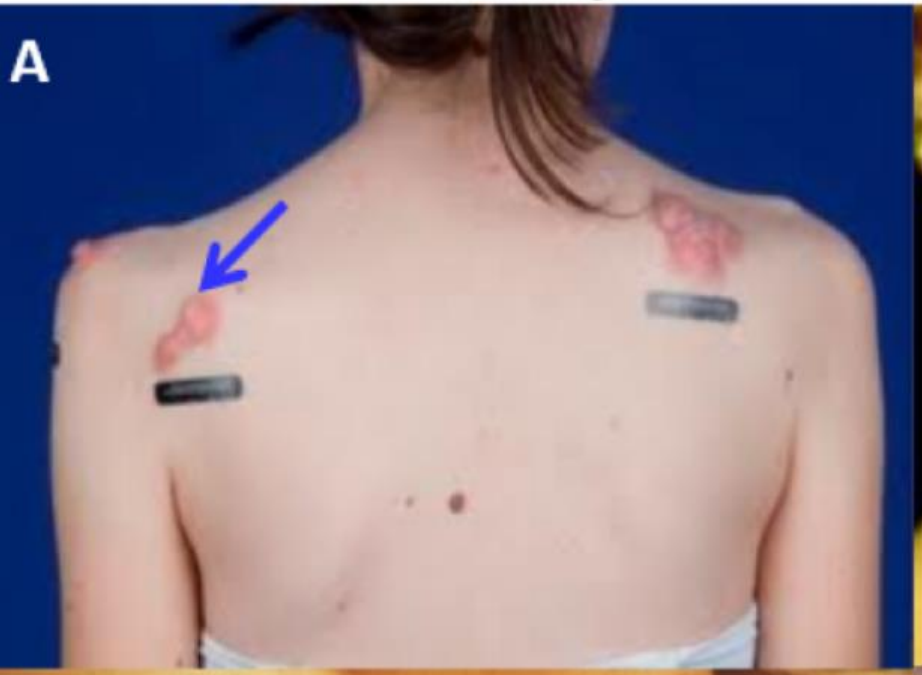

بسم الله النور

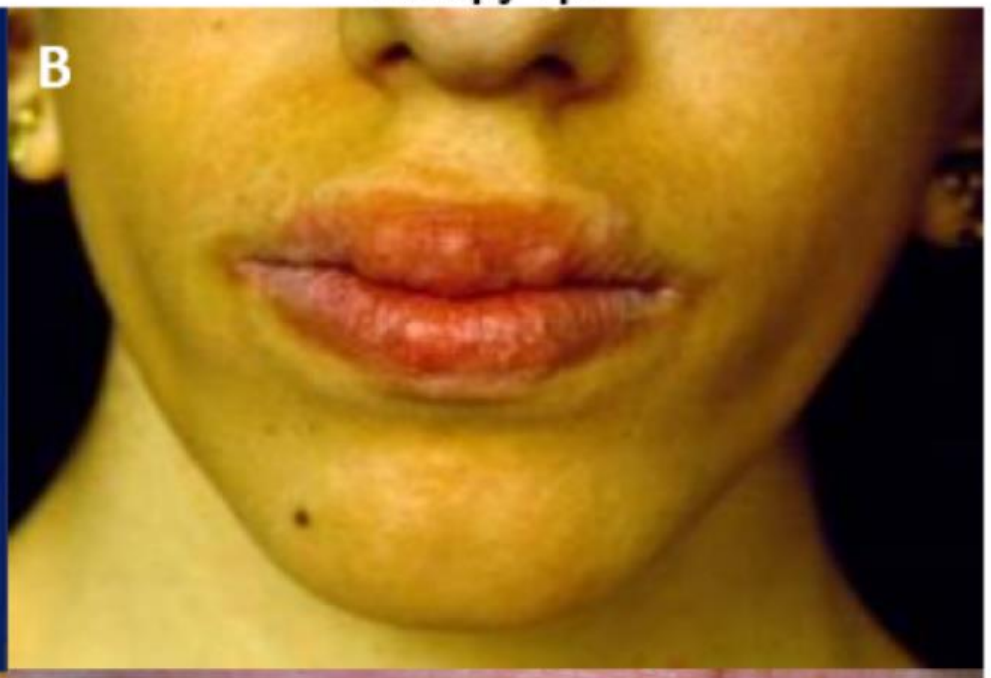
Update on the Diagnosis of Medullary Thyroid Cancer

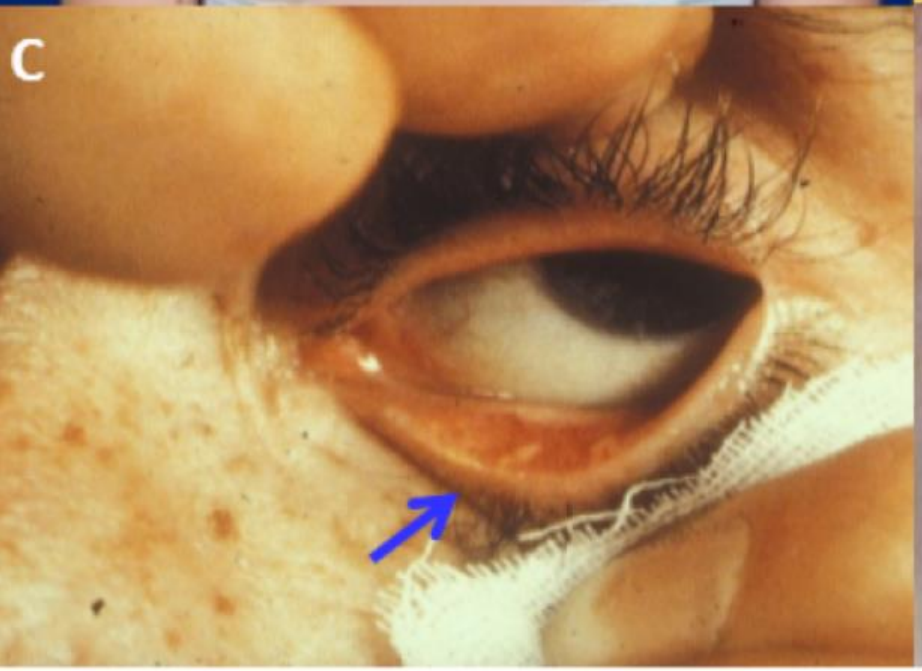
What Has Changed in Recent Years?

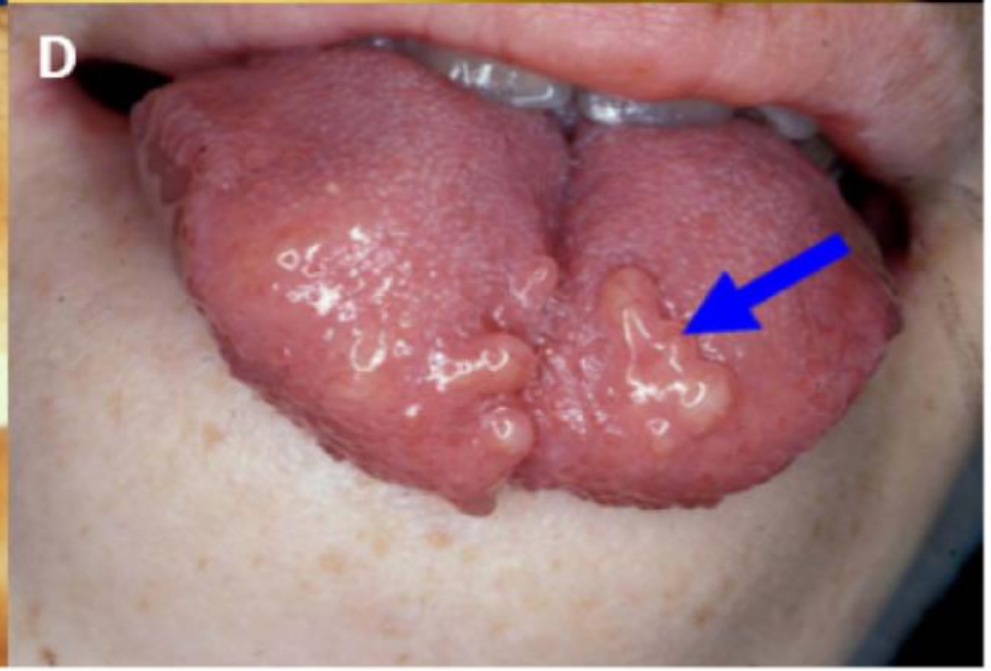
Coetaneous lichen amyloidosis

Bumpy lips









Eyelid Mucosal neuroma

Tung Mucosal neuroma

MTC

- A rare calcitonin secreting neuroendocrine tumor that arises from parafollicular C-cells
- The most aggressive and life-threatening of the pediatric thyroid malignancies
- incidence in children **0.03 per 100 000 population per year**
- 3 to 5% of thyroid malignancies
- **E**qual female to male ratio
- **The age at diagnosis is 0–17 years**

Clin Cancer Res; 2018

J Pediatr Oncol 2015

RET gene

- **protooncogene** :**A gene involved in normal cell growth**
- The RET gene is a protooncogene encoding a protein that is part of the receptor for tyrosine kinase

- is expressed in the neural crest-derived cell types, including thyroid parafollicular cells, neuronal cells, and adrenal medullary chromaffin cells
- localized on the chromosome 10 and contains 21 exons

- *J Pediatr Oncol. 2015*

RET gene

- Tyrosine kinases are important mediators for cell proliferation, differentiation, migration, metabolism and programmed cell death.
- Mutations in a proto-oncogene may cause it to become an oncogene, which can cause the growth of cancer cells
- MTC caused by germline, activating mutations in the RET proto-oncogene

- *J Pediatr Oncol. 2015*

Hereditary MTC

- The majority of pediatric MTC is **hereditary**
- inherited **autosomal dominant manner**

Cancers 2022

Hereditary MTC

- Is as a part of multiple endocrine neoplasia
- **MEN** **T**ype 2A — **changes at codons 609, 618, 620 and 634**
- **MEN** **Type** 2B — M918
- ***FMTC***

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Somatic RET mutation

- *The most common* ***somatic Ret mutation*** *in sporadic patients*
- Approximately **23 to 70%** of true sporadic MTC have been shown to harbour somatically *RET mutations*

Exon 16	**Codon918T**	**50%**
Exon 11	Codon 630, 634	
Exon 10	Codon 609, 620	
Exon 15	Codon 891	
RAS gene	20–25% of cases	

De novo RET mutations

- **In 5%–9% of patients with MEN2A, and 50 percent of cases with MEN2B**
- RET mutation arises **de novo** and almost always from the **paternal allele**

De novo activating mutations

- patients with de novo germline mutations
- **Are not** recognized early in life
- present with locally advanced or metastatic MTC
- **Even 6–10%** of apparently sporadic cases of MTC demonstrate *de novo germ-line RET mutations*

Sporadic MTC

- Sporadic MTC is very **rare** in children <5%
- The onset of the disease in sporadic cases is between the ages **of 50 and 60 years with worse prognosis**
- **1%–7% of patients** with presumed sporadic MTC actually have **hereditary disease**
- Patients with sporadic MTC should have genetic counseling and direct DNA analysis to detect a mutated RET allele
- Seminars in Pediatric Surgery 2020

Sporadic MTC

- While the majority of adult MTC are typically sporadic (65%-75%)
- Mutations involving **codons C630 and A883, as well as H568 and S1024,** are mainly reported in sporadic cases
- Somatic mutation in the RAS gene reported in sporadic cases

The importance of genetic in diagnosis of MTC

- Recognition of the genetic events responsible for MEN 2 have significantly improved our ability to diagnose and manage the disease before the onset of disease symptoms and the associated **morbidity or mortality**

Why should we do genetic counseling?

- specific *RET* mutation and facilitate family screening
- To detect the age at initial diagnosis of MTC
- Eliminates the need for biochemical testing in negative cases
- It avoids unnecessary thyroidectomy

Up to date2023

Why should we do genetic counseling?

- **To reduce the incidence of MTC** in the families affected by these
- To reduce MTC carrying
- Identifying people are at risk of inheriting a RET mutation??
- Identify people who have inherited a *MEN2-RET* mutation before the onset of disease symptoms and the associated morbidity or mortality
- If a member of a family with a known *MEN2-RET mutation is found not to* have that mutation, **they are not considered at risk of MEN 2** and should not require further screening.

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What people should be Genetic counseling?

- Children of patients with MEN2B should undergo *RET analysis at **birth***
- **parents whose** infants or young children have the classic phenotype of MEN2B
- In an MEN2 family, all subjects of unknown status in that family requires *RET* genotyping

- *Children of patients with **MEN2A or FMTC** should undergo RET analysis **before age six***
- *Thus making **genetic testing** worthwhile in **all patients with MTC***

What people should be Genetic counseling?

- When the index patient is positive for a germline mutation, family members should be offered genetic counseling and genetic screening

What people should be Genetic counseling?

- *RET* mutation analysis should be performed in **first- and second-degree family member of index** case with MTC for guides surveillance and management
- For populations at high risk for hereditary MTC, such as patients with CLA and **patients with HD**

- Families whose infants or young children **have HD**

Is it possible to have a negative genetic result despite the disease?

- **In very rare cases**, *RET mutations **are not found** despite clear familial MTC.*
- *Thus, **all children** with an **affected parent** in this setting retain **a 50% risk of MTC,** and surgical decisions must rely **solely on clinical testing.and** **frequent biochemical screening***

prenatal diagnostic testing

Prenatal testing can be performed in the first or second trimester by

- Chorionic villus sampling
- Amniocentesis
- Prenatal testing on **fetal blood cells obtained** from maternal blood **(Cell free DNA)**

ATA 2015

prenatal diagnostic testing

- During the last decade, cfDNA has received special attention because of its potential application as a non-invasive, rapid, and sensitive tool for molecular prenatal diagnosis
- Detected in maternal plasma from **4th week of pregnancy** and is promptly cleared and disappears within 2 h of delivery
- Is a source of fetal genetic material for the development of non-invasive prenatal diagnosis (NIPD)
- .

prenatal diagnostic testing

- HRM analysis in serum samples as a new primary diagnosis method suitable for the detection of C634Y mutations in MEN2A patients.
- simultaneously, we have applied the increase of sensitivity of **COLD-PCR assay approach combined with HRM** genotyping analysis for the NIPD of a C634Y fetal mutation using pregnant woman serum

prenatal Diagnostic Testing

- prenatal diagnostic testing should be considered for **all RET mutation carriers of childbearing age**, particularly those with **MEN2B**
- Preimplantation genetic diagnosis is done as part of in vitro fertilization ,single embryonic cells are tested for the *RET* mutation.
- Only embryos without a *RET* mutation are then transferred to the uterus.
- This is particularly important for mutations associated with the onset of **MTC before 5 years of age**
- PGD may be an option for parents if one of them has MEN2 with RET mutations in **codons 634 and 918**

ATA 2015

prenatal diagnostic testing

- **PGD is now used to prevent various types of inherited cancer conditions based on**
- Development of PGD technology
- Assisted reproductive techniques
- *in vitro* fertilization (IVF)

prenatal diagnostic testing

Not indication PGD for MEN2A because

- MEN2A who have been treated by prophylactic thyroidectomy and are alive without evidence of recurrent MTC decades later
- parents to spend a substantial amount of money

prenatal diagnostic testing

- Parents who do not wish to have prenatal RET mutation testing should be offered genetic counseling their child to detect a mutated RET allele.
- This is particularly important for mutations associated with the onset of MTC before 5 years of age.

When should we test the entire RET coding region?

- patients with **clinical features or family history highly** suggestive of hereditary MTC who demonstrate no mutations in exons 10, 11, or 13 through 16
- **A discrepancy between** the MEN2 phenotype and the expected genotype

Detection of RET mutations in MEN2A

- Patients with MEN2A usually have mutations in **>98%**
- Exon 10 (codons 609, 611, **618** or 620)
- Exon 11 (**codon 634,630)** **87%**
- Mutation in exon 11 first manifestation develops **before age six and sometimes before age two**
- RET codon **634 mutations** are associated with a high penetrance of **PHEO, HPTH**
- RET codon **634 mutations** develop MTC in the first years of life

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MEN2A

Develops during early childhood, usually before **age six** and sometimes **before age two**

- Autosomal dominant
- MTC **>90%**
- Bilateral pheochromocytoma **50%**
- Multiple tumors of parathyroid glands **10-25%**
- **Rare variants** of MEN2A are also associated with cutaneous lichen amyloidosis and Hirschsprung disease **16%**

MEN2A

There should be four variants

- Classical : MTC and the less frequent PHEO, or HPTH, or both
- MEN2A with CLA
- MEN2A with HD
- FMTC : subtype MEN2A
- FMTC: individuals with RET germline mutations who have MTC **but neither PHEOs nor HPTH**

PHEO& MEN2A

- **Pheochromocytoma** **634**
- Exon **11,** 16 **634 , 918** **50%**
- Exon **10** **(609**,611,**618 and 620)** **17%**
- Exon 13-15 (791 and 804)
- PHEO **is rare in families** with mutations in codons 533,, 630, 633, 666, 768, 790, and 891

PHEO& MEN2A

- Almost always **benign** and are usually **multicentric, bilateral, and confined to the adrenal gland.**
- The tumors are usually associated with **diffuse nodular adrenal medullary hyperplasia**
- Patients with MEN2A and a unilateral PHEO usually develop a **contralateral PHEO within 10 years**
- It is **unusual to precede** the development of MTC
- Extraadrenal PHEO is rare in MEN2A
- **less than 10%** is malignant

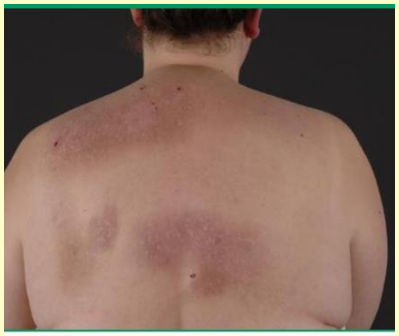
HPTH

- The HPTH in patients with classical MEN2A is usually **mild &multiglandular and asymptomatic**
- Mean age at diagnosis was *33 years*
- But children diagnosed as young as **two years of age**
-
- RET codon **609, 611, 618, and 620**
- RET codon **634** **Exon 11**
- **Exon 10**
- Yearly screening for HPTH should be done **concurrently with screening for PHEO**

MEN2A and CLA

- The CLA may be present at a young age and, thus serving as a precursor for the syndrome **prior to the onset of clinically evident MTC**
- with RET codon **634& 804**

Erythematous, maculopapular eruptions, or tumor nodules that develop on the upper chest, neck, or scalp



MEN2A and HD

- **Exon 10** **609 , 611 ,618 , 620**
- HD was found **in 50 %** of children in families with a **C620 mutation**
- HD occurs in approximately **7% of patients with MEN2A**
- Conversely, **2%–5% of patients with HD have MEN2A**
- it is important to exclude HD in **older patients** with MEN2A
- In patients with **early expression of HD**, it is useful to test for MEN2A, and this is especially important **if a family history of HD or MEN2A is present**
- the RET mutations associated with HD are ‘‘loss of function RET mutations

When should we think to MEN2A with negative RET mutation?

- There are very rare families **with features of classical MEN2A** who have **no identifiable RET germline mutation**

- . In this situation the diagnosis of classical MEN2A can be made if **one or more first-degree relatives** have characteristic clinical features of the entity
- **In the absence of an autosomal dominant** inheritance pattern or *RET* mutation, **at least two of the classical** clinical features of MEN2A are required to make the diagnosis

Detection of RET mutations in MEN2B

For the index patient with the MEN2B phenotype,initial testing included

Exon 16 RET codon**M918T** **95%**

And if negative

- **Exon 15** RET codon **A883F** **5%**

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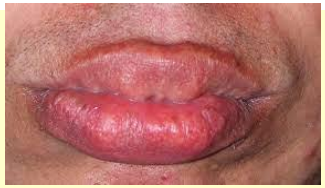
MEN2B

- while **25% of cases occur** in families with previous or current manifestations of hereditary MEN2B.
- **75% of cases are sporadic** and affected patients have **de novo RET mutations** which usually occur on the paternal allele and **phenotypically normal parents**

ATA2015

MEN2B

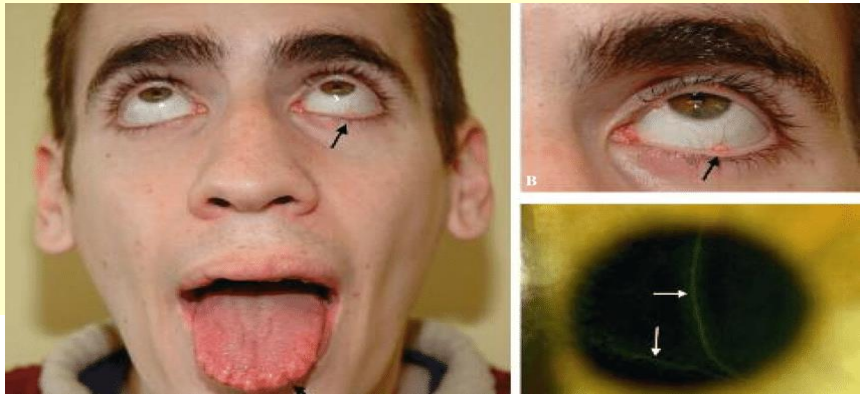


Approximately 5–10% of the MEN type 2 cases typically feature

- Median age of onset 10 years earlier than seen inMEN2A
- Early onset MTC
- pheochromocytoma **50%**
- Ganglioneuroma of buccal membranes & GI chronic constipation and megacolon 40%
- Bumpy lips and tongue
- Asthenic marfanoid body habitus **65%**
- Skeletal deformations (kyphoscoliosis or lordosis)
- joint laxity
- Neurofibromas

- *short stature*

Clinical Endocrinology. 2021



MEN2B

- inability to make tears in infancy
- Thickened and everted eyelids
- Mild ptosis
- prominent corneal nerves
- marfanoid body habitus, narrow long facies, pes cavus, pectus excavatum, high-arched palate, scoliosis, and slipped capital femoral epiphyses
- Generalized **ganglioneuromatosis** throughout the aerodigestive tract.
- Most patients have abdominal symptoms characterized by bloating, intermittent constipation, and diarrhea, and some patients require surgery for intestinal obstruction

MEN2B

- .presents **during the first year of life**
- **Highly aggressive**
- Metastasizing early to regional lymph nodes and beyond. if they do **not undergo** prophylactic thyroidectomy before **age one**
- Phenotype is usually often **not apparent at early childhood**
- Death in **50 %** versus **9.7 %** with MEN2A

MEN2B

- **Without this intervention**, the average survival expectancy is **about 21 years**
- It is important to establish the diagnosis of **MEN2B at an early age** when there is a possibility that **thyroidectomy will be curative**.
- The reality is that most patients with MEN2B are diagnosed when The MTC is clinically evident and **too advanced to be cured**

Comparison of patients with MEN 2B with and without endocrine problem

The patients with nonendocrine manifestations were

- Younger
- lower preoperative serum Ctn levels
- Tumors smaller than 10mm
- lower incidence of extrathyroidal extension
- Fewer lymph node metastases
- lower incidence of distant metastases
- Cured biochemically following thyroidectomy

When should we think to MEN2B if genetic is negative *?*

- In the absence of an autosomal dominant familial inheritance pattern or *RET* mutation
- Majority of **classical clinical features** of MEN2B are required to make a clinical diagnosis of MEN2B.

Detection of RET mutations in Familial MTC

- Only careful **genetic screening** can distinguish between inherited and sporadic forms of FMTC
- Many of the same mutations responsible for MEN 2A have also been found in FMTC

Have mutation in

- Exon 10,11
- Exon 8 **532,533**
- Exon 13 **790,791,768**
- Exon 15 **883,891**
- Exon 16 **912**
- Exon 14 **804,844**
- Codon 609,611,618,804,891

RET mutations and their associated phenotypes

Exon	*Codon No*	*Base pair change*	*Amino acid change*	*Phenotype*
10	609	TGC to CGC	Cys to Arg	MEN 2A, FMTC
		TGC to TAC	Cys to Tyr	MEN 2A
	611	TGC to TAC	Cys to Tyr	MEN 2A
		TGC to TGG	Cys to Trp	MEN 2A, FMTC
		TGC to GGC	Cys to Gly	FMTC
	618	TGC to TTC	Cys to Phe	MEN 2A
		TGC to TCC	Cys to Ser	MEN 2A, FMTC
		TGC to AGC	Cys to Ser	MEN 2A, FMTC
		TGC to GGC	Cys to Gly	MEN 2A
		TGC to CGC	Cys to Arg	MEN 2A, FMTC
		TGC to TAC	Cys to Tyr	MEN 2A, FMTC
		TGC to TGA	Cys to Stop	MEN 2A
	620	TGC to CGC	Cys to Arg	MEN 2A, FMTC
		TGC to TAC	Cys to Tyr	MEN 2A
		TGC to TTC	Cys to Phe	MEN 2A
		TGC to TCC	Cys to Ser	MEN 2A
		TGC to GGC	Cys to Gly	MEN 2A
11	630	TGC to TTC	Cys to Phe	FMTC
	634	TGC to TAC	Cys to Tyr	MEN 2A, FMTC
		TGC to CGC	Cys to Arg	MEN 2A
		TGC to TTC	Cys to Phe	MEN 2A, FMTC
		TGC to GGC	Cys to Gly	MEN 2A
		TGC to TGG	Cys to Trp	MEN 2A
		TGC to AGC	Cys to Ser	MEN 2A
		TGC to TCC	Cys to Ser	MEN 2A, FMTC
13	768	GAG to GAC	Glu to Asp	FMTC
	790	TTG to TTT	Leu to Phe	MEN 2A, FMTC
		TTG to TTC	Leu to Phe	MEN 2A, FMTC
	791	TAT to TTT	Tyr to Phe	FMTC
14	804	GTG to TTG	Val to Leu	FMTC
		GTG to ATG	Val to Met	
	804 & 806	804- GTG to ATG 806- TAC to TGC	Val to Met Tyr to Cys	MEN 2B
15	883	GCT to TTT	Ala to Phe	MEN 2B
	891	TCG to GCG	Ser to Ala	FMTC
16	918	ATG to ACG	Met to Thr	MEN 2B

FMTC

- When **four or more members s**how the MTC, this family is an excellent family in terms of FMTC
- Considered the least aggressive with a later onset than MEN 2A or 2B.
- Families or individuals with RET germline mutations who have MTC but **neither PHEOs nor HPTH** RET codon G533C mutation
- Only about **2% of cases of** familial MTC **are not** associated with detectable RET germline mutation

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FMTC

- **A variant of MEN2A**
- less aggressive
- Delayed onset
- isolated
- Harbor mutations similar to MEN2A
- **Not appearing until** the **second or the third decade of life**
- it is often difficult to determine FMTC based upon a family history

FMTC

- There is ongoing debate on **what age** the thyroidectomy should be recommended for FMTC patients.
- Some clinical institutes suggest the prophylactic surgery at **age 10–15**, depending upon the exact mutation and family history
- While recommending **yearly test of calcitonin levels prior to** deciding the surgery

Correlation *between survival & RET Gen mutation*

- Classical MEN2A families with a ***RET*** **codon 634 mutation** the average life span was 48 years compared with 60 years in FMTC variant families with a **codon 618 mutation**
- There is greater morbidity and mortality in MEN2B than in MEN2A.

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Genotype-phenotype correlation

- There are **strong correlations** of MEN2 disease phenotype and specific *RET sequence* changes
- The distinct clinical course of the disease in a family depends upon the **specific *RET* gene germline mutation** that is present.
- There are tissue specific **differences in sensitivity to RET** activation, with thyroid being most sensitive and parathyroid least sensitive

Genotype-phenotype correlation

- Mutations of *RET* ***exons 13, 14, and 15*** may represent lower penetrance mutations with a less aggressive
- the RET M918T mutation is usually associated with poor prognosis
- Mutations of **Codon 634** belong to the high-risk category
- RAS mutations are found in less aggressive cases with a more favorable prognosis

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Does the type of mutation play a role in the severity of the disease?

Mutation in A883F and M918T

Associated with

- Aggressive clinical course
- lymph node metastasis
- Distant metastases
- lack of response to treatment

ATA Guidelines designations to define categories of RET mutations

- The original ATA Guidelines used **A, B, C, and D**
- with increasing aggressiveness (from A to D) of the MTC
- D category be changed to a new category, ‘‘highest risk’’ (HST)

- Category C be changed to a new category, ‘‘**high risk’’ (H)**
- A and B categories be combined into a new category

‘‘moderate risk’’ (MOD)

ATA Guidelines designations to define categories of RET mutations

The ATA-HST category includes

- patients with MEN2B and the RET codon **M918T** mutation

The ATA-H category includes

- patients with RET codon **C634** and RET codon **A883F** mutation,

The ATAMOD category includes

- patients with RET codon mutations other than M918T, C634, and A883F
- ATA2015

ATA Risk category

- **ATA-HST** — **RET codon mutation 918**
- **ATA –H** — **RET codon mutation 883,634**
- **ATA- MOD** — **RET codon mutation 553, 609,**

611,618,620,630,666,768,790,804,891,912

The age of screening of PHEO *in patients with MEN2?*

- **Yearly screening** for PHEO in children should begin at
- ATA-HST 11 **years of age**
- ATA-H 11 **years of age**
- ATA-MOD **16 years of age**

The age of screening of HPTH *in patients with MEN2?*

- **Yearly screening** for HPTH in children should begin at

- **Age 11 years** **in high-risk patients**
- **Age 16 years** **in moderate-risk patients**
- patients in the **highest risk category** are not at risk for developing hyperparathyroidism

Clinical monitoring for PHEO and HPTH in carriers of a mutation in the *RET* gene

		Pheochromocytoma*	Hyperparathyroidism
Risk	*RET* codon mutation	Recommended age to begin annual screening for pheochromocytoma¶	Recommended age to begin annual screening for hyperparathyroidism$^{\Delta}$
Highest	918	11 years	Not applicable
High	634, 883	11 years	11 years
Moderate	533, 609, 611, 618, 620, 630, 666, 768, 790, 804, 891, 912	16 years	16 years

Follow up patients with negative RET mutation

- **In very rare families** who meet the clinical criteria for MEN2A or MEN 2B with **Negative sequencing** of the entire RET coding region
- **Biochemical testing** can be performed to detect **MTC, PHEO, and HPTH**
- After the initial evaluation, **screening should continue at 1- to 3-year intervals**
- **Yearly testing starting at age five** and continuing until at least **age 35** years or until a positive test occurs
- **ATA 2014**

Follow up patients with negative RET mutation

- For families with a clinical diagnosis of MTC **prior to age five years**,
- Biochemical screening for MTC should begin **at the youngest age of first diagnosis.**
- Pentagastrin or a calcium stimulation test can be used to screen for C-cell hyperplasia/MTC > 200pg/ml
- Perform test for PHEO& HPTH
- prophylactic thyroidectomy should always be dependent on preoperative Ct serum concentration rather than risk class with exception **of MEN 2B where operation should be performed as soon as possible**

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Choice of biochemical test for MTC

- **Calcium stimulated calcitonin levels above**
- **32.6 pg/mL** **females**
- **192 pg/mL** **males**
- Had the best accuracy to differentiate normal subjects from patients with C-cell hyperplasia or MTC

- **sCT <2 times bCT may not be suggestive of MTC,**

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Prophylactic Thyroidectomy

- **is most applicable for patients with hereditary cancer syndromes and ideally should meet the following criteria**
- **1- T**he genetic mutation causing the malignancy is characterized by complete or near complete penetrance
- 2- There is a highly reliable test for detecting the mutation
- 3--The precancerous organ can be removed with minimal morbidity and virtually no mortality
- 4-There is a reliable test to determine if the operation has been curative

Age of operation for prophylactic thyroidectomy

Ages 0–1	*Highest risk*	*(ATA-D)*
Before age 5	*High risk*	*(ATA-C)*
after age 5	*lower risk* *or moderate*	*(ATA-B or "ATA-A)*

ATA-HST &prophylactic thyroidectomy

includes patients with

- **Hereditary MEN2B** **Codon M918T**

Associated with

- lowest age of onset of the disease
- Highest risk of metastasis and death
- Macroscopic MTC and nodal metastases may occur during the first year of life
- Do not require monitoring
- Thyroidectomy should be performed **before one year of age or even 6 months of age, or during neonate**
- **Because cancer is present at birth**
- The exact timing determined by the surgeon and pediatrician in consultation with the child's parents

ATA-HST &prophylactic thyroidectomy

De novo RET codon M918T mutations

- Could be monitored and thyroidectomy delayed until they **are older and the operation is less risky.**
- Mean age at diagnosis was 14.2 years (range 1–31 years)
- Central neck dissection in older children with a palpable nodule and elevated serum Ctn levels, since they are at high risk for lymph node metastases and the benefits of central neck dissection outweigh the potential risks associated with the procedure

problems that exist in infant with MEN2B

- Serum Ctn levels are extremely high in the first months of life and of limited value in timing thyroidectomy.
- parathyroid glands can be very difficult to identify intraoperatively, creating an inordinate risk of hypoparathyroidism.
- **In the absence of suspicious lymph nodes**, the decision to perform a central neck dissection should be based on whether the **parathyroid glands are identified** and can either be preserved in situ or **autotransplanted**
- The surgeon should consider foregoing a central neck dissection if he cannot identify the parathyroid glands.

Calcitonin in infant and children

- is particularly high **during the first week of life and in low birth weight and premature infants**

Reference range of

- < 40 pg/mL **<6 months of age**
- <15 pg/mL **6 months and 3 years of age**
- **first year of life 2.0–48.9 pg/mL**
- **second year of life, 2.0–14.7 pg/mL**
- **ICMAs** that are highly sensitive and specific for monomeric Ctn
- Serum Ctn values in children **more than 3 years** of age were indistinguishable from those observed in adults
- Ctn levels are **higher in males** compared with female
- **>30 pg/mL and >34 pg/mL**

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predictive of MTC based on calcitonin

basal calcitonin values higher than

- **100 pg/ml** are 100% predictive of MTC
- **50 and 100** pg/ml are 25% predictive of MTC
- **20 to 50 pg/ml** are only 8.3% predictive of MTC

ATA-H category &prophylactic thyroidectomy

- MEN2A RET **codon 634 &883F**

- Often develop MTC **during the first years of life**

Recommend

- Annual physical examination
- Cervical US
- Measurement of serum Ctn levels should **begin at 3 years of** age

ATA-H category &prophylactic thyroidectomy

- should have thyroidectomy **at or before 5 years of age**,
- with the timing and extent of surgery guided by Ctn levels

- **A central neck dissection should be performed in children with**
- serum **Ctn levels above** **40 pg/mL**
- or Lymph node involevment with **evidence on imaging** or direct observation of lymph node metastases
- Almost all patients with MEN2A **require thyroidectomy**
- The surgeon , pediatrician caring for the patient, in consultation with the child's parents, should decide the timing of thyroidectomy.

ATA-H category &prophylactic thyroidectomy

- RET mutation carriers should be operated as soon as possible at a young age, especially those carrying a H-risk RET mutation ,**when Ct levels are within normal range**
- **To avoid**
- Developing microMTC
- Relapse of the disease that may occur even at long-term.

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ATA MOD category &prophylactic thyroidectomy

- **ATA MOD** **B**

- includes patients with RET codon mutations **other than** M918T, C634, and A883F
- Mutation in Exon10 **codon 609 611 618,620**
- Mutation in Exon 11. **Codon 630**

ATA MOD category &prophylactic thyroidectomy

- **ATA MOD** **A**
- Exon13 **Codon 768 ,790, 791**
- Exon 14 **Codon 804**
- Exon 15 **Codon 891**
- lowest risk level
- lower calcitonin level
- lower tumor stage
- Higher chance of recovery after thyroidectomy.
- MTC occurs at an older age
- The rate of invasion and mortality is less
- The penetration rate of these mutations is also less

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ATA MOD category &prophylactic thyroidectomy

Recommended

6-month or annual evaluations may extend to several years or decades

Begin monitoring at age five years

- physical examination
- US of the neck
- Screening

ATA MOD category &prophylactic thyroidectomy

If there is

- No problem in the ultrasound
- low Ctn levels
- No aggressive MTC in the family

.**Thyroid surgery can be postponed**

- Child's parents and surgeon should decide the timing of thyroidectomy

- **After the age of 5 (Chilhood, adolescent or adult)**

ATA MOD category &prophylactic thyroidectomy

- **if parents don't wish to embark on a lengthly period of evaluation witch might lost for years or decades**
- **Or serum Ctn become elevated 40 pg/ml**
- The surgeon and pediatrician caring for the patient, in consultation with the Child's parents

Is genetic testing alone sufficient for thyroidectomy?

- is no longer based on **direct DNA analysis alone**, rather is based on clinical data, **basal or stimulated serum Ctn level**

- Timely thyroidectomy for MTC favorably alters the associated **morbidity and mortality**, thus, the question is not whether prophylactic thyroidectomy should be performed in patients with hereditary MTC, **but at what age**
- No correlation **between serum Ct and the ATA risk level** was observed at the time of thyroidectom
- Thyroid Res. 2013

Is genetic testing alone sufficient for thyroidectomy?

- time of prophylactic thyroidectomy should always be dependent on preoperative Ct serum concentration rather than risk class **with exception of MEN 2B where operation should be performed as soon as possible**.
- **Increasing Ct level (both basal and stimulated) was correlated with more advanced medullary cancer**
- . Decision about the timing of prophylactic thyroidectomy needed to be reinforced by the Ct serum level
- Thyroid Res. 2013;

When can we delayed thyroidectomy?

TT in RET carriers can be delayed beyond 5 years old if

- when the preoperative basal serum Ctn is **less than 40 pg/mL**,
- or when the primary tumor was **smaller than 5-10mm**
- No lymph node metastases
- **In case of the above conditions** , total thyroidectomy **without** central (level VI) neck dissection **is adequate therapy**.

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What should be done in cases where calcitonin is unmeasurable?

- RET mutation carriers with undetectable serum Ct levels the time of TT can be personalized and safely planned when

basal and/or stimulated Ct becomes positive, independently of the type of RET mutation and its associated level of risk

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What topics should be monitored?

We monitor Annually

- physical examination
- Neck ultrasound
- Measurement of serum calcitonin

Serum calcitonin above the upper limit of normal is an indication for surgery.

Prognosis

Numerous factors influence prognosis.

- Baseline biomarker levels
- Tumor extent
- Presence of metastases (local and distant)
- Sex
- Age of surgery
- Specific RET mutational risk profile
- preoperative calcitonin level
- Cancers 2022

Prognosis

- bCtn and CEA doubling times are considered good tools for assessing prognosis
- **Ten-year survival** was **8, 37, and 100 percent** for doubling times **under six months, between six months and two years, and greater than two years**

- CEA may also be used as a predictive biomarker
- **Histological findings**, **poorly differentiated** histology is correlated with rapid tumor progression.
- High expression of Ki-67 comes with less favorable prognosis
- younger age is associated with longer survival time
- Lymph node metastases are associated with a higher mortality rate

Up to date 2023

prognosis

- **Tumor stage** which also indicates that more **active interventions** should be performed in the treatment for pediatric patients
- patients with microMTC, independently of the age at surgery, after an early thyroidectomy require a life-long follow-up, **since recurrences** can occur even at long-term interval

Survival analysis of all population

The 3-, 5- and 10-year OS rates were significantly higher in pediatric patients than adult patients

98.80%, 98.80% and 91.74% vs

86.97%, 82.56% and 73.19%

P < 0.001)

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