12º ENDO SUL

SBEM SC

Carcinoma Medular de Tireoide: Genótipo e Fenótipo

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80 ANOS 1934|2014 UFRGS

Conflict of Interests (last 5 years)

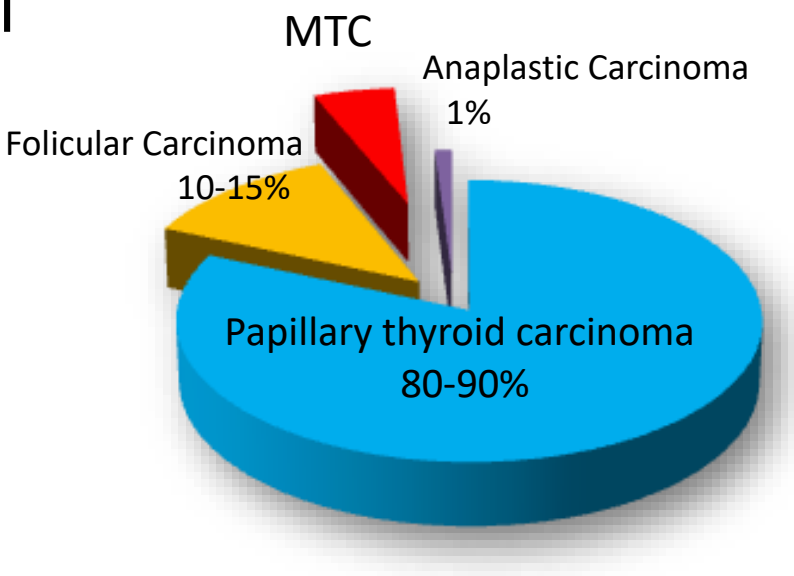
- Research grants CNPq, FAPERGS, NIH, FIPE
- Consultant or Advisory Role (AstraZeneca, Sanofi)
- Principal Investigator, Coordinator Center, Multi-Center Study, AstraZeneca.

Molecular Diagnosis of MTC

- ✓ Overview
- ✓ Implications of diagnosis of germline RET mutations: hereditary MTC
- ✓ Role of RET polymorphisms
- ✓ Somatic mutations in sporadic cases
- ✓ Impact on therapy

Medullary Thyroid Cancer

- Rare thyroid C cell malignant tumor that accounts for 3-4% of thyroid gland neoplasia.
- MTC secretes a variety of products, but calcitonin is the most important biomarker.
- Accounts for nearly 15% of all thyroid cancer-related deaths



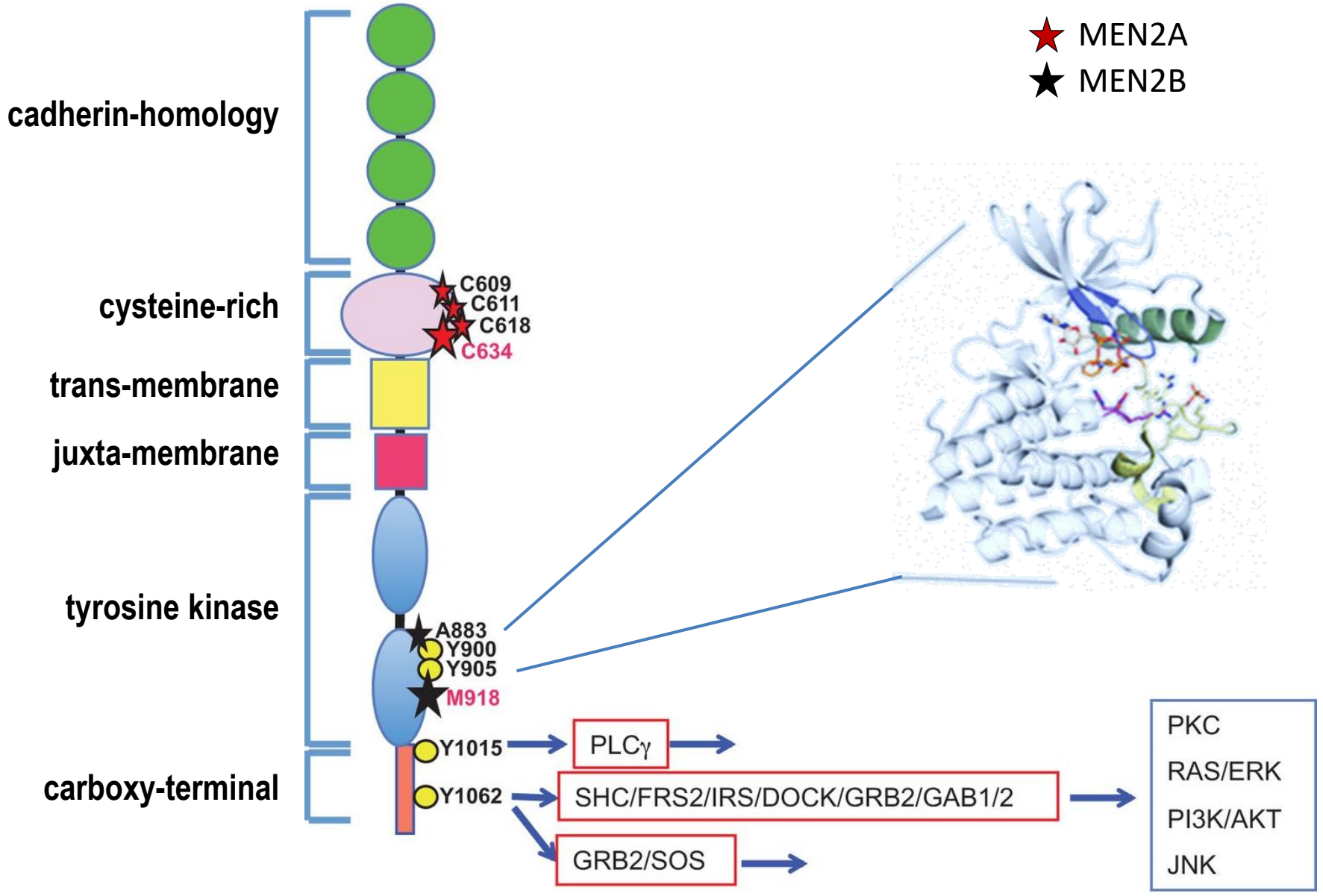
- MTC may occur sporadically (75%) or be inherited. Hereditary MTC appears as part of the MEN 2 syndrome.

Multiple Endocrine Neoplasia Type 2 (MEN2)

- MEN 2A
  MTC (100%), pheochromocytoma (20-50%), and/or hyperparathyroidism (10-25%);
  rarely associated with cutaneous lichen amyloidosis or Hirschsprung's disease.

- MEN 2B
  MTC, pheochromocytoma, ganglioneuromatosis, and marfanoid habitus

RET: susceptible gene for Hereditary MTC



Modified from Castellone & Melillo. Endocr Relat Cancer 2018 T105-T119 ; Plaza-Menacho, Endocr Relat Cancer 201825 77–88

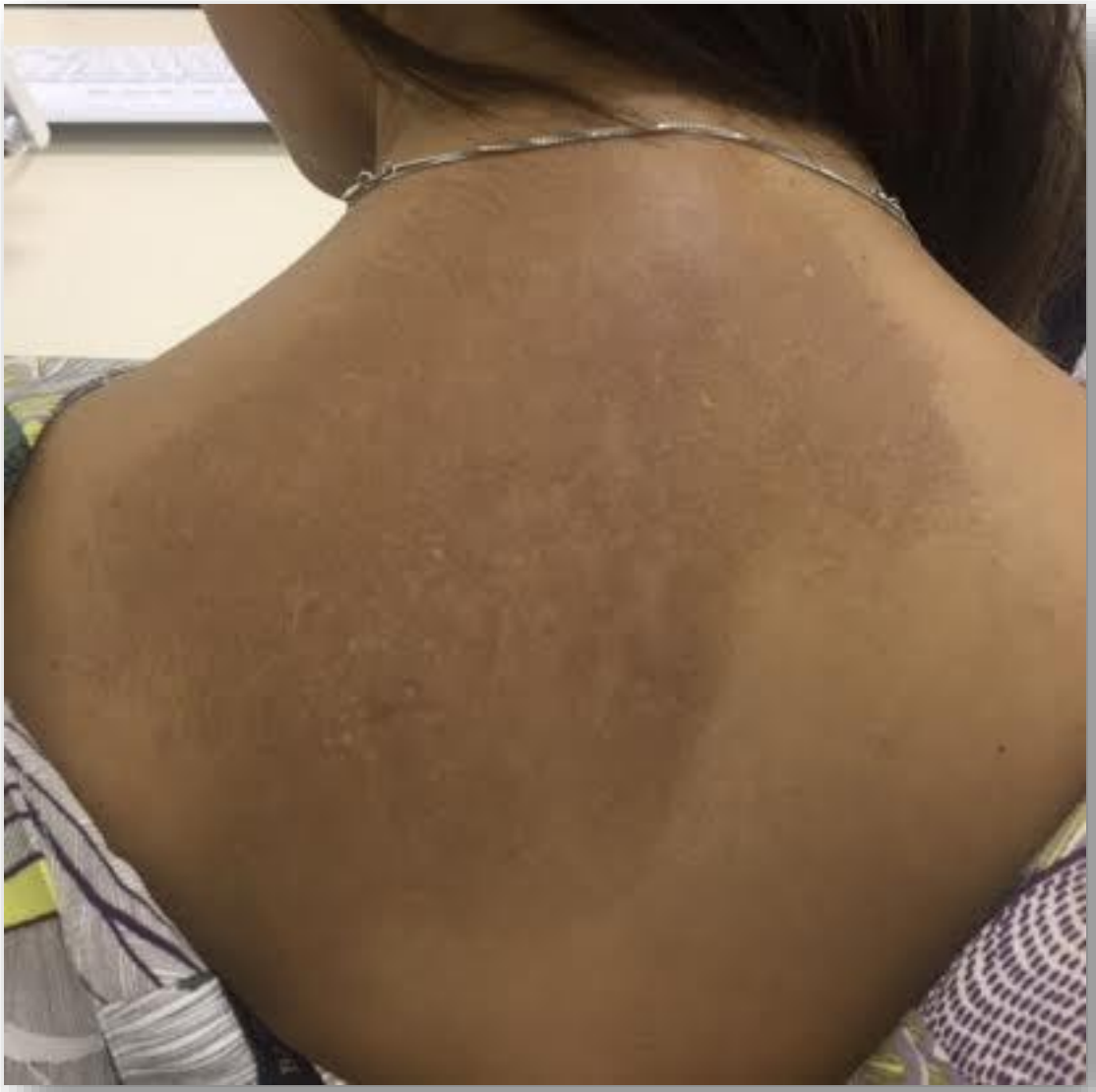
TABLE 4. RELATIONSHIP OF COMMON *RET* MUTATIONS TO RISK OF AGGRESSIVE MTC IN MEN2A AND MEN2B, AND TO THE INCIDENCE OF PHEO, HPTH, CLA, AND HD IN MEN2A

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]	*CLA*[d]	*HD*[d]
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

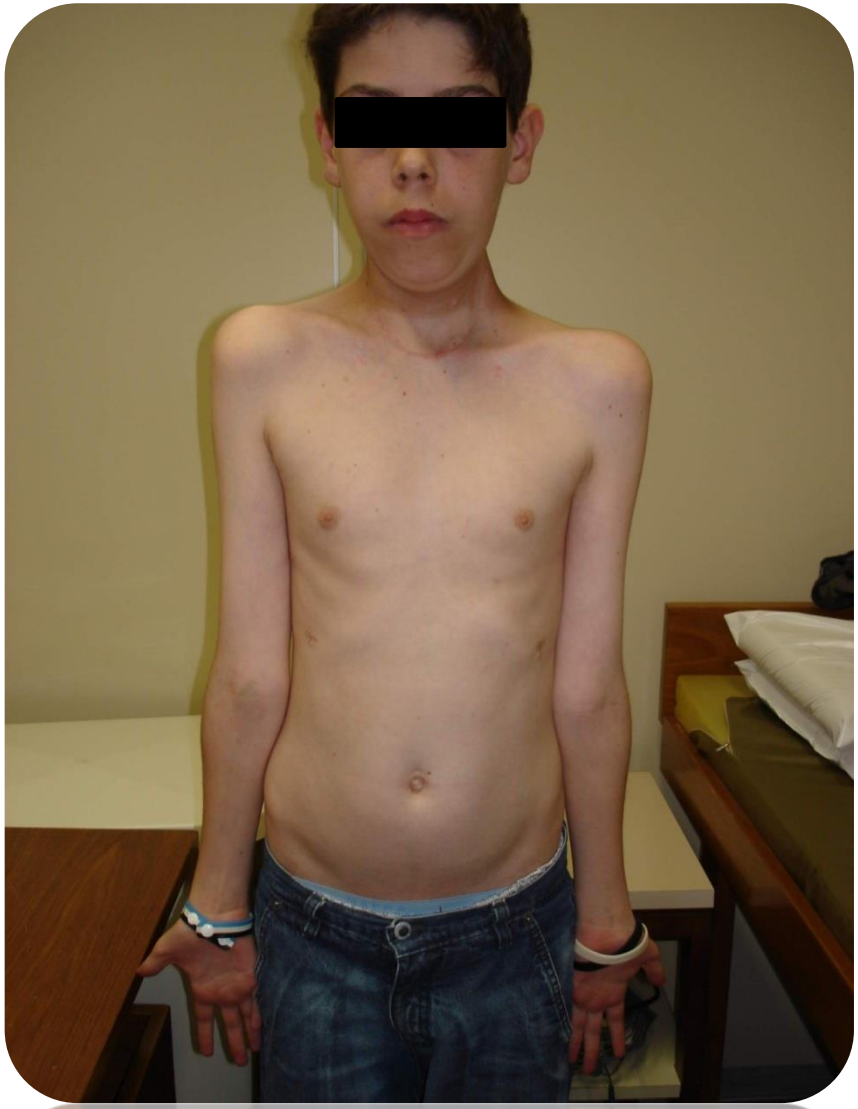
[a]The references for each of the *RET* mutations can be found in the Supplementary Information, where all reported *RET* mutations in MTC are listed.
[b]Risk of aggressive MTC: MOD, moderate; H, high; HST, highest.
[c]Incidence of PHEO and HPTH: + = ~10%; ++ = ~20%–30%; +++ = ~50%.
[d]Y, positive occurrence; N, negative occurrence.

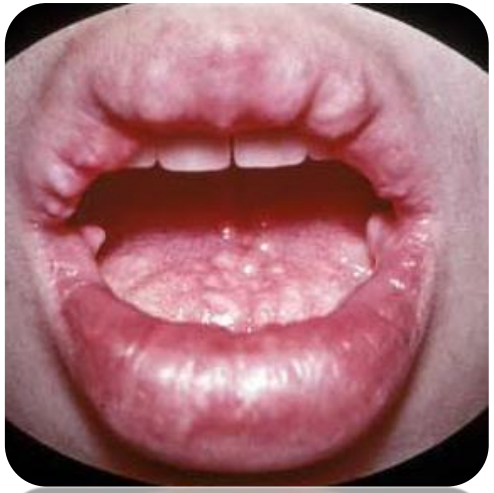
ATA MTC guidelines, Thyroid 2015

Cutaneous Lichen Amyloidosis

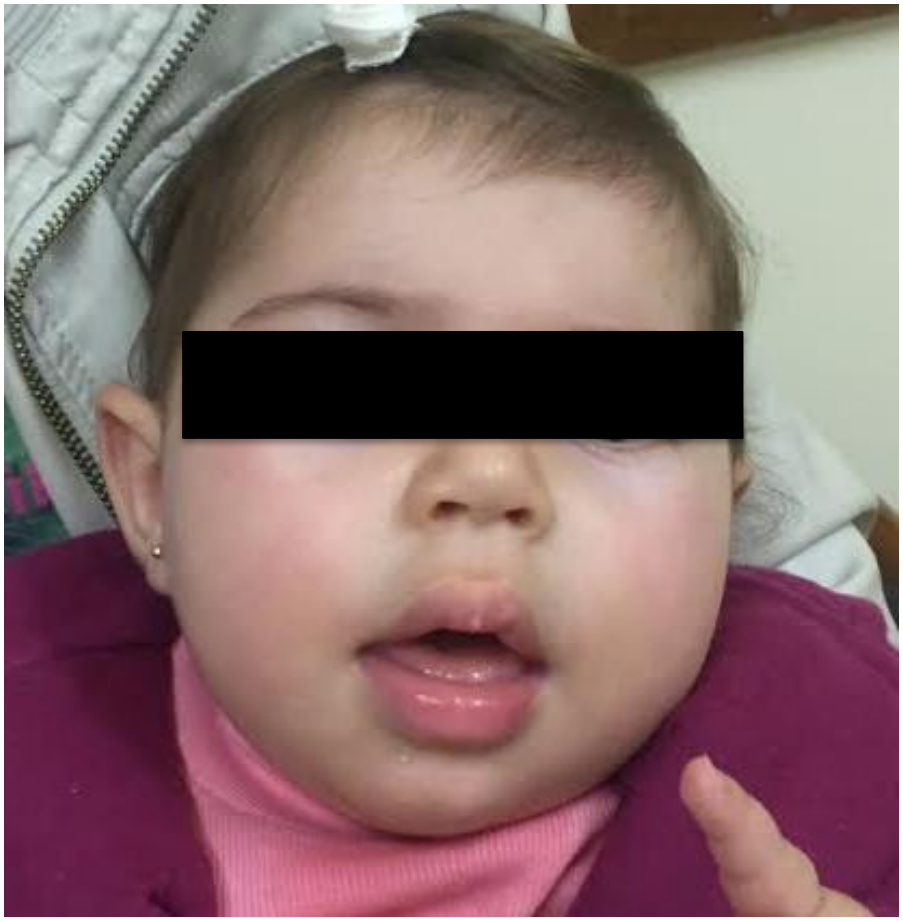


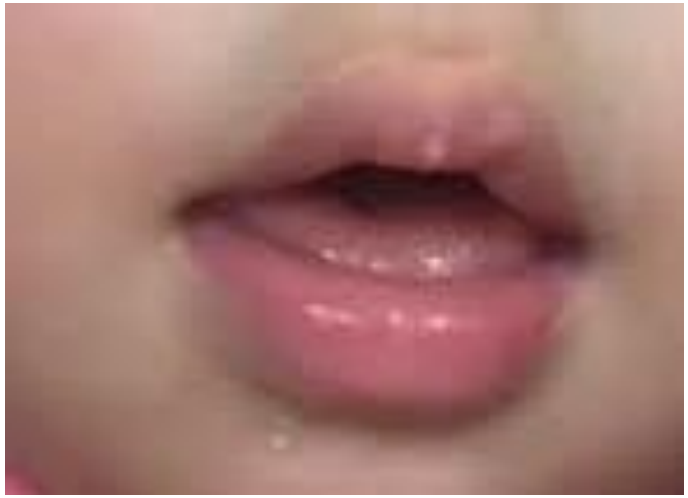
Multiple Endocrine Neoplasia Type 2B

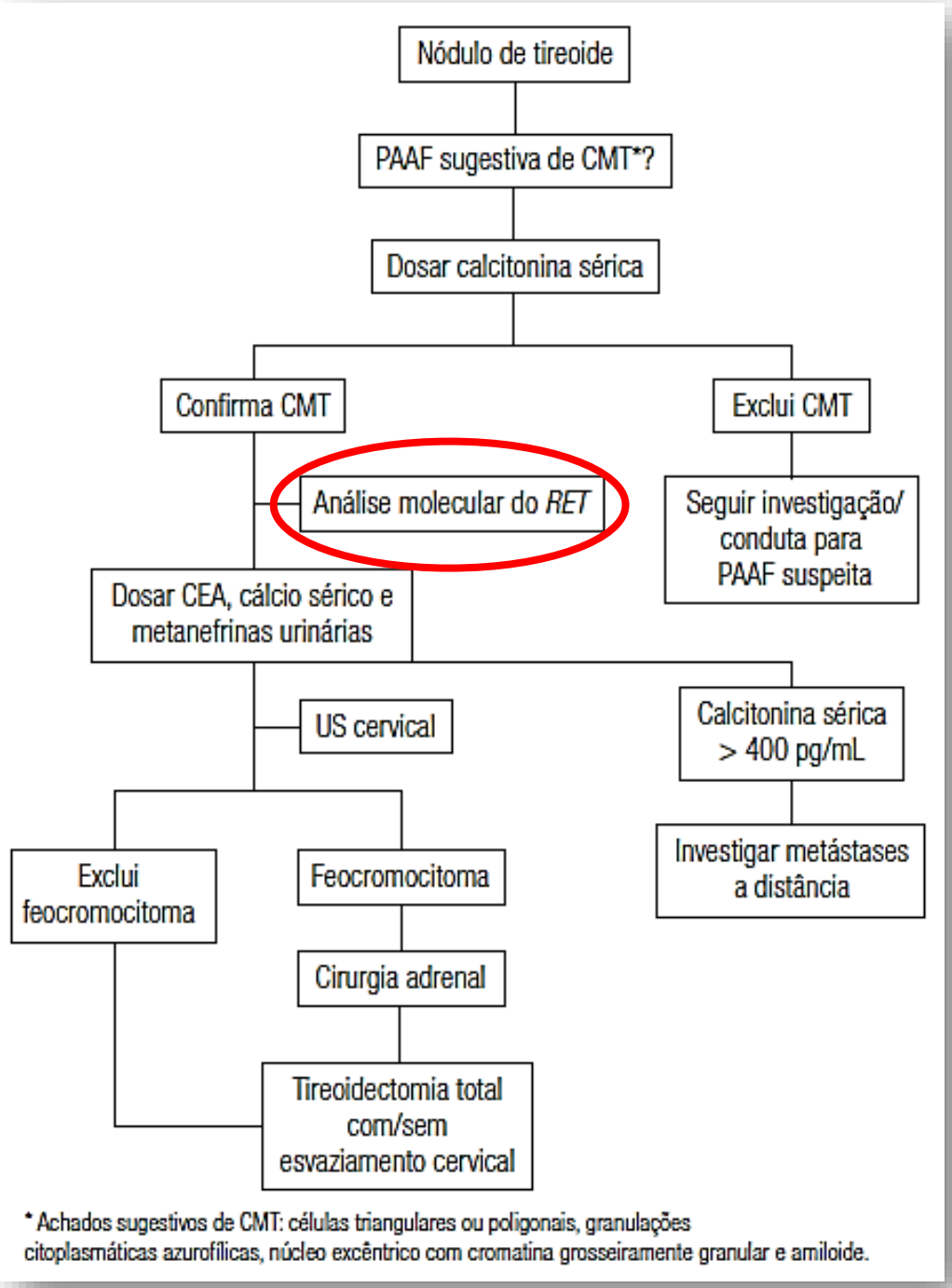




Neoplasia Endocrina Multipla 2B







Maia et al, ABEM 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Screening as Compared with DNA Analysis in Families with Multiple Endocrine Neoplasia Type 2A

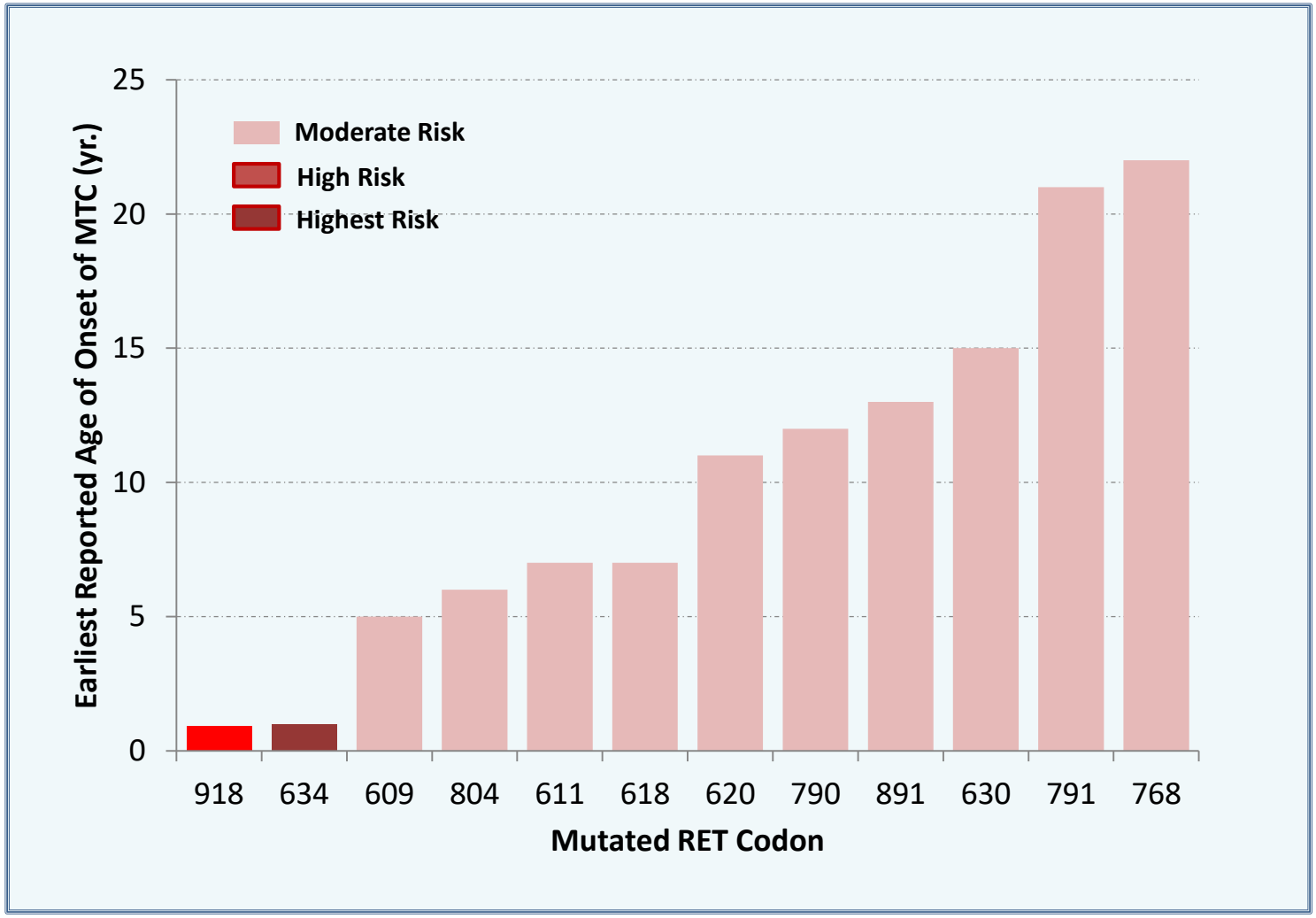
Cornelis Lips, Rudy M, Landsvater, Jo Hoppener, Rolf A, Geerdink, Geert Blijham, Joke M, Jansen-Schillhorn van Veen, Adriaan van Gils, Mireille J, de Wit, Richard A, Zewald, Marianne Berends, Frits A, Beemer, Joanneke Brouwers-Smalbraak, Rumo Jansen, Hans Kristian Ploos van Amstel, Theo van Vroonhoven, and Thea M, Vroom

Molecular analysis allows an unequivocal diagnosis of asymptomatic patients with NEM 2 syndrome.

Autosomal dominant, penetrance of 100%

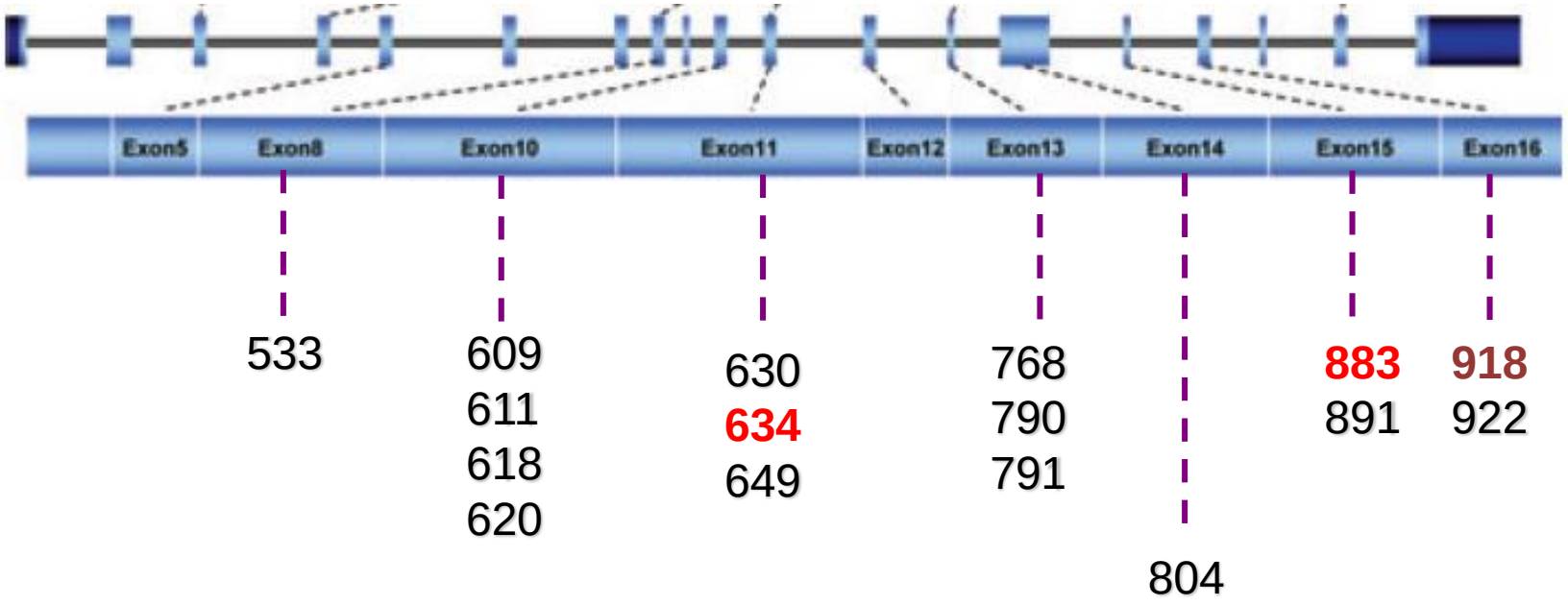
N Engl J Med 1994, 331:828-835

Genotype-Phenotype Correlations and ATA Risk Level



Adapted from Cote GJ et al, NEJM 2003; ATA Guidelines 2015

Prophylactic thyroidectomy: When?



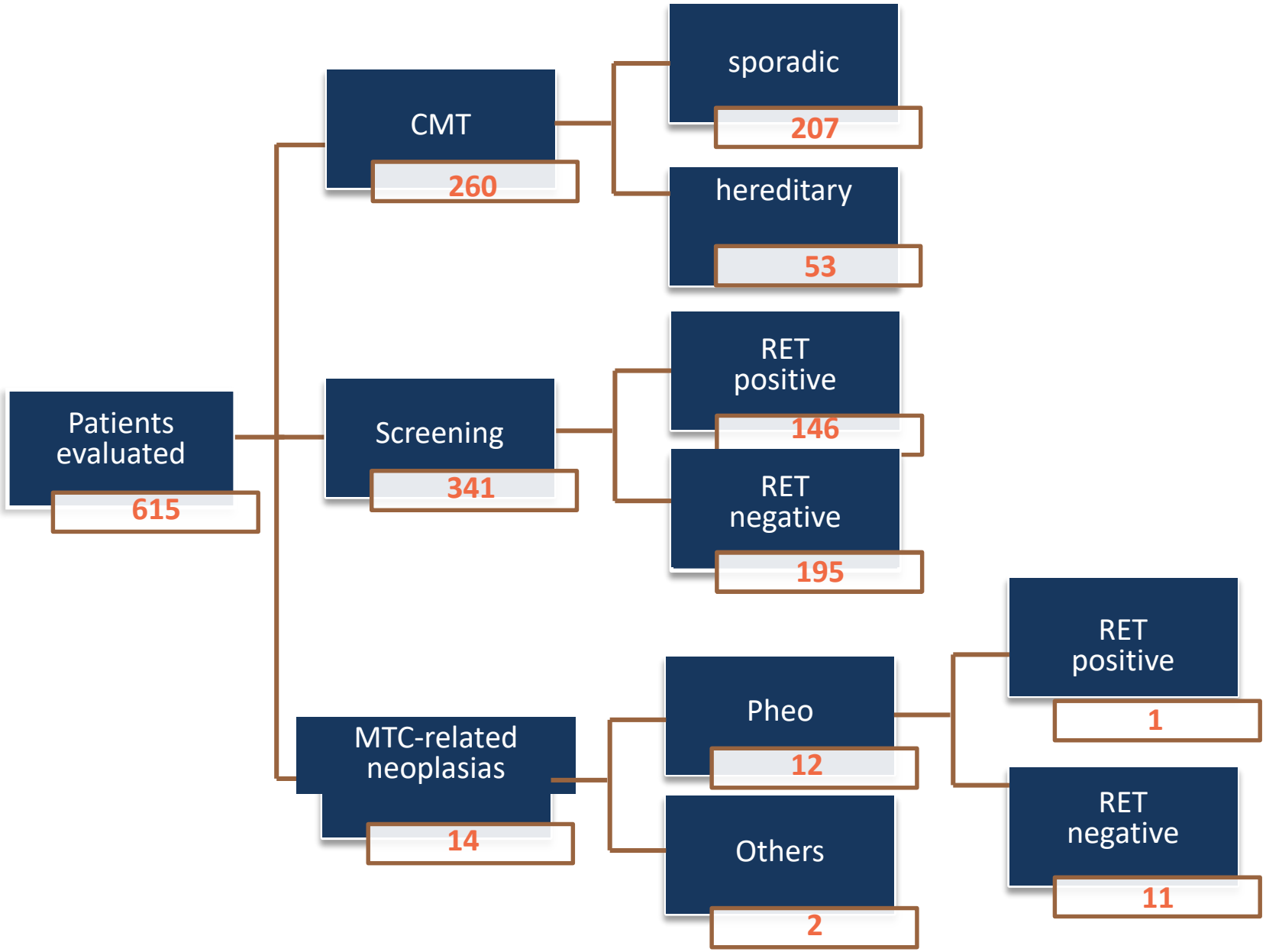
HST risk - Immediately

H risk < 5 years of age

MOD risk - based on Ct levels

ATA Guidelines (2015)

Medullary Thyroid Carcinoma
Hospital de Clínicas de Porto Alegre: 1997 - 2017



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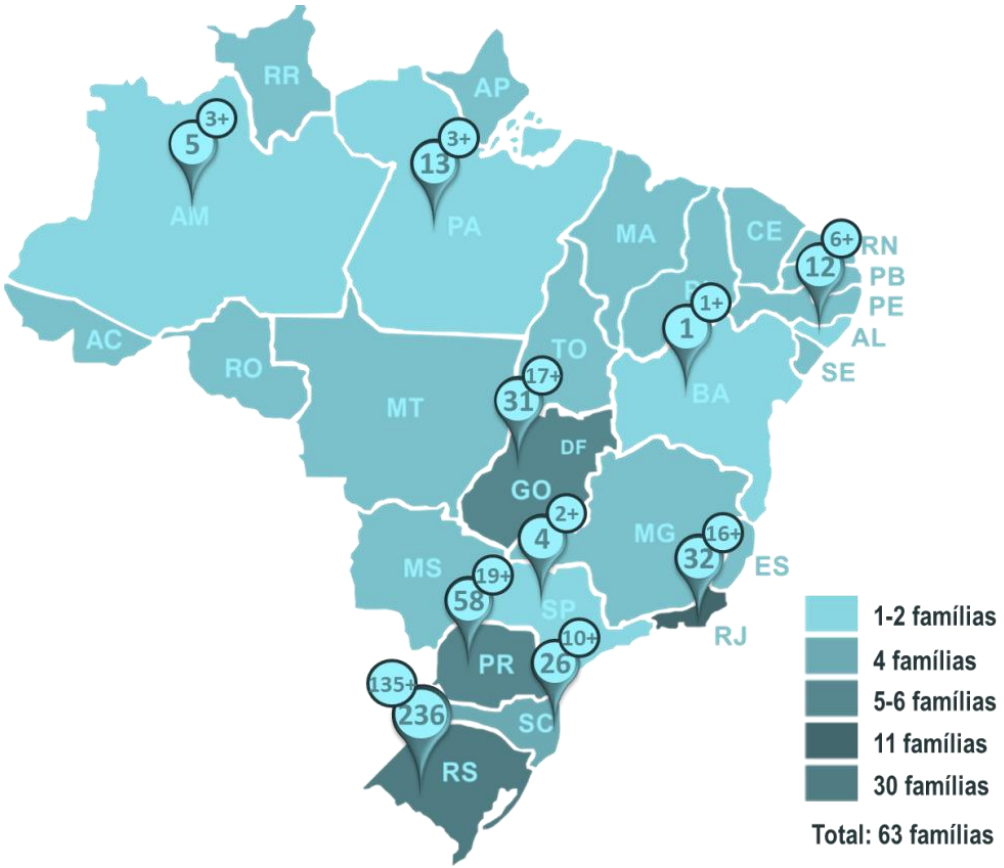
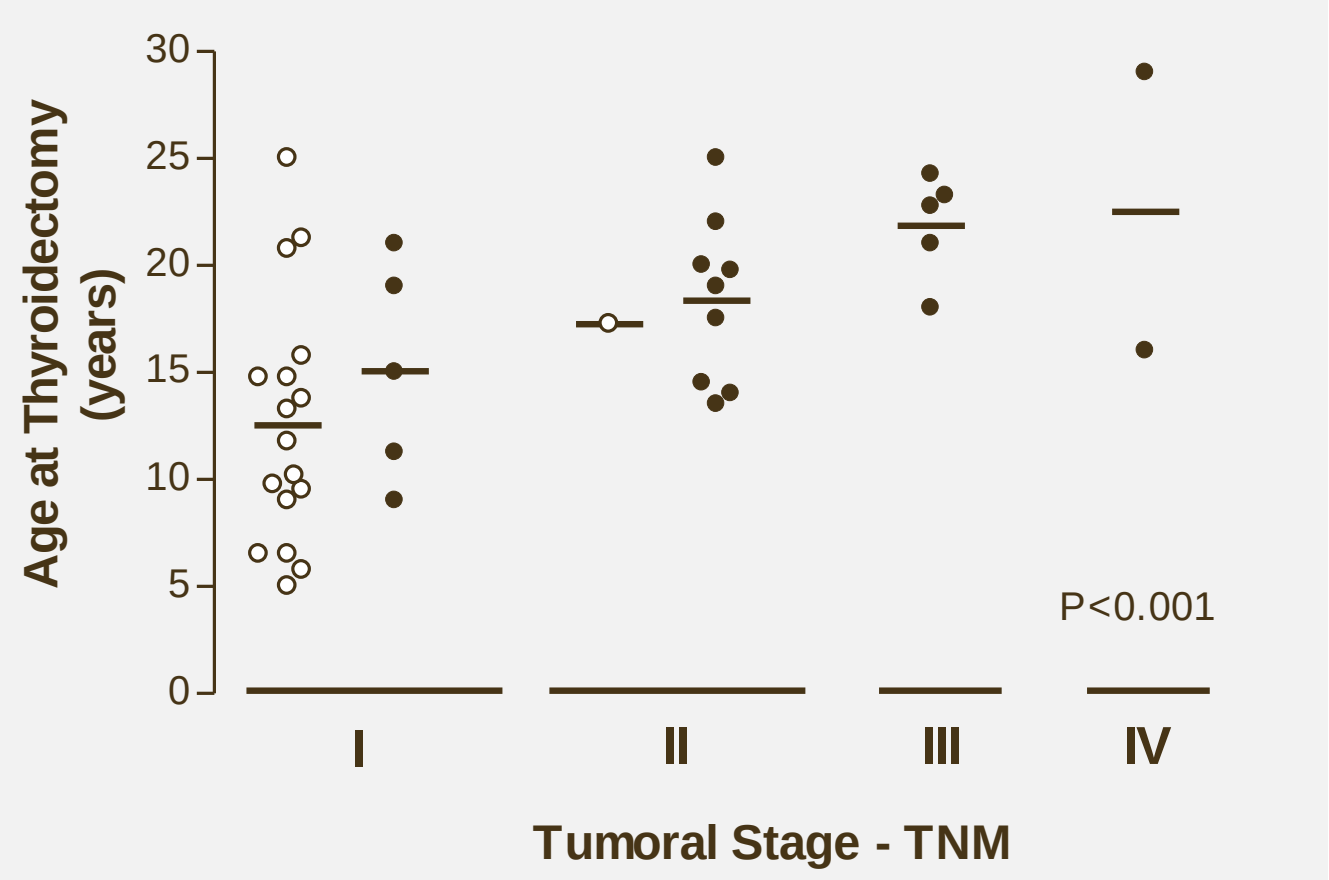


Mutação no RET	Nº de famílias	Nº de indivíduos portadores
C609Y	1	5
C618F	1	2
C618R	1	2
C620G	1	9
C620R	2	9
DEL631	1	1
C634R	11	27
C634S	1	1
C634W	2	7
C634Y	10	88
S649L	1	3
E768D	4	11
L790F	1	2
V804M	3	5
S891A	2	12
S904F	1	2
M918T	12	17

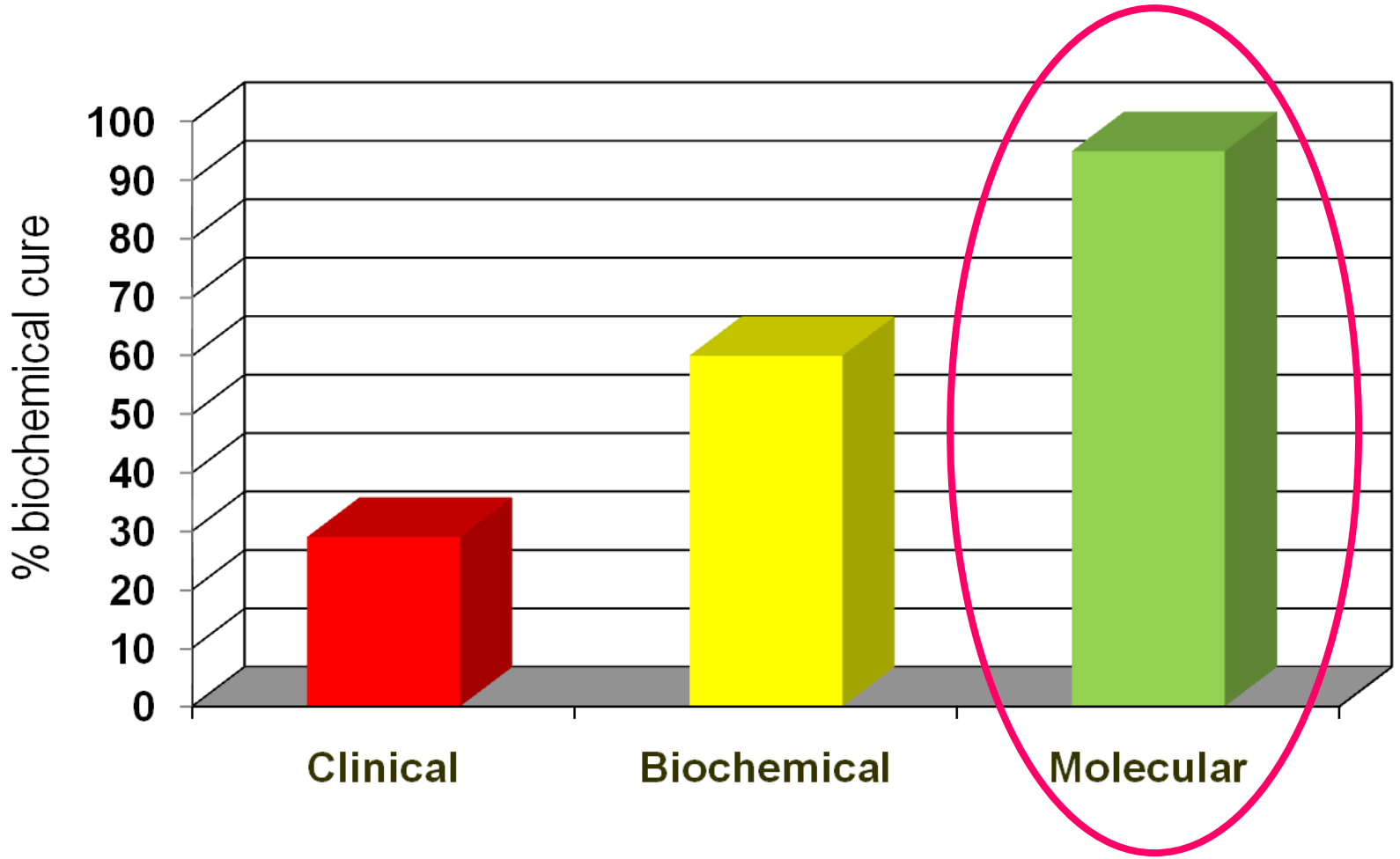
328 MTC patients
185 hMTC (78 screening)
143 sMTC

Correlation between age at surgery and TNM stage of MEN 2A patients under 25y who underwent therapeutic or prophylactic total thyroidectomy.



Puñales et al, *Thyroid* 2008

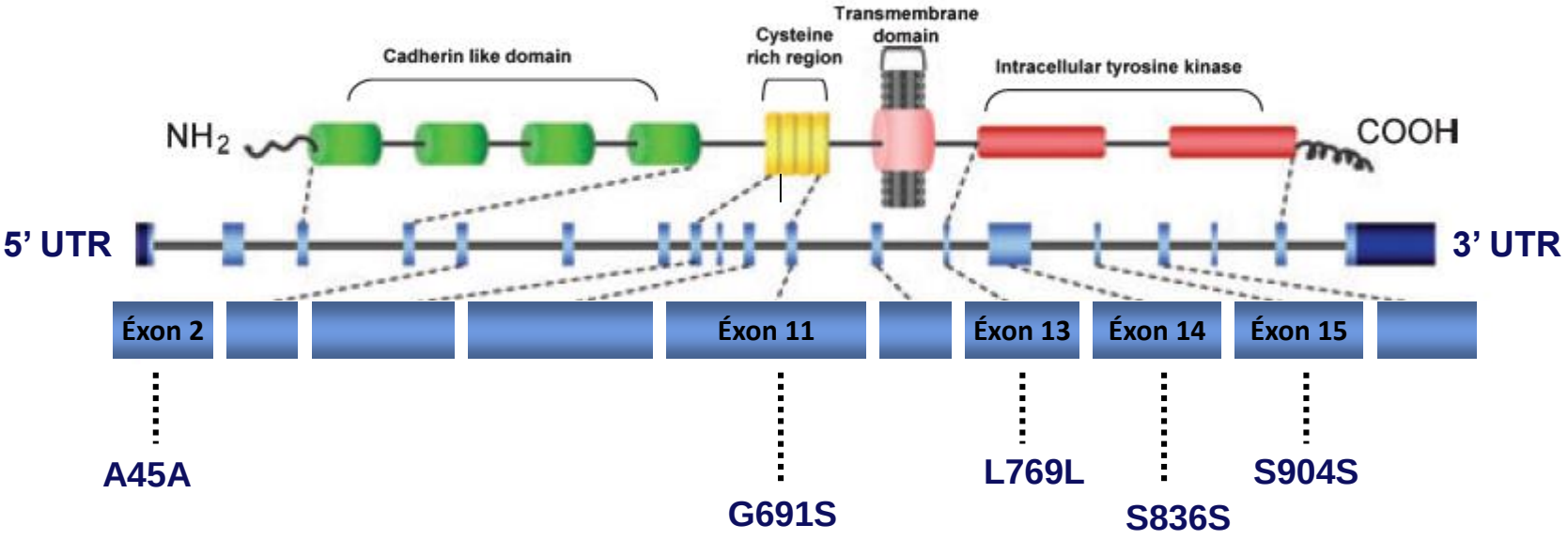
Early diagnosis improves biochemical cure



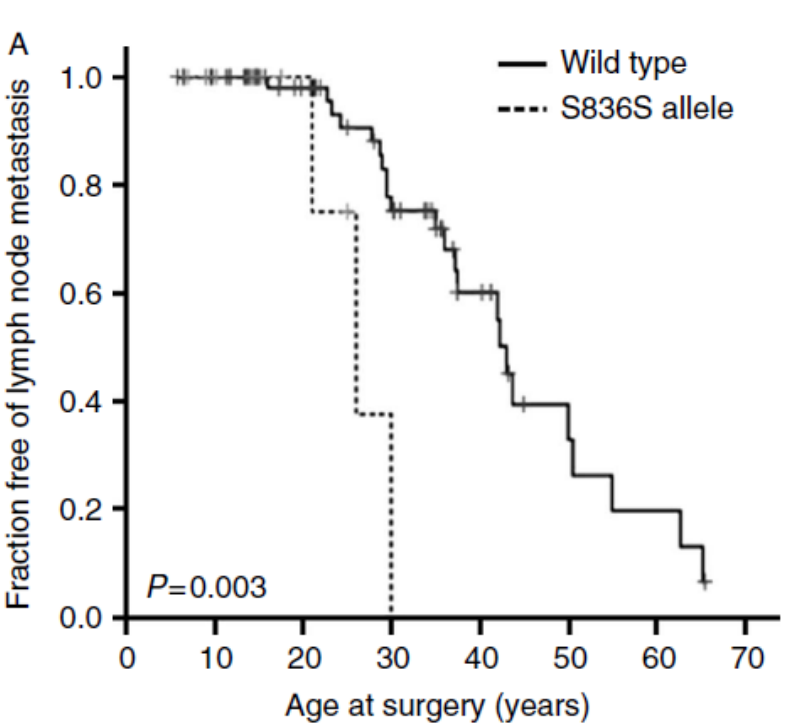
However, we still do not understand…

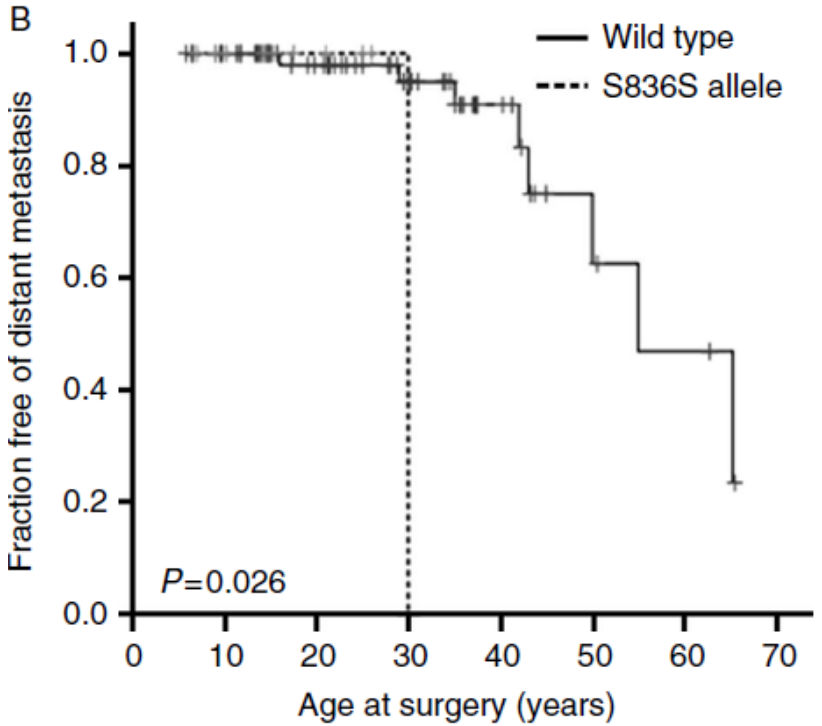
- ✓ Genotype-phenotype correlations have not been clarify yet: clinical variability and aggressiveness in members of the same family.
- ✓ Although the different levels of RET activation induced by the different mutations could partially explain it, the differences might suggest a role for genetic modifiers in the clinical course of MTC.

Polimorfismos genéticos do *RET*
(*single nucleotide polymorphisms* - SNP)



The RET polymorphic allele S836S is associated with early metastatic disease in patients with hereditary or sporadic medullary thyroid carcinoma.





Siqueira DR et al, *Endo-Related Cancer* 2010

Additive effect of *RET* polymorphisms on sporadic medullary thyroid carcinoma susceptibility and tumor aggressiveness

Table 5 Additive effect of *RET* polymorphic alleles on medullary thyroid carcinoma susceptibility.

Risk alleles	MTC, *n*=107 (%)	Controls, *n*=308 (%)	OR (95% CI);	*P*
None	26 (24.3)	110 (35.7)	1	
One or two	70 (65.4)	184 (59.7)	1.57 (0.9–2.7);	0.10
Three or four	11 (10.3)	14 (4.5)	3.79 (1.5–9.5);	0.004

The distribution of *RET* risk haplotypes were significantly different between MTC patients and controls ($P=0.02$). *P*=adjusted OR, 95% CI and *P* values for the comparisons between cases and controls. The independent variables included in the multiple regression analyses were age, gender, and number of *RET* polymorphic alleles in the haplotype.

Ceolin et al, ***European J Endocrinol*** 2012

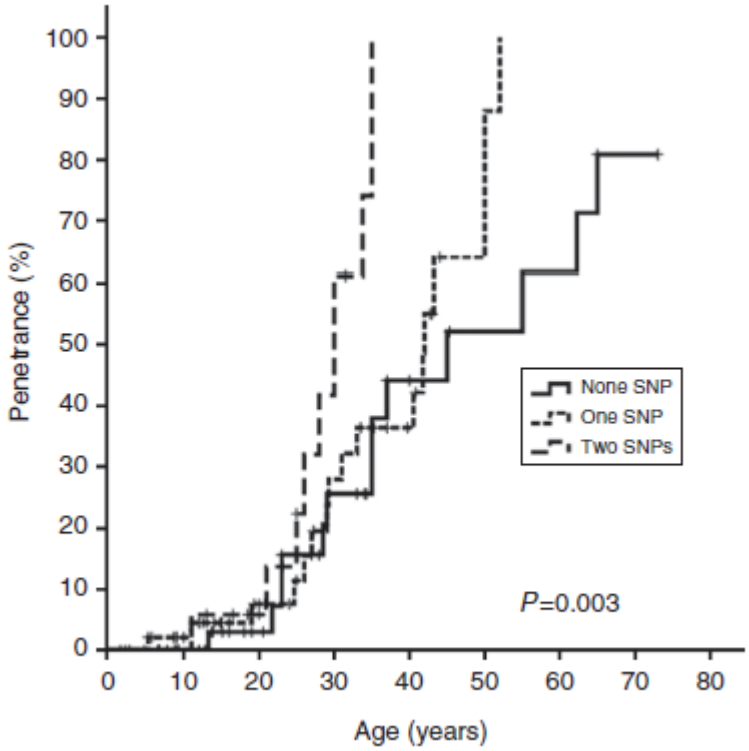
Role of *RET* genetic variants in MEN2-associated pheochromocytoma

Débora Rodrigues Siqueira, Lucieli Ceolin, Carla Vaz Ferreira, Mírian Romitti, Silvana Cavalcante Maia, Léa Maria Zanini Maciel[1] an

Table 4 Additive effect of *RET* polymorphic alleles o pheochromocytoma susceptibility ($n=135$). The independen variables included in the multiple regression analyses were age *RET* germline mutations (codons 618, 620, 634, and 918), an number of *RET* polymorphisms.

Risk alleles	PHEO (+)[a]	PHEO (−)[b]	OR (95% CI)	*P*
None	14 (34.1)	39 (41.5)	1	
One	17 (41.5)	43 (45.7)	1.3 (0.8–2.3)	0.365
Two	10 (24.4)	12 (12.8)	2.63 (1.4–5.0)	0.004

[a]Data available for 41 patients with PHEO.
[b]Data available for 94 patients without PHEO.



Eur J Endocrinol. 2014 Jun;170(6):821-8.

The penetrance of MEN2 pheochromocytoma is not only determined by *RET* mutations

Frederic Castinetti, Ana Luiza Maia, Mariola Peczkowska, et all

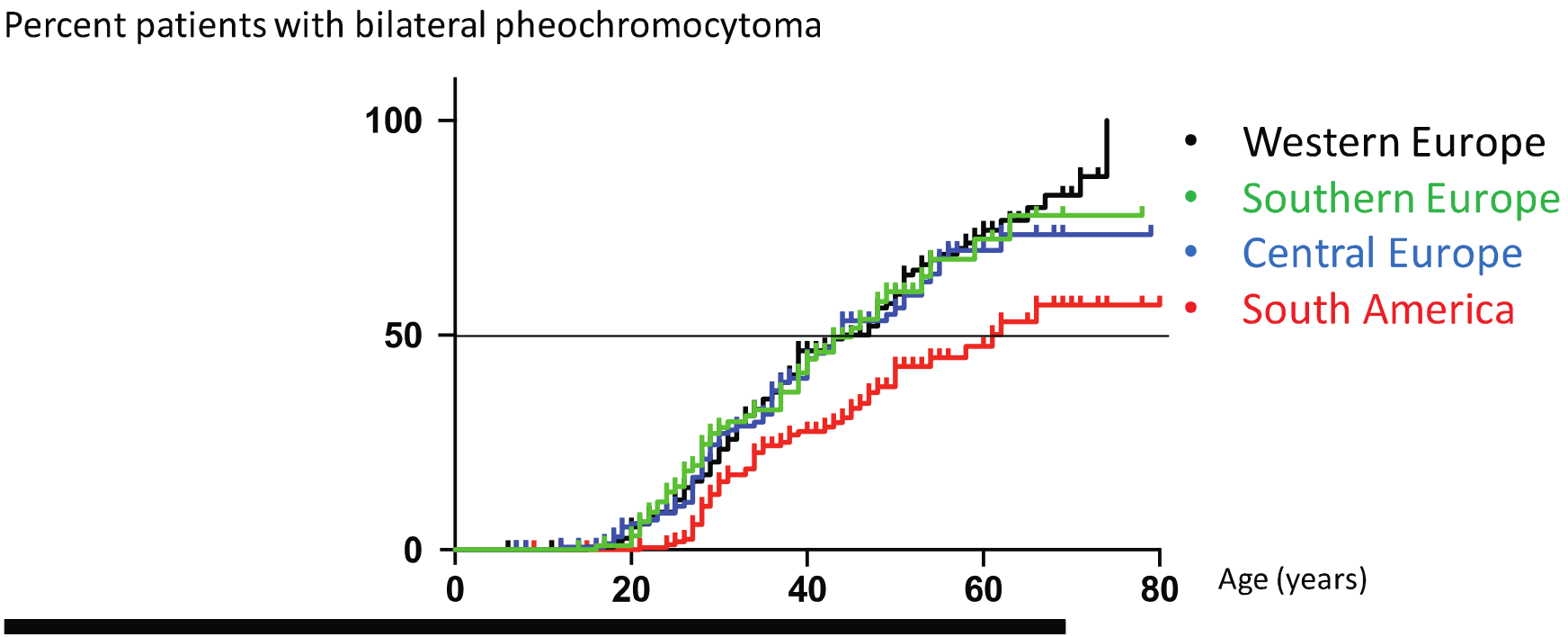
Table 1 Characteristics of pheochromocytoma based on geographic area.

	Southern Europe	Central Europe	Western Europe	South America	*P*
Patients	185	174	190	263	
Pheochromocytoma	93 (52%)	118 (68%)	141 (74%)	110 (41%)	0.038
Unilateral	35 (38%)	44 (37%)	45 (32%)	44%)	ns
Bilateral	58 (62%)	74 (63%)	96 (68%)	56%)	ns
Synchronous	51 (88%)	48 (65%)	70 (73%)	42 (68%)	0.012
Metachronous	7 (12%)	26 (35%)	26 (27%)	20 (32%)	0.016
Patients with mutations in					
Exon 10	17/90 (19%)	9/35 (25%)	15/36 (42%)	9/78 (12%)	0.021
Exon 11	76/95 (81%)	109/139 (75%)	126/154 (81%)	101/185 (53%)	0.033
Patients with mutations in codon					
609	3/25 (12%)	3/10 (30%)	3/4 (75%)	0/0	ns
611	2/2 (100%)	1/6 (17%)	3/3 (100%)	0/6	ns
618	3/18 (17%)	3/11 (27%)	8/27 (30%)	4/17 (25%)	ns
620	9/45 (20%)	2/8 (25%)	1/2 (50%)	5/55 (9%)	0.049
634	76/95 (80%)	109/139 (78%)	126/154 (81%)	101/185 (55%)	0.038
Mean age at last follow-up (years) (min–max)	45 (12–90)	42 (7–79)	51 (6–95)	43 (7–96)	ns

Gender, male/female. For RET exon and codon lines, the rate represents the number of patients with pheochromocytoma vs the total number of patients.

Endocr Relat Cancer. 2017 24(8):L63-L67

The penetrance of MEN2 pheochromocytoma is not only determined by *RET* mutations

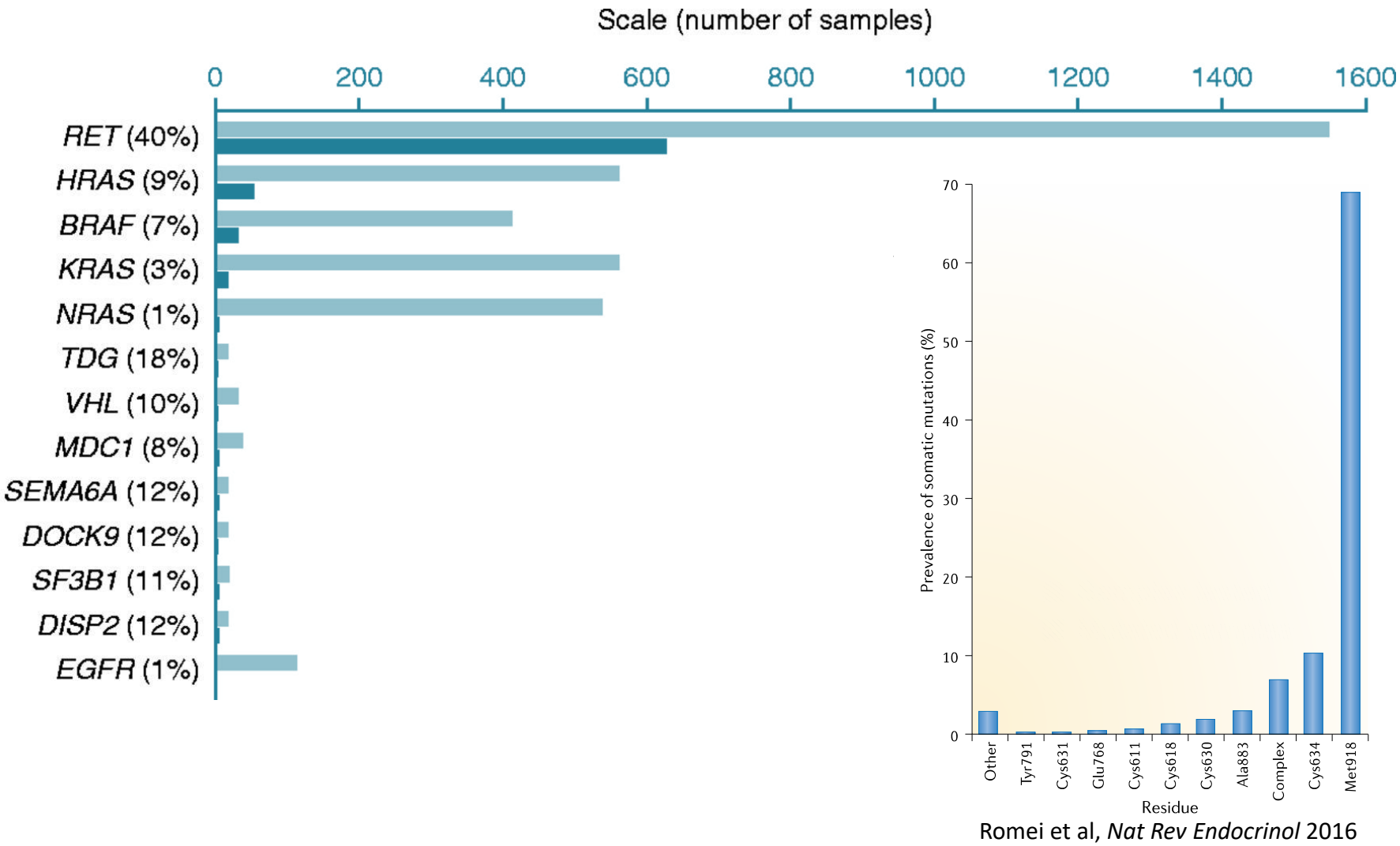


Endocr Relat Cancer. 2017 Aug;24(8):L63-L67

Sporadic Medullary Thyroid Carcinoma

- ✓ The pathogenesis is still poorly understood.
- ✓ Somatic mutations of *RET* proto-oncogene have been reported at a variable frequency ranging from 23% to 79%.
- ✓ What is the predisposing genetic event?

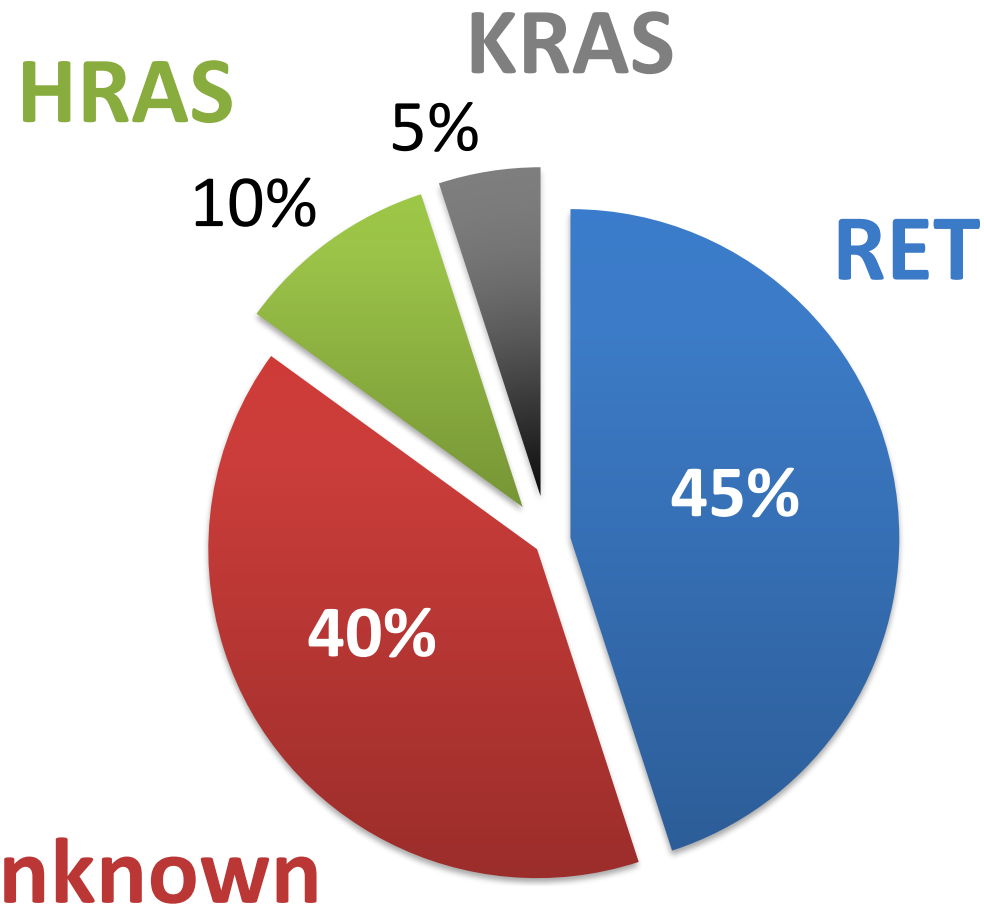
Most frequently mutated genes in sporadic MTC tumor



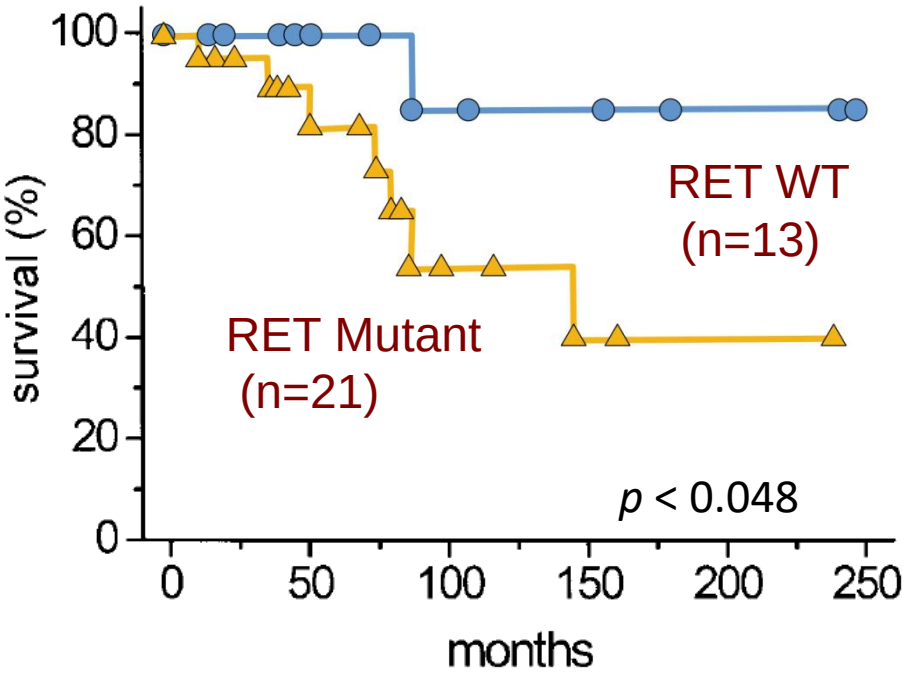
Romei et al, *Nat Rev Endocrinol* 2016

Moura *et al*. Endocr Relat Cancer 2015;22:R235-R252

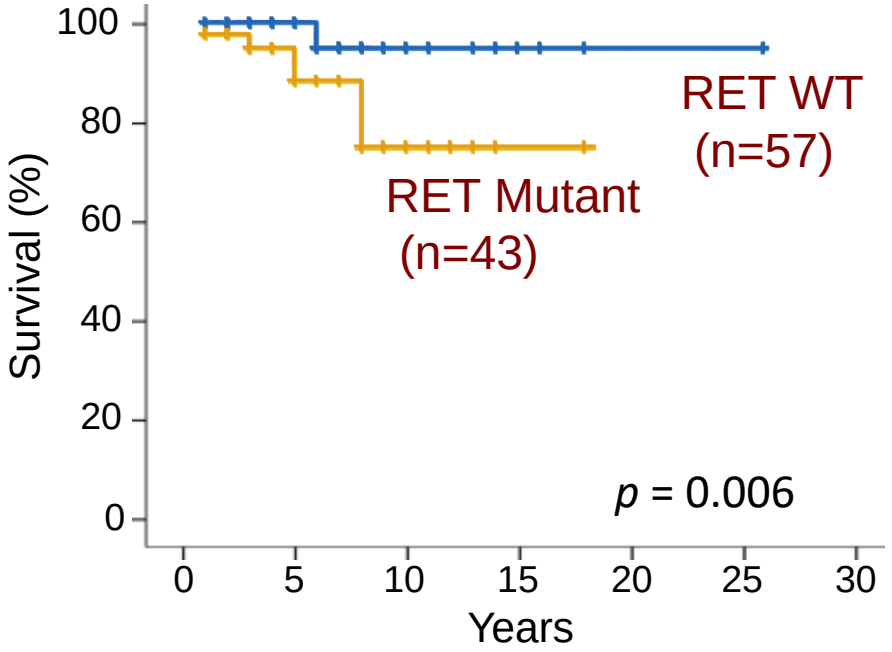
How does **molecular diagnosis** impact MTC patient care?



Somatic RET mutation is generally thought to confer worse outcome



Adapted from Schilling, T. et al.
Int J Cancer, *95*, 62–66 (2001)



Adapted from Elisei, R. et al.
JCEM, *93*, 682–687 (2007)

Table 1. Tyrosine kinase inhibitors and results of clinical trials within thyroid cancer patients

Investigational drugs	Molecular targets	Partial response/ stable disease (%)	Serious adverse events (Grade ≥ 3)
Phase 1 and 2 clinical trials			
Motesanib	VEGFR-1–3, c-Kit, RET, PDGFR	2/48	Diarrhea (13%), fatigue (8%), hypertension (10%)
Sorafenib	VEGFR-2–3, c-Kit, RET	6/50	Diarrhea (10%), hand-foot-skin reactions (14%), hypertension (10%), neurologic infection (10%)
Sunitinib	VEGFR-1–3, RET, c-Kit	28/46	Fatigue (11%), diarrhea (17%), hand/foot syndrome (17%), cytopenias (46%)
Axitinib	VEGFR-1–3, c-Kit	18/27	Hypertension (12%)
Imatinib	RET, c-Kit, PDGFR	0/27	Hypothyroidism, rash, malaise, laryngeal mucosal swelling
Lenvatinib	VEGFR-1–3, FGFRs 1–4, PDGFRα, RET, c-KIT, SCFR	50/43	Weight loss (12%), hypertension (10%), proteinuria (10%), diarrhea (10%), fatigue (9%), dehydration (9%)

Drugs approved	Molecular targets	PFS drug vs. placebo (months)	Hazard ratio	Serious adverse events (Grade ≥ 3)
Phase 3 clinical trials				
Vandetanib	VEGFR-1–3, RET, EGFR	30.5 vs. 19.3	0.46	Diarrhea (11%), hypertension (9%), ECG QT prolonged (8%)
Cabozantinib	VEGFR-2, RET, c-MET	11.2 vs. 4.0	0.28	Diarrhea (15.9%), hand/foot syndrome (12.6%), fatigue (9.3%)

Maia et al, Current Opinion in Oncology 2017

Tumor Localization & Somatic Mutation Profiles

	No.	Median Progression-Free Survival, wk		Hazard Ratio (95% Confidence Interval)	*P*
		Placebo	Cabozantinib		
All cabozantinib patients[a]	330	17	49	0.28 (0.19-0.40)	<.0001
Mutational subgroups					
RET mutational status					
RET mutation–positive	169	20	60	0.23 (0.14-0.38)	<.0001
RET mutation–negative[b]	46	23	25	0.53 (0.19-1.50)	.2142
RET mutation–unknown	115	13	48	0.30 (0.16-0.57)	.0001
RET mutations of unknown function	21	13	24	0.47 (0.14-1.60)	.3280
RET M918T mutational status					
RET M918T mutation–positive	126	17	61	0.15 (0.08-0.28)	<.0001
RET M918T mutation–negative	107	24	25	0.67 (0.37-1.23)	.1875
Non-M918T *RET* mutation–positive	43	24	36	0.70 (0.26-1.87)	.4729
RET M918T mutation–unknown	97	12	49	0.27 (0.13-0.56)	.0002
RAS mutational status					
RAS mutation–positive	16	8	47	0.15 (0.02-1.10)	.0317
RET and RAS mutation–negative[b]	30	23	24	0.88 (0.24-3.22)	.8330

[a] The hazard ratio for the entire study population was calculated with stratification factors.
[b] The hazards are not proportional.

Sherman et al, Cancer 2016

Key Points

- ✓ The cumulative understanding of molecular mechanisms involved in MTC pathogenesis had significantly impacted the diagnostic, treatment and prognosis of patients with MTC.
- ✓ Comprehensive genomic profiling of genetic alterations to identify the oncogenic drivers involved in MTC pathogenesis will hopefully refine targeted therapy in the near future.

XVII LATIN AMERICAN THYROID SOCIETY CONGRESS 2019

SAVE THE DATE!

20 AL 23 DE JUNIO DE 2019

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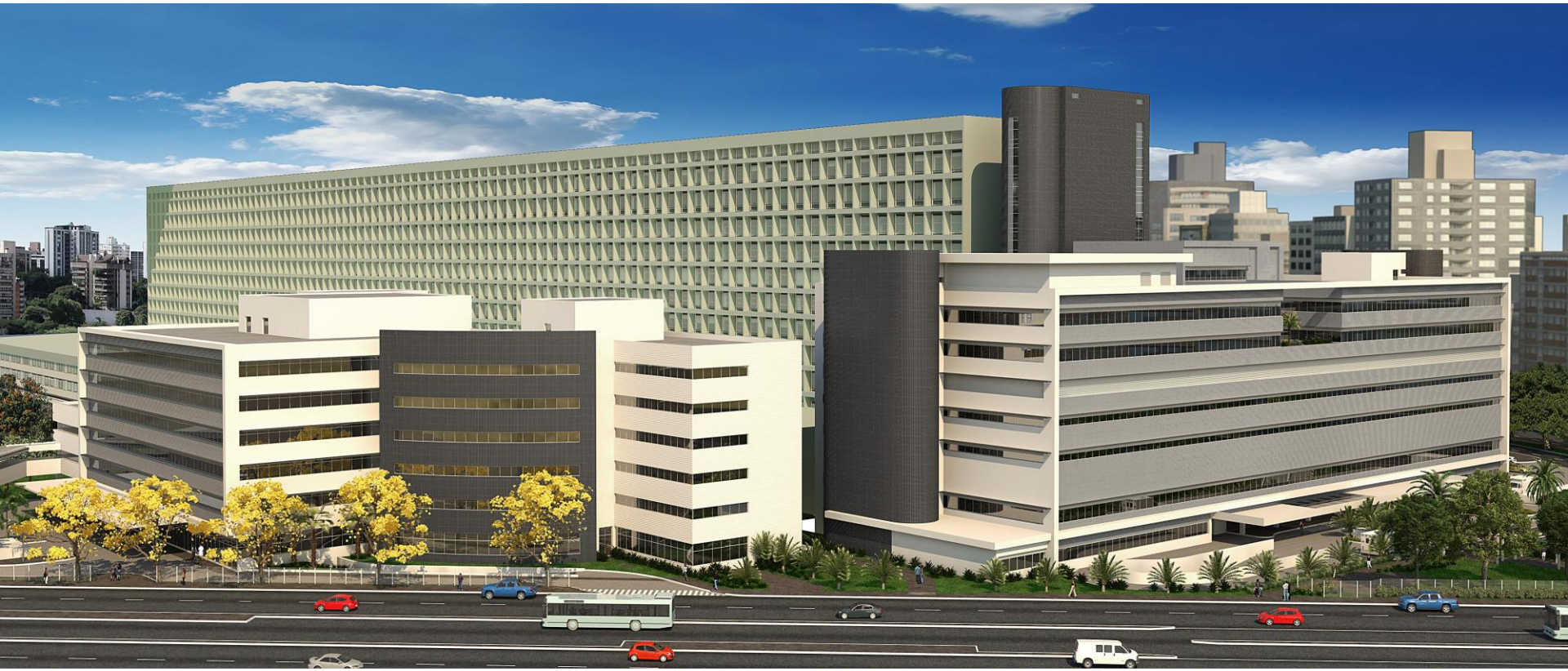

Obrigado pela atenção!