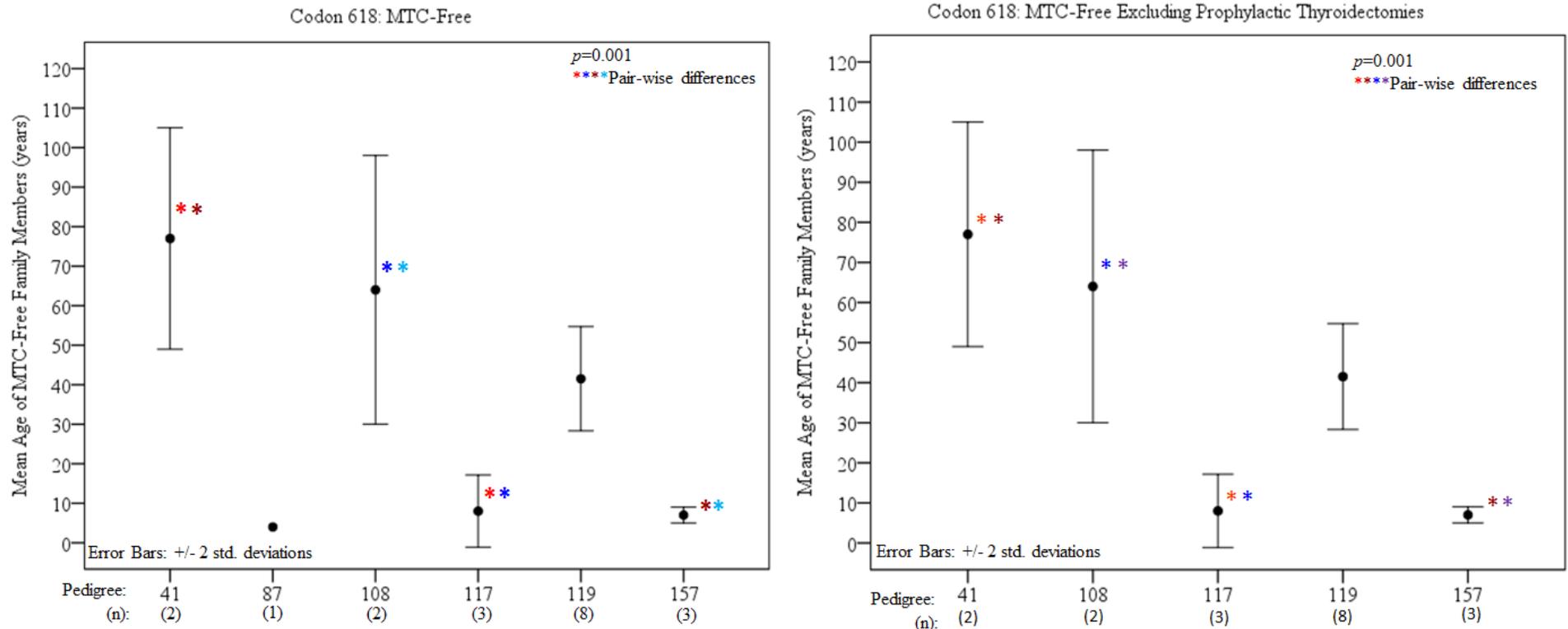
Figure 6: Mean Age of MTC-Free Family Members for Families with Mutations in Codon 618

Significant differences were found among the mean age of MTC-free individuals even after excluding those with prophylactic thyroidectomies for families with a mutation in codon 618.

Pedigree 41 has an older mean age of family members with and without MTC and is represented by three generations of *RET* mutation carriers. The first MTC diagnosis dates back to the mid-1900s, but several MTC diagnoses were not made until genetic testing became available in the late 1990's. Pedigree 108 has an older mean age of MTC-free members and is represented by individuals in generations above the proband.

Among pedigrees with younger mean ages of family members with and without MTC, all pedigrees (117 and 157 for MTC-free and 117 and 119 for MTC diagnoses) are represented by individuals in generations below the proband.

Proportion of family members

No differences were found among the proportion of family members with metastases at presentation or at most advanced MTC stage even after excluding individuals with symptomatic presentation. No differences were found in the proportion of family members with MTC progression after excluding individuals with symptomatic presentation even after excluding individuals with symptomatic presentation (figure 7).

Figure 7: The Proportion of Family Members with Metastases at Diagnosis and Most Advanced MTC Stage
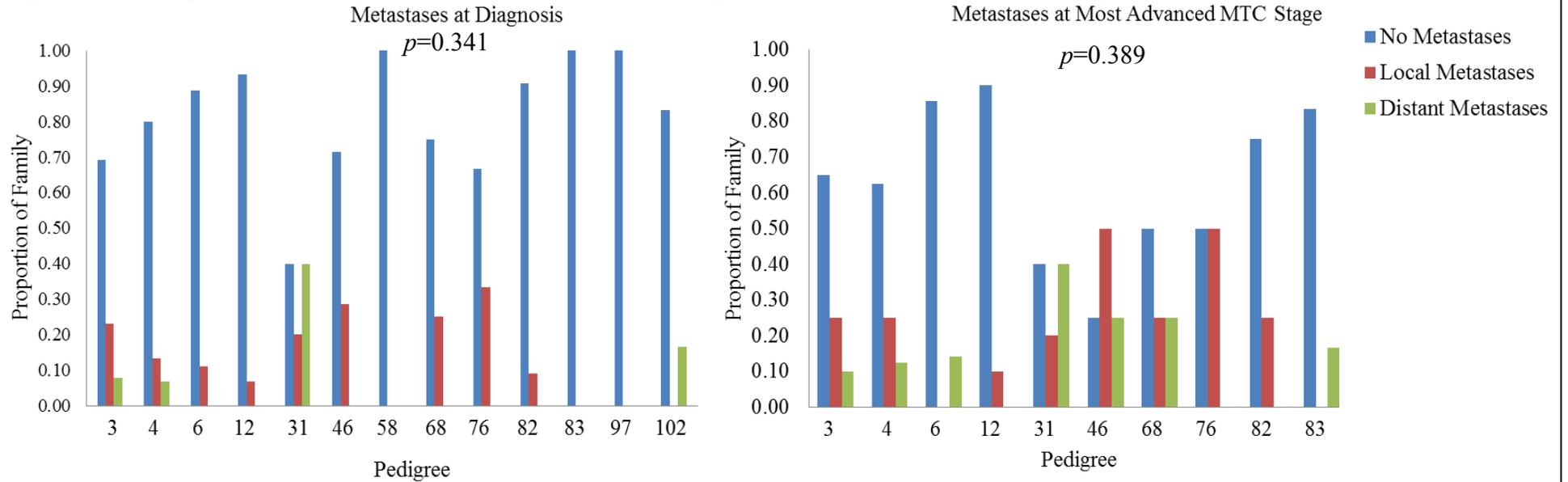
No differences were found among the proportion of family members with metastases at diagnosis or at most advanced MTC stage. No differences were found after excluding individuals with symptomatic presentation ($p=0.957$ at diagnosis, $p=.715$ at most advanced MTC stage.

Discussion

The current study aims to assess if MEN2A kindreds with the same mutated codon have different family histories from each other based on several novel measures of MTC aggressiveness. We assessed differences in the mean age of family members with and without MTC controlling for prophylactic thyroidectomy to determine whether some families have an earlier age of onset of MTC than others. We assessed differences in the proportion of *RET* mutation carriers with MTC who had metastases both at the time of diagnosis and at the time of most advanced MTC stage and the proportion with MTC progression in an attempt to have a measure of biological aggressiveness of MTC within each family. Information about patients followed at outside institutions was included to increase the number of eligible patients and to minimize ascertainment bias.

At first glance, our results suggest that there may be inter-familial variability of MTC age of onset between kindreds with mutations in the same codon. However, two factors appear to consistently contribute to inter-familial variability: generational differences in ascertainment of *RET* mutation carriers and the availability of genetic testing. Families with a younger mean age of presentation tend to have a greater proportion of members ascertained in generations below the proband, while families with an older mean age of presentation are primarily represented by individuals in generations above the proband. This observation can be appreciated in pedigrees 68 and 102 (figure 8) and suggests that differences in mean age are due to generational differences of family members in relation to the proband.
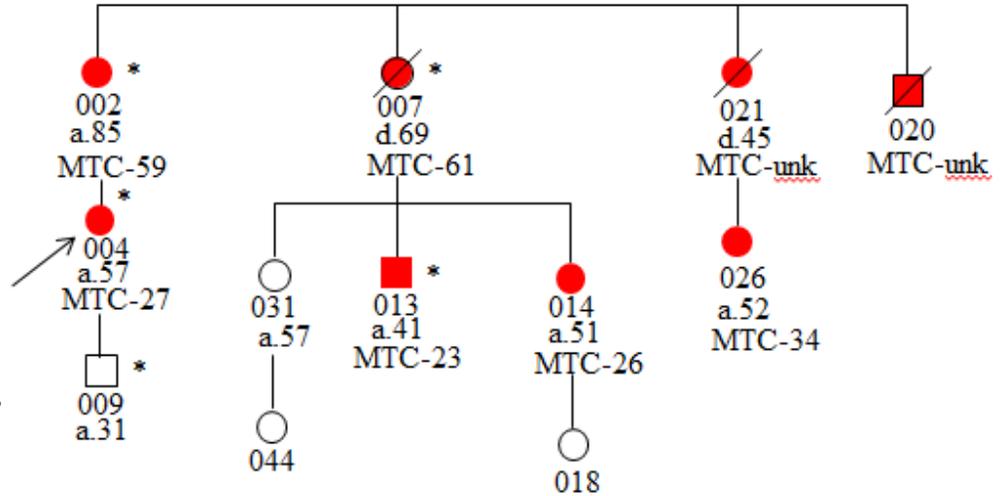
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Figure 8: Generational differences in the ascertainment of RET mutation carriers and Mean Age of

MTC Diagnosis

● MTC Diagnosis
○ MTC-free RET mutation carrier
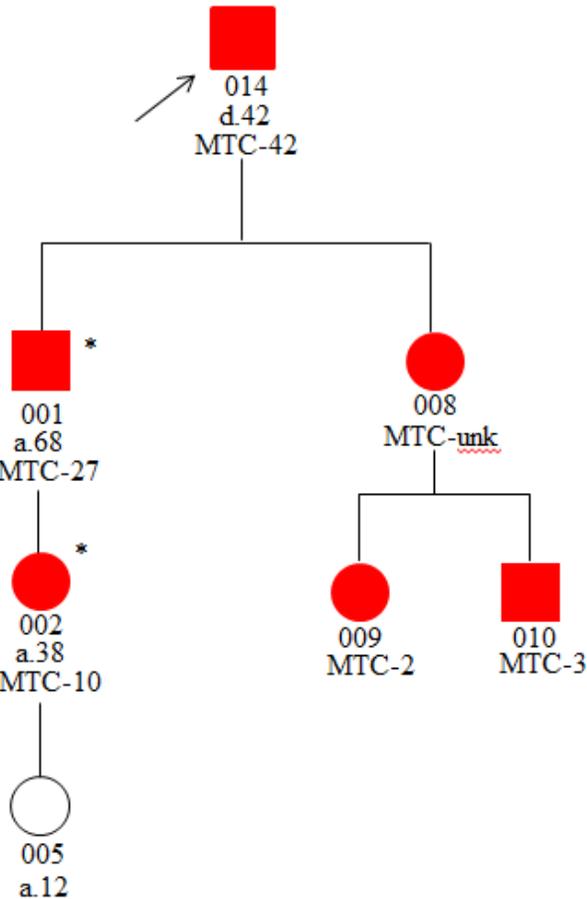

Pedigree 68

Mean Age of MTC
Diagnosis: 40.6 years

Pedigree 102

Mean Age of MTC
Diagnosis: 5.0 years

Note that pedigree 68 has an older mean age of MTC diagnosis and all family members with MTC

are in the same generation or in a generation above the proband. Pedigree 102 has a younger mean

age of MTC diagnosis and all family members with MTC are in generations below the proband.

It is possible that information about the proband's MTC diagnosis and/or *RET* mutation status is being communicated to family members who opt to have themselves and subsequently their children screened.

It also appears that some families with an older presentation came to attention before genetic testing was available. The ages and years of MTC diagnosis for pedigree 41 highlight this observation (figure 9).

Figure 9: The Availability of Genetic Testing and Mean Age of MTC Diagnosis

Pedigree 41

Mean Age of MTC Diagnoses:
63.5 years
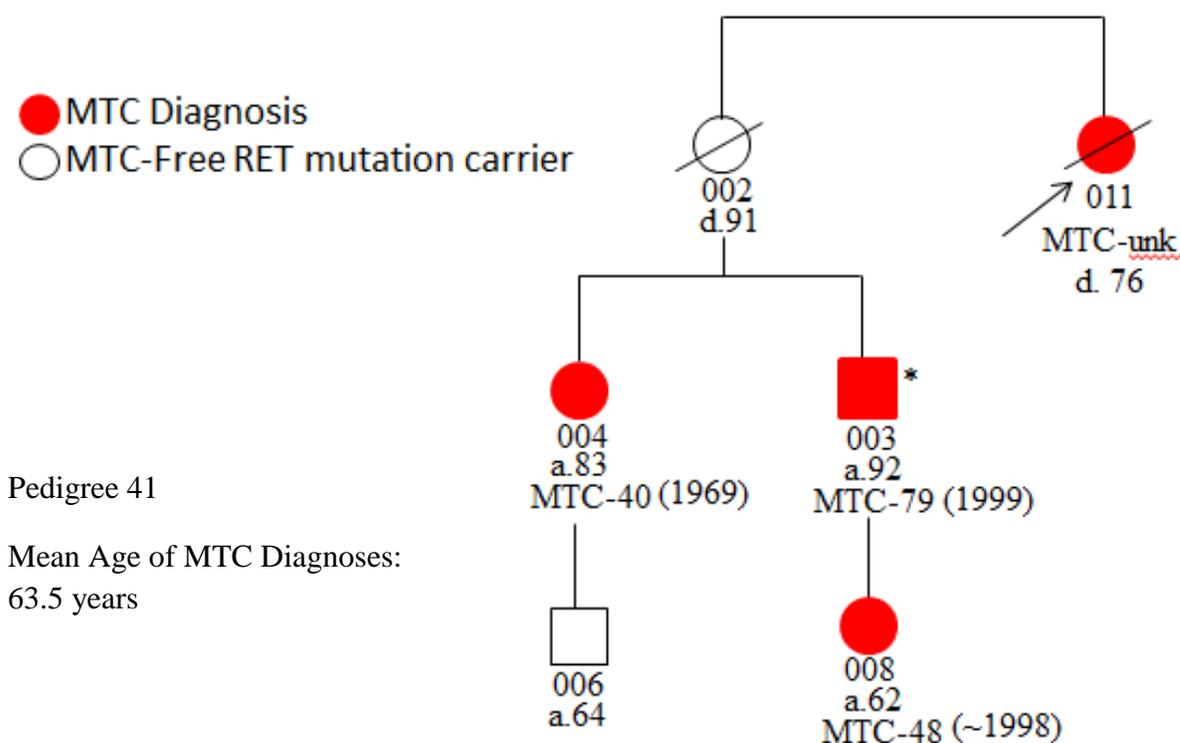
Note the years of MTC Diagnoses. Patient 003 did not come to clinical attention until his sister's diagnosis of MTC and subsequent *RET* testing in the mid01990's. He and his daughter were found to carry the familial *RET* mutation and were positive for MTC on thyroidectomy.

It also appears that some families with an older presentation came to attention before genetic testing was available. The ages and years of MTC diagnosis for pedigree 41 highlight this observation (figure 9). Additionally, this suggests that since genetic testing has become available, family members are opting to test once a mutation is found in the family, making young MTC diagnosis likely.

Overall, the current study suggests that apparent differences in the presentation of MTC between families with the same mutated *RET* codon are due to ascertainment of family members in generations older or younger than the proband and the availability of genetic testing as opposed to true biological differences. To our knowledge, this is the first study attempting to quantify familial MTC aggressiveness and compare these measures between families with the same mutated *RET* codon. The primary limitation is the number of eligible patients. Several analyses could not be performed including assessing differences in families with mutations in codons other than 609, 618, and 634. Additionally, many of our analyses were dependent upon the accuracy of the historian and the genetic counselor as a scribe.

Current MEN2A recommendations state that prophylactic thyroidectomy may be delayed if certain criteria are met. One criterion is a less aggressive family history of MTC, which implies that some families have a more aggressive disease course than other with mutations in the same codon. The results of the current study do not support inter-familial variability between families with mutations in the same codon based on average age of MTC onset and the proportion of the family with metastatic disease at diagnosis and most advanced MTC stage.

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<u>VITAE</u>

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