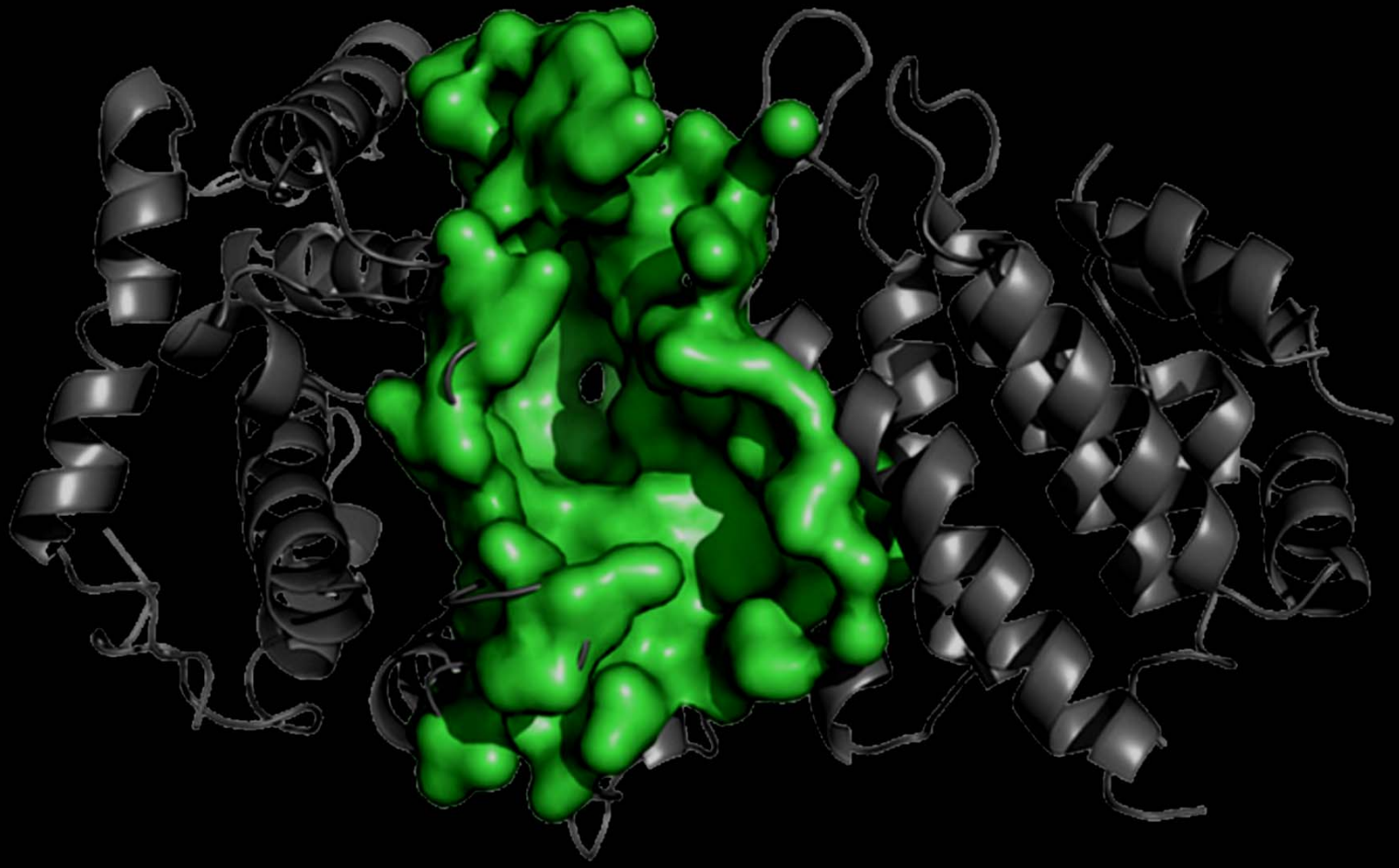
The Multiple Endocrine Neoplasias and the success of positional cloning?



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MEN1 and MEN2

Rare autosomal dominant familial cancer syndromes

Prevalence 1 per 100,000
Presentation 5 to 81 years

MEN1
Parathyroid tumours
Pancreatic islet cell tumours
Anterior pituitary tumours
Adrenal cortical tumours
Carcinoids
Angiofibromas, lipoma
collaginomas, meningiomas

Isolated familial syndromes
Hyperparathyroidism
Prolactinomas/Acromegaly
Carcinoids

Prevalence 1 per 500,000
High penetrance

MEN 2A (60%)
Medullary thyroid carcinoma
Phaeochromocytoma
Parathyroid hyperplasia

MEN 2B (5%)
Medullary thyroid carcinoma
Phaeochromocytoma
Marfanoid habitus
Mucosal neuromas
Ganglioneuromatosis/megacolon

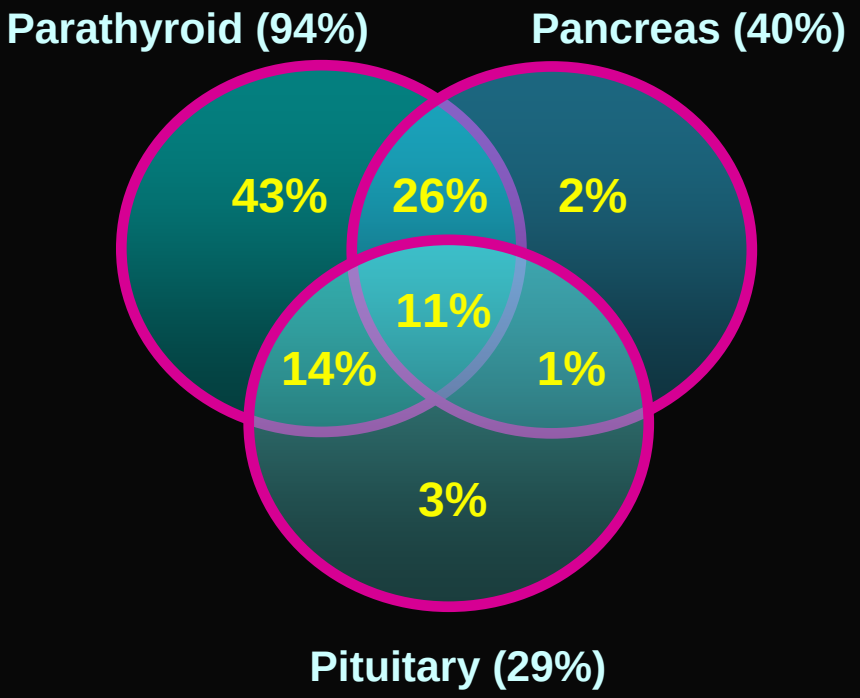
Isolated familial syndromes (35%)
Familial MTC
Familial Phaeo

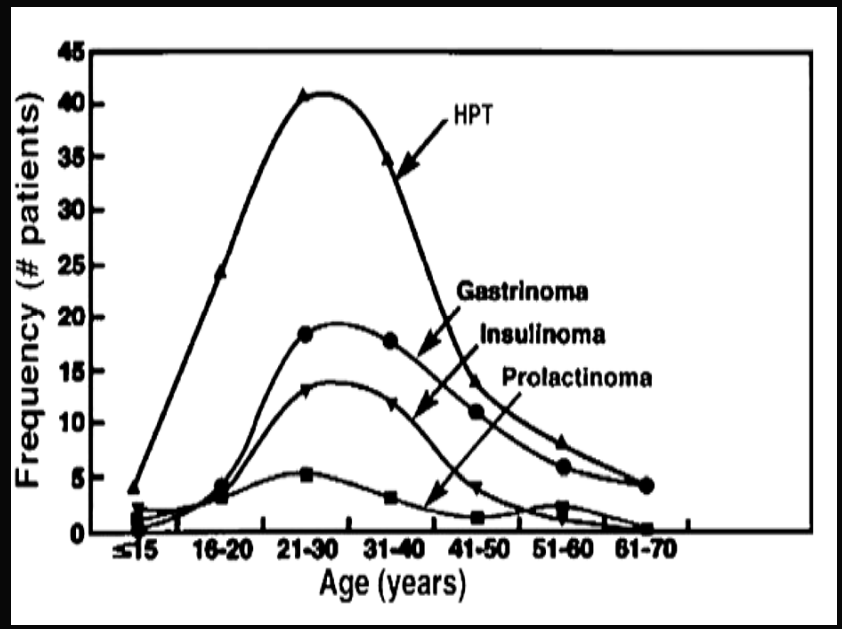
Complex Multiple Endocrine Neoplasias

McCune Albright *(GNAS1)*	Thyroid nodular hyperplasia (TTX) Adrenal hyperplasia (Cushing's) Somatotrophinomas (Acromegaly) Hyperprolactinaemia
Neurofibromatosis I *(Neurofibromin)*	Phaeochromocytoma Hyperparathyroidism Carcinoids (Medullary thyroid carcinoma)
Von Hippel-Lindau *(VHL)*	Phaeochromocytoma Pancreatic Islet cell tumour
Carney's Complex *(PRKAR1A)*	Thyroid tumours Parathyroid tumours Adrenal tumours Pituitary tumours

Multiple Endocrine Neoplasia Type 1

Multiple Endocrine Neoplasia Type 1





Associated tumours
Carcinoid 4%
Adrenocortical 5%
Phaeochromocytoma 0.5%

Cutaneous tumours
Angiofibromas 88%
Collaginomas 72%
Lipomata 30%

(Jensen RT 2008 Cancer 113:1807-1843; Verges B 2002 JCEM 87:457-465)

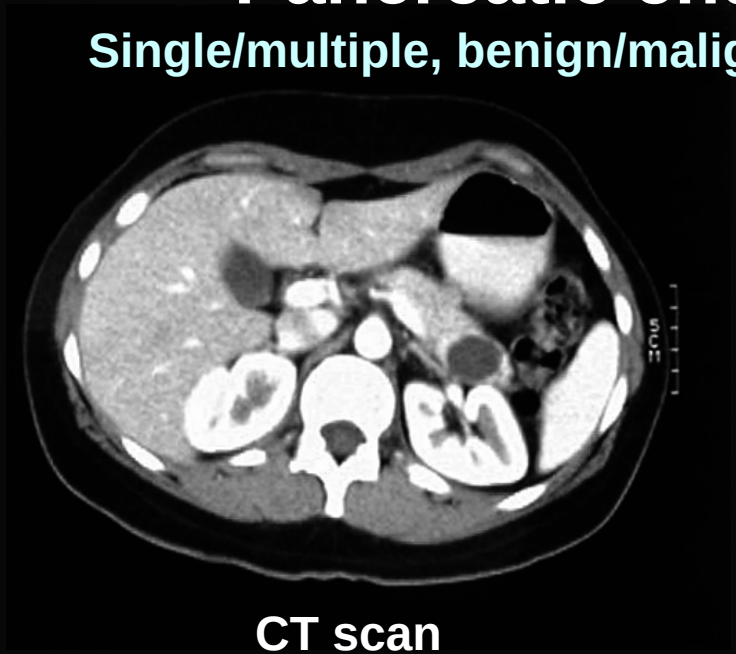
1^0 Hyperparathyroidism

- 1^0 Hyperparathyroidism (95%)
  - Frequently the first presenting feature
  - Differs from sporadic disease
    - Early age of presentation peak 20-25 years
    - Multiple gland hyperplasia rather than adenoma
    - High recurrence rate (50% by 10 years)

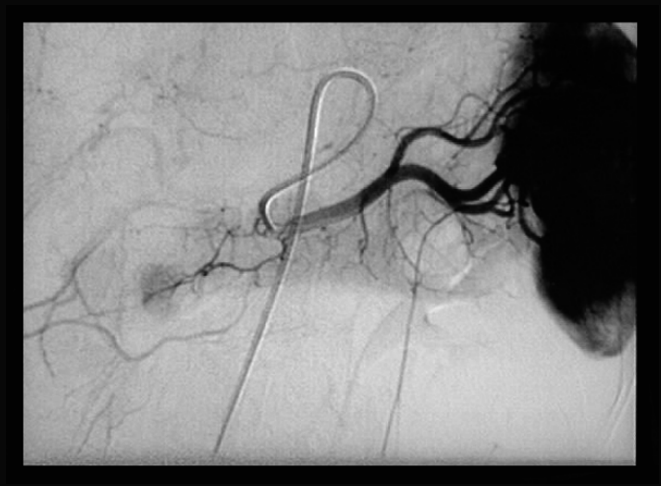
- Presentation
  - Hypercalcaemia
  - Polyuria, polydipsia, nephrocalcinosis, renal stones
  - Abdominal pain, N/V, constipation
  - Dyspepsia, peptic ulceration, pancreatitis
  - Osteofibrosacystica
  - Psychiatric disturbance

Pancreatic endocrine tumours

Single/multiple, benign/malignant, functional/non-functional



CT scan



Angiography

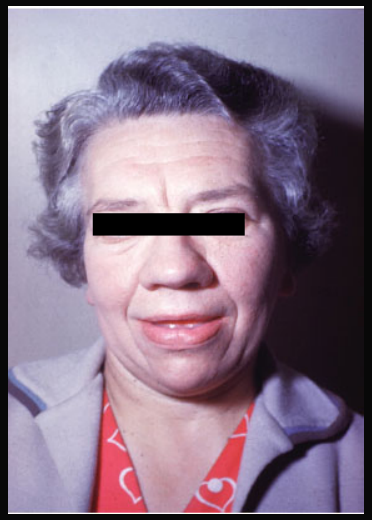
Pancreatic endocrine tumours (50-100%)

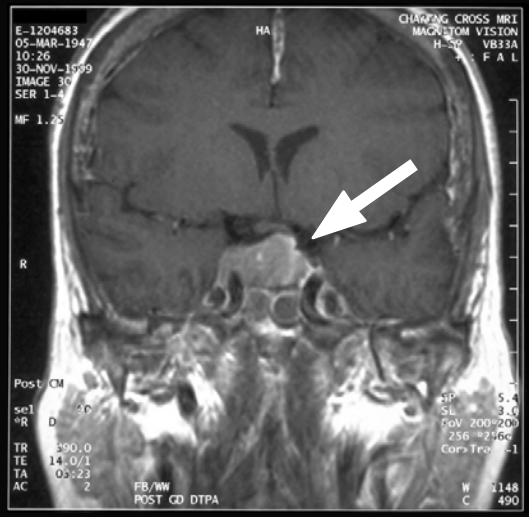
Non-functional (PPomas)	asymptomatic can metastasize if >3cm	(80-100%)
Gastrinoma (ZE)	Peptic ulceration, diarrhoea and steatorrhoea	(48%)
Co-secreting	Mixed symptoms	(22%)
Insulinoma	Hypoglycaemic symptoms, Hunger, Wt gain	(14%)
Glucagonoma	NME, DM, Wt loss, diarrhoea, DVT/PE	(5%)
VIPoma	Severe watery diarrhoea	(2%)
Somatostatinomas		(Rare)

(Jensen RT 2008 Cancer 113:1807-1843)

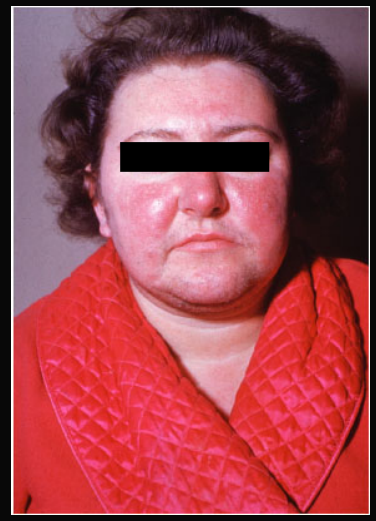
Anterior pituitary tumours

Acromegaly





Cushing's



Pituitary Adenomas (40%)

- Mean age of onset 40 years (5-83)
- Initial lesion in 17% and more frequent in females
- More aggressive than sporadic disease
- 85% macroadenomas and 37% invasive

Clinical features of pituitary adenomas

Lactotrophinomas (Prolactinomas) (Prolactin producing 63%)

Menstrual irregularity, galactorrhoea, reduced libido, impotence, infertility

Somatotrophinomas (Acromegaly) (GH producing 23%)

Headache, sweating, ↑soft tissue, ↑hands and feet, prognathism, nerve compression, cutaneous fibromas, acanthosis nigricans, HT, LVH, cardiomyopathy, arrhythmias, colonic malignancy

ACTHomas (Cushings disease) (ACTH producing 4%)

Hirsuitism, centripedal obesity, buffalo hump, purple striae, HT, glucose intolerance, proximal myopathy, infertility, psychiatric problems

Non Functional tumours (15%)

Headache, bitemporal hemianopia, hypopituitarism, cranial nerve palsies menstrual irregularity, galactorrhoea, reduced libido, impotence, infertility

Co-secreatory (9%)

Other MEN1 associated tumours

Adrenocortical (20-50%)

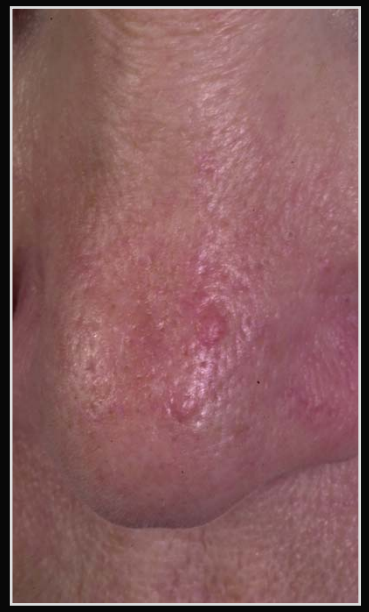
- Clinically silent adrenal adenomas or hyperplasia
- rarely carcinomas

Carcinoid Syndrome (15%)

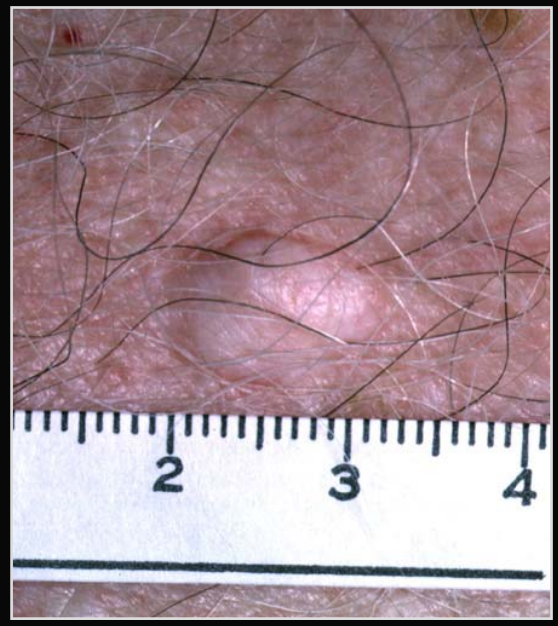
- 70% foregut; gastric (70%), thymic (15%), and bronchial (15%)
- Flushing, palpitations, wheezing, diarrhoea, tricuspid insufficiency and pulmonary stenosis

Dermatological features of MEN1

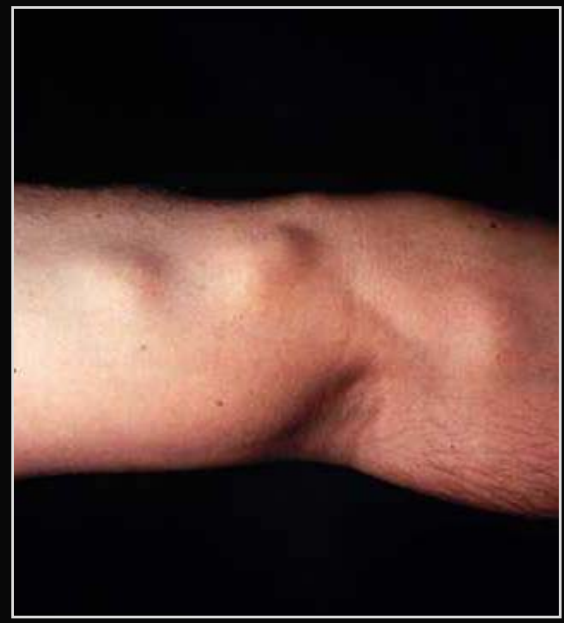
Benign lesions no treatment required



Multiple facial angiofibromas (5- 88%)



Hypopigmented collagenomas (0-72%)



Lipomas (3-34%)

2001 Consensus screening schedule

If possible identify mutant gene carriers
Clinical screening from 5 years
Biochemical evidence may occur 10 years before clinical disease

Tumour	From Age	Annual	3 yearly
1^0HPT	8	Ca, PTH	None
Insulinoma	5	Insulin, fasting Glu	None
Gastrinoma	20	Gastrin	None
Other pancreatic	20	CgA, glucagon, proins	CT/MRI/SRS
Anterior pituitary	5	PRL, IGF1	MRI pit
Carcinoids	20	None	CT

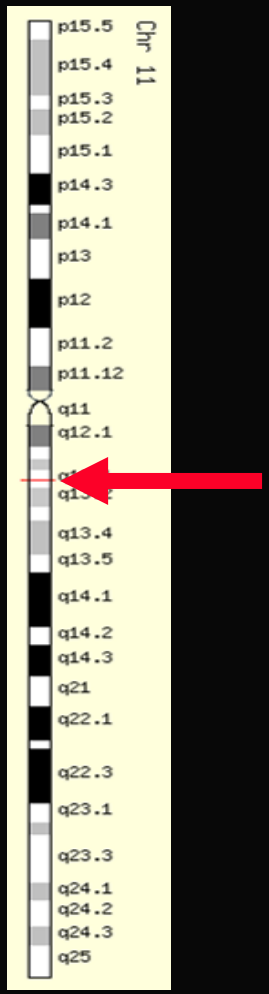
Annual	3 yearly
Ca/PTH	Abdo MRI/CT
Gut hormones	SRS/
PRL/IGF1	Pit MRI
Fasting Glu	CT thorax
(?EUS/CT thorax)	

(Brandi ML 2001 JCEM 86:5658-5671; Engelien AM 2003 Euro J Endocrinol 149:577-582)

MEN1 is caused by loss of function mutations in a tumour suppressor gene that encodes MENIN

The *MEN1* gene

Chr 11



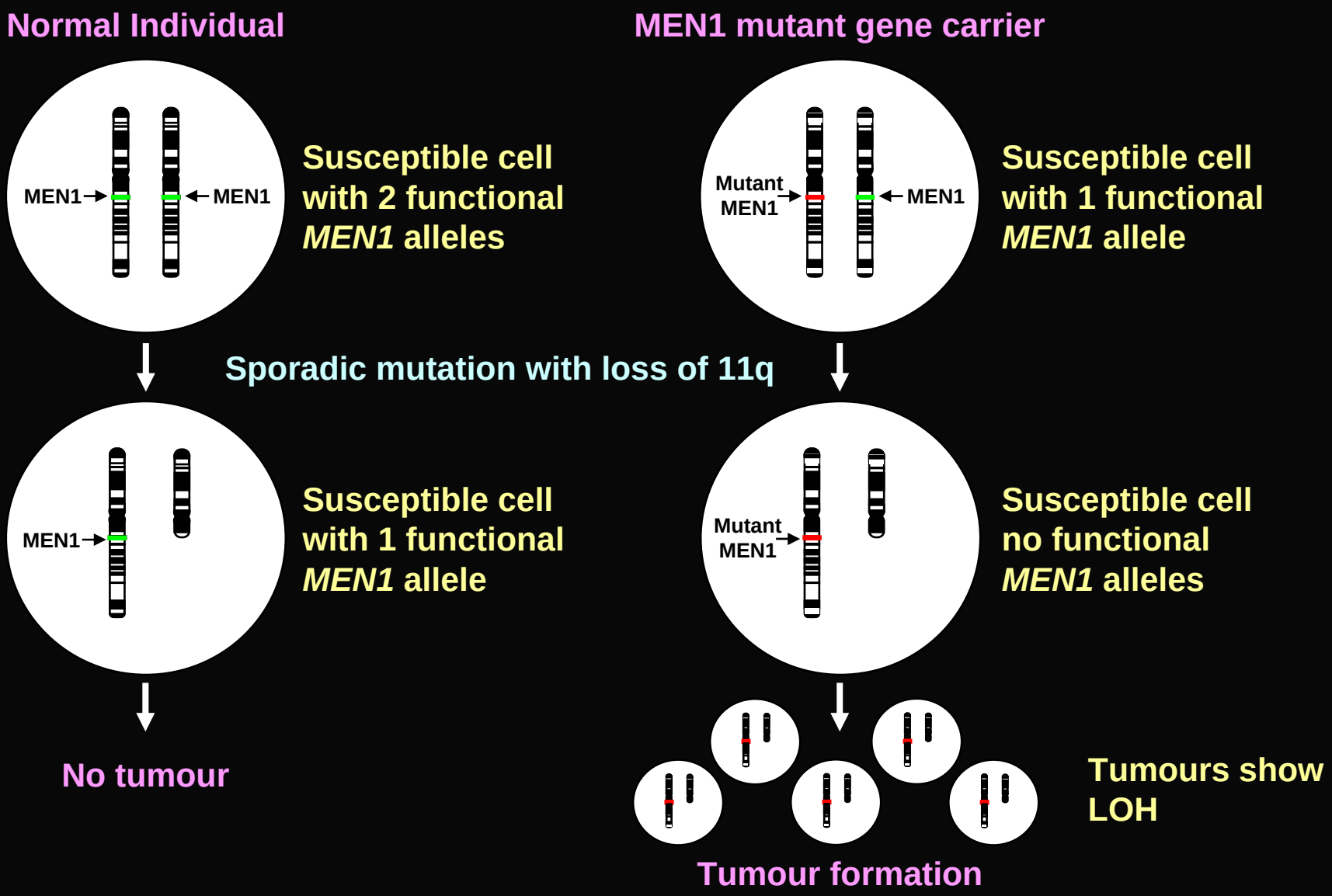
Located at chromosome 11q13

- 10 exons
- 2.8Kb mRNA transcript
- 610 amino acids protein Menin
- 6 alternative splice variants (5’ UTR)

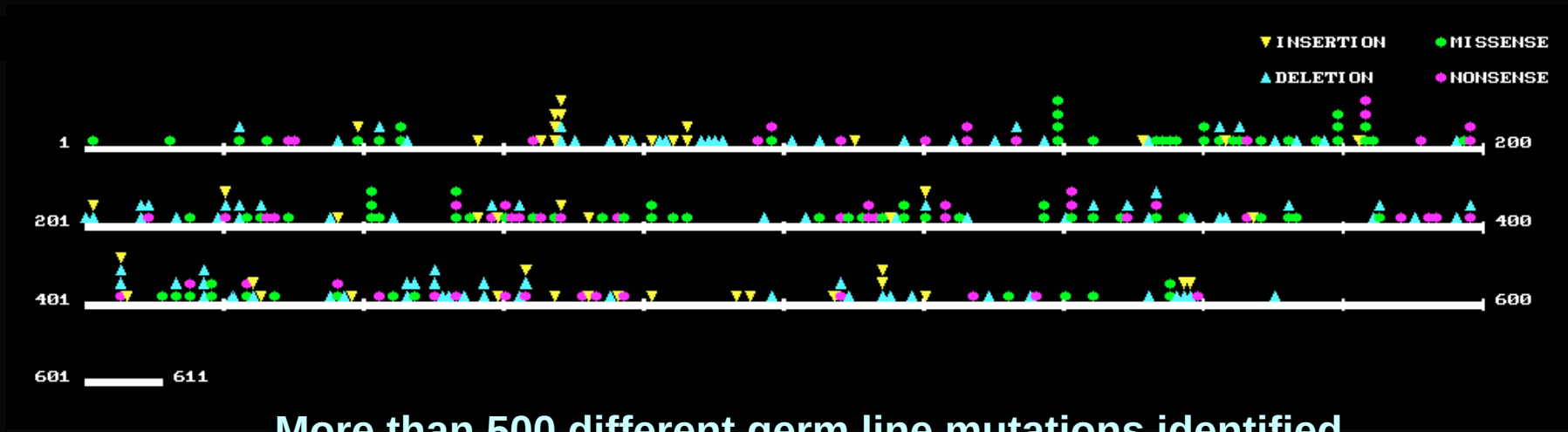
Menin is a tumour suppressor gene

- MEN1 is caused by Menin loss of function mutations
  - 80% predict truncated or absent protein
  - Rapid proteasome-degradation of mutant Menin
- Tumour specific loss of the normal MEN1 allele (LOH)
  - “Knudsons two hit hypothesis”
- Over-expression of Menin in Ras-transformed cell lines reverts the transformed phenotype

Tumour suppressor genes and tumour formation



Mutation are scattered throughout *MEN1* gene



More than 500 different germ line mutations identified

¾ predict a truncated or absent protein

No hot spots, scattered throughout coding region

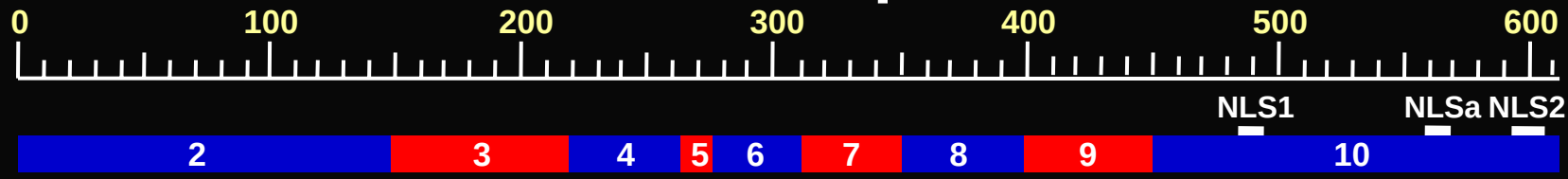
Nonsense	23%
Frameshift deletion/inertion	41%
Large deletions	1%
In frame deletion/insertion	6%
Missense	20%

10% occur *de novo*

5-10% of patients do not have mutations in coding region

(Thakker RV 2010 Best Pract Clin Endo Metab 24:355; Human Gene Mutation Database Cardiff)

The MENIN protein



MENIN is a 67kDa protein, 3x NLS and binds DNA

- Nuclear localisation but cytoplasmic in dividing cells

No homology or functional motifs

Conserved from man to molluscs

- *Drosophila 70% identity*

Expressed from earliest stages of embryogenesis

Expressed ubiquitously in all adult tissues

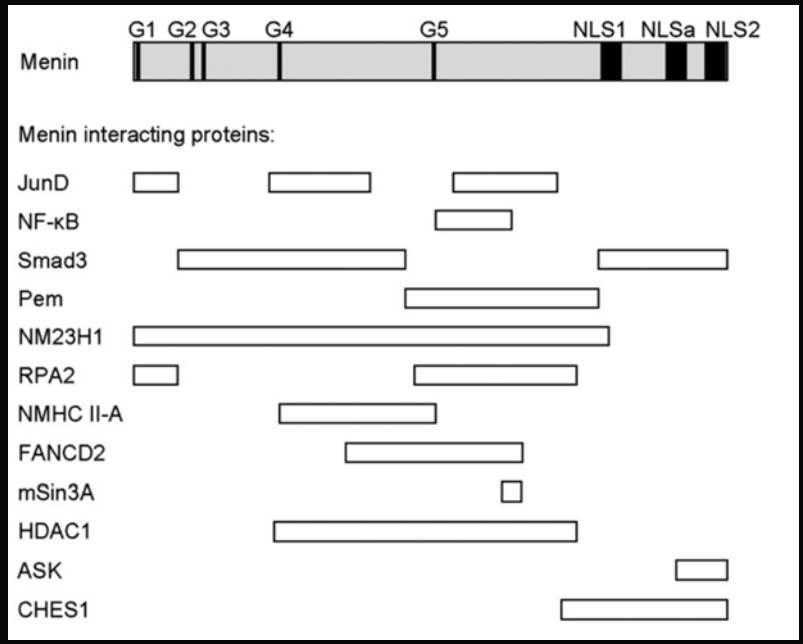
- Expression inversely correlated with proliferation (cell cycle)
- Expression varies with the cell type
- Menin negatively regulates its own expression
- Somatostatin induces Menin expression

Multiple protein interactions have been identified

Precise cellular function of Menin remains uncertain

The pattern of MENIN expression cannot explain the endocrine nature of associated tumours

MENIN interactions and function



Function	Interacting partner
Transcription regulation	JunD
	NFκB (P50, P52, P65)
	pem
	Sin3A
	HDAC
	Smad1
	Smad3
	Smad5
	Runx2
	MLL histone methyltransferase complex
	ERα
	CHES1
	Double-stranded DNA
Genome stability	RPA2
	FANCD2
Cell division	NMHC II-A
	GFAP
	Vimentin
Cell cycle control	nm23[a]
	ASK

Two hybrid screening, co-immunoprecipitation GST-pull-down studies

(Chandrasekharappa SC 2003 J Int Med 253:606 ;Thakker RV 2010 Best Pract Clin Endo Metab 24:355)

Transcriptional regulation by Menin

Interacts with JunD and C-Jun to suppresses transcription

JunD/mSin3A/HDAC histone deacetylase recruitment

Binds NFκB (p50, p52 and p65) suppressing transcriptional activation

Inhibits TGFβ and BMP-2 signally by binding Smad3 and Smad1/5

Menin is component of MLL histone methyltransferase complex

Activates gene transcription by H3-K4-timethylation

Menin binds and act as co-activator for ERα, VDR and PPARγ

Menin binds β-catenin

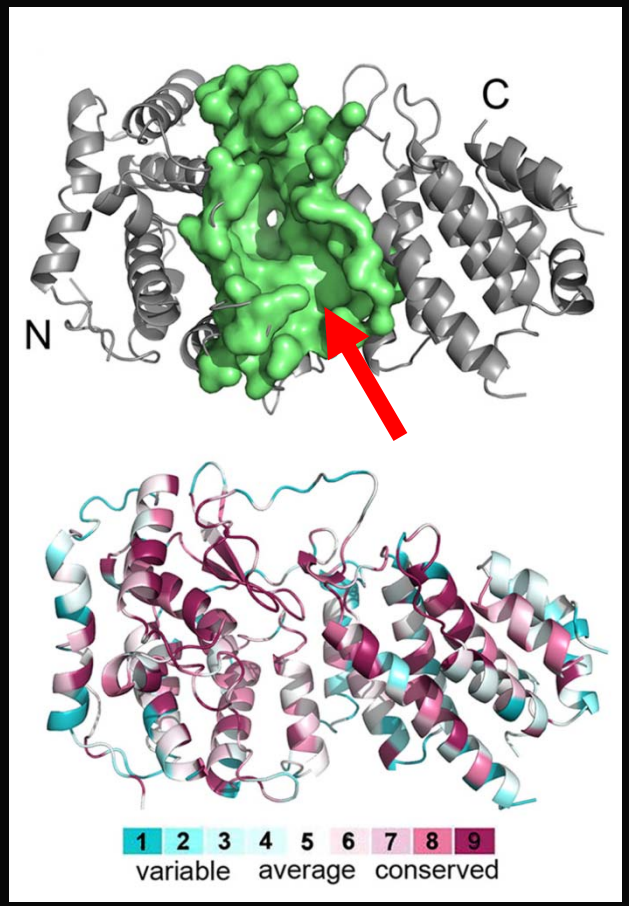
Effects β-catenin cellular location and Wnt signalling

"Menin may act as an adapter protein regulating many molecular complexes involved in tumorigenesis, proliferation, differentiation, apoptosis, growth factor and stress responses, DNA repair and epigenetic modification"

(Balogh K 2010 Mol Cell Endo 326:80; Thakker RV 2010 Best Pract Clin Endo Metab 24:355)

Mixed lineage leukaemia histone methyltransferase complex

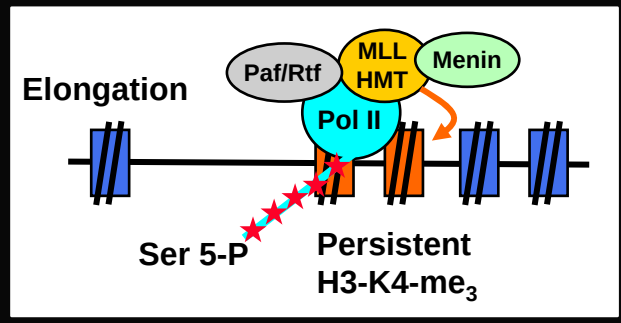
Menin MLL binding pocket



Sea anemone menin

Menin is key component of MLL-HMT complex

- Trimethylation (H3-K4-me$_3$)
- Epigenetic transcriptional regulation



Menin dependent MLL-HMT activity regulates

- CDK inhibitor expression (*p18* and *p27*)
- Hox gene expression (*Hoxa9, Meis1*)

Acute leukaemia

- MLL fusion proteins have poor prognosis
- Menin is a critical oncogenic cofactor

(Ng HH 2003 Mol Cell 11:709; Hughes CM 2004 Mol Cell 13:587; Murai MJ 2011 JBC 286:31742)

Importance of CDK inhibitors $p27^{Kip}$ and $p18^{ink4c}$

$p27^{Kip}$ and $p18^{ink4c}$ double KO mice (3 month old) *(Franklin Ds 2000 MCB 20:6147)*

- Parathyroid and pituitary adenomas, Islet cell and duodenal hyperplasia
- Thyroid c-cell hyperplasia and Phaeochromocytomas

MenX rats: spontaneously occurring AR disorder *(Pellegata 2006 NS PNAS 103:15559)*

- Homozygous frameshift mutation of $p27^{Kip}$ (8nt duplication exon 2)
- Parathyroid adenomas, pancreatic islet cell hyperpasia,
- Thyroid C-cell hyperplasia,
- Bilateral phaeochromocytomas and paragangliomas

Analysis of *CDKN1B/p27* in MEN1 mutation negative families

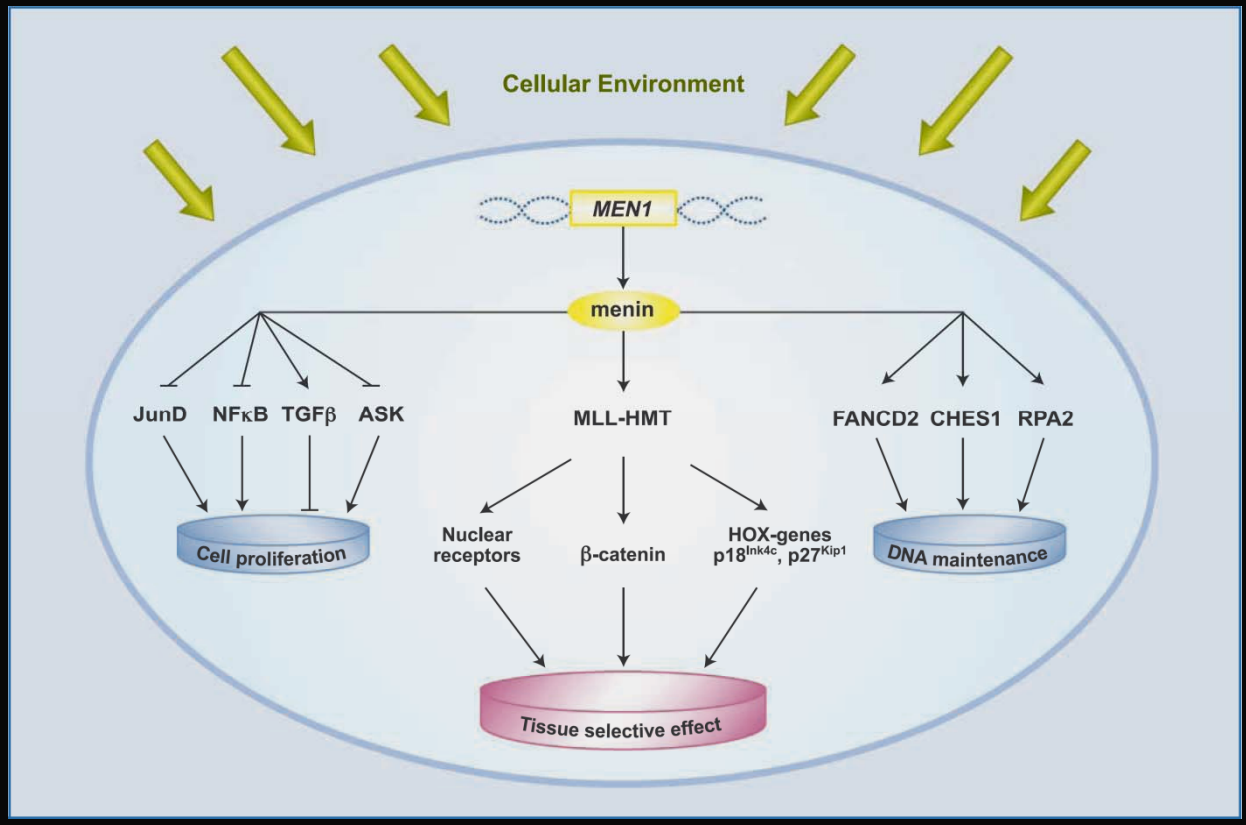
- 2% heterozygous for germline mutations of *CDKN1B* (5 identified)
- Parathyroid, pituitary (GH and ACTH), pancreatic (Gastrin and NF)
- Adrenal tumours and renal angiomyolipoma
- Small cell cervical carcinoma (show LOH)

$p27^{Kip}$ and $p18^{ink4c}$ have key roles in preventing neoplasia in endocrine tissues

There regulation by MLL-HMT may help explain the phenotype of MEN1

(103:15558; Georgitsi M JCEM 2007 92:3321; Agawarl SK JCEM 94:1826)

Summary of MENIN's function



The pattern of tumorigenesis in MEN1 is likely to be a consequence of the specific inability of endocrine cells to compensate for the loss of Menin

(Gracanin A 2009 Cancer Res 69:6371-6374)

Animal models of MEN1

Global *Men1* knockout mice

***Men1*$^{(-/-)}$ die *in utero* E11.5-13.5**

- **Craniofacial, neural, cardiac and hepatic abnormalities**

Men1*$^{(+/-)}$ (deletion of exon 3-8)** ***(Crabtree JS 2001 PNAS 98:1118)

- **Parathyroid, pancreatic (Ins), pituitary (Prl) and adrenocortical tumours**
- **LOH in tumours**
- **Hyperplasia is nonclonal in some tissues (islet cells)**

Men1*$^{(+/-)}$ (deletion of exon 3)** ***(Bertolino P 2003 Mol Endo 17:1880)

- **Parathyroid, pancreatic (Ins/Gast/Glu), pituitary (Prl/GH) and adrenal**
- **Thyroid, Leydig, ovarian and mammary tumours**

***Men1*$^{(+/-)}$ (deletion of exon 1 and 2)**

(Loffler KA 2007 Int J Cancer 120:259; Harding B 2009 Endo Related Cancer 16:1313)

- **Parathyroid, pancreatic, pituitary tumours**
- **Thyroid, adrenal and gonadal tumours**

Endocrine tissues in humans and mice have different abilities to compensate for the loss of menin

Animal models of MEN1

Conditional *Men1* knockout mice

β cell specific deletion of *Men1* by E11.5 (*Men1*$^{(\Delta Rip/\Delta Rip)}$ mice)

- Normal islet cell architecture
- 100% islet hyperplasia at 2 months
- 88% insulinomas at 8 months
- Loss of one *Men1* allele leads to hyperplasia, 2 alleles to atypical hyperplasia but further somatic events are required for adenoma formation

Hepatocyte specific deletion of *Men1* (*Men1*$^{(\Delta Alb/\Delta Alb)}$ mice)

- Normal livers no tumours
- 89% and 63% reduction CDK inhibitors p18^{Ink4c} and p27^{Kip1} respectively

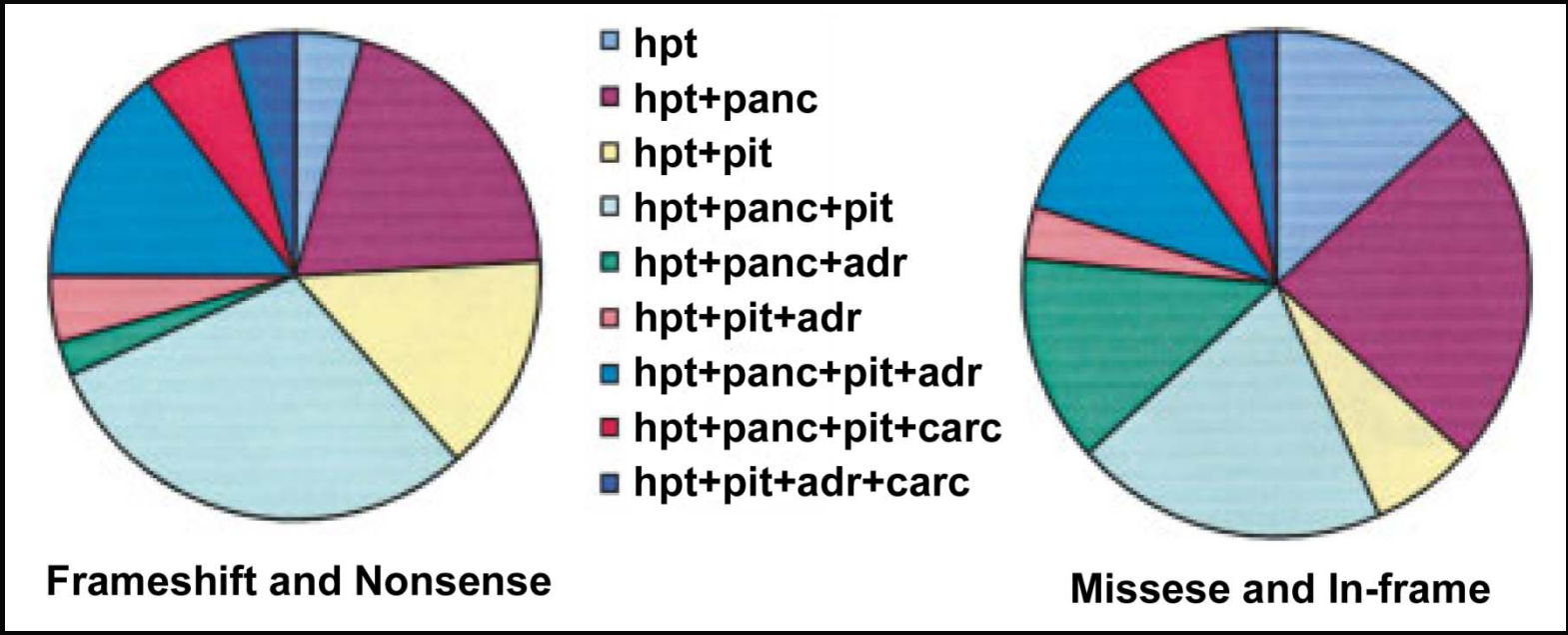
Tamoxifen inducible deletion (Cre-ER x *Men1*$^{flox/flox}$)

- Pancreatic hyperplasia and islet enlargement within 14d
- Decreased expression of CDK inhibitors p18^{Ink4c} and p27^{Kip1}
- Accelerated S phase entry in cell cycle

(Crabtree JS MCB 2003 98:1118, Bertolino P Can Res 2003 4836, Scacheri PC Mam Gen 15:872, Schnepp RW Can Res 2006 66:5707)

Genotype phenotype correlation and genetic testing in MEN1

Genotype phenotype correlation in MEN1



There is no evidence of a phenotype genotype correlation in MEN1

- Wide phenotypic variation within families
- Menin is a tumour suppressor
- Mutations are scattered with no hot spots
- 75% of mutations predict absent or truncated protein
- Mutant Menin proteins are rapidly degraded

(Wautot V 2020 Hum Mut 20:35)

Genetic testing in MEN1

(Exeter and Oxford)

Genetic testing should be offered to

- **Sporadic cases (2 of 3 main MEN1 tumours)**
- **Familial cases (2 of 3 main MEN1 tumours + 1st degree relative with 1)**
- **Suspicious/atypical cases with 2 or more MEN1 related tumours**
- **Multiple/recurrent parathyroid tumours (<30y) or familial 1^0HPT**
- **Gastrinoma or multiple islet cell tumours**
- **Family members at risk (<10 years)**

***MEN1* mutation screening is by direct sequencing**

Screening MEN1 exons 2 to 10	**£350**
Dosage analysis (MLPA)	**£100**
Known MEN1 mutation in family member	**£100**

If no *MEN1* mutation identified and likely to be familial

Linkage analysis	**£245**
***CDKN1B* 1-2**	**£105**

(Brandi ML 2001 JCEM 86:5658; Ozawa A 2007JCEM 92:1948)

Genetic testing for MEN1

Probability of identifying a germline MEN1 mutation

- **75-95% of familial MEN1 probands**
- **30-45% of sporadic MEN1**
- **10% of familial 1^0HPT probands**
- **1% familial pituitary tumours**

Benefits of *MEN1* genetic screening

- **Confirms the diagnosis in the proband**
- **Targets biochemical screening to mutant gene carriers**
- **Prevents unnecessary screening of unaffected family members**

MEN1 genetic screening DOES NOT

- **Prevent cancer**
- **Predict phenotype**
- **Alter clinical management**

(Ellard S 2005 Clin Endo 62:169; Ozawa A 2007JCEM 92:1948)

MEN1 Summary

MENIN is a tumour suppressor and oncogenic cofactor in leukaemia
MEN1 due to inactivating mutations throughout the coding region
Many cellular functions have now been ascribed to MENIN
- Transcriptional regulation
- Chromatin modification
- Cell cycle control
- Genome stability, DNA replication and repair
- Apoptosis regulation

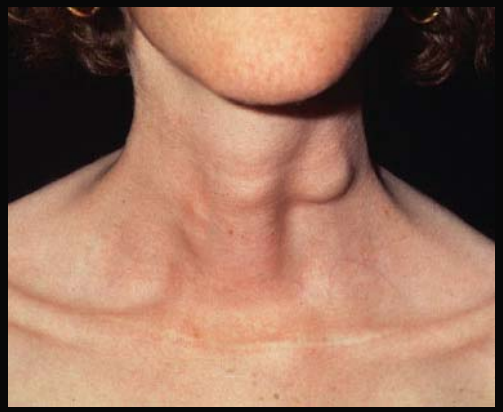
No phenotype genotype correlation in MEN1
Genetic testing confirms diagnosis and identifies mutant gene carriers

Target deletion in mice suggest
- Menin induces expression of cell cycle inhibitors p18 and p27
- Susceptible tissues
  - Are unable to compensate for reduced P18 and P27 levels
  - Menin haploinsufficiency predisposes to hyperplasia
  - Menin loss leads to atypical hyperplasia
  - Additional somatic events required for tumour formation

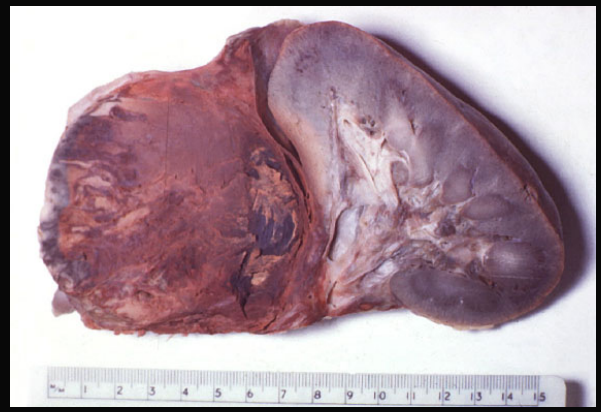
Multiple Endocrine Neoplasia Type 2

MEN2A and FMTC

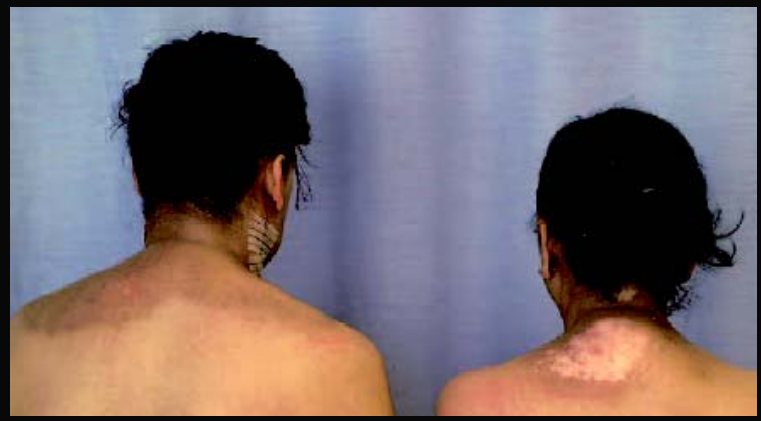
MEN2 AD disease, high penetrance, prevalence >1/500,000



MTC



Phaeochromocytoma



CLA

MEN 2A (60%)	**Medullary thyroid carcinoma**	**90-100%**
(5-10% de novo)	**Phaeochromocytoma**	**50%**
	Parathyroid hyperplasia	**20-30%**
MEN2A with Hirschsprungs		**(25 families)**
MEN2A with cutaneous lichen amyloidosis		**(30 families)**

FMTC (35%)	**Medullary thyroid carcinoma**
(5-10% denovo)	**(Requires >10 carriers and multiple >50y)**

Multiple Endocrine Neoplasia Type 2A
(Sipples Syndrome)

C-cell hyperplasia or MTC (100% by 30 years)

- Thyroid nodule or mass uni/bilateral, diarrhoea in late stages
- First presenting feature of MEN2

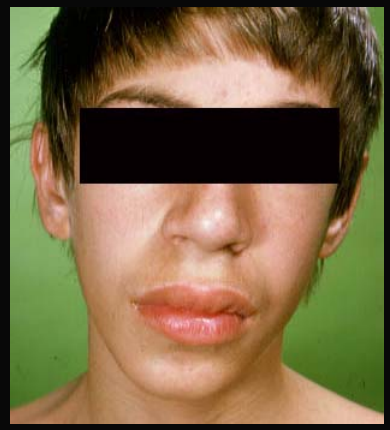
Phaeochromocytoma (20-50% uni or bilateral)

- Sweating, anxiety, palpitations, HT, headaches, stroke, glucose intolerance
- Often occurs 10y after MTC

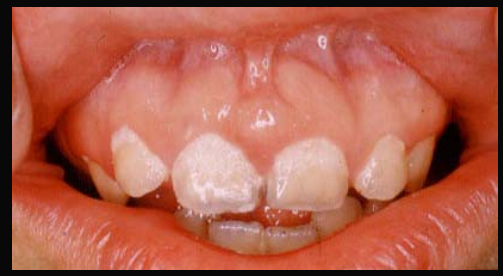
Parathyroid hyperplasia/adenomas (5-20%)

- Symptoms as in MEN1
- Frequently late onset

MEN2B only 5% of MEN2 and 50% Denovo



Marfanoid habitus



Mucosal neuromas

Medullary thyroid carcinoma (100%)
- More aggressive than in MEN 2A, < 2y
- Total thyroidectomy at the earliest age 4-5y

Phaeochromocytoma (50%)
- As for MEN2A

Mucosal neuromas (>90%)
- Tongue, lips and sub conjunctival and GI tract

Marfanoid habitus, pes cavus, scoliosis (>90%)
- Pectus excavatum, slipped femoral epiphysis

GI ganglioneuromatosis / megacolon
- Diarrhoea, colic, colonic obstruction and dilation

Biochemical Screening in MEN2

If possible identify family members with mutation
Clinical screening from the age of 1 to 2 years for life

Tumour	Age Start	Annual
MTC	Prophylactic thyroidectomy	
MTC	1 to 2	Calcitonin, Pentagastrin
Phaeochromocytoma	8-20y	3x Urinary catacholamines
1^0HPT	8-20y	Ca, PTH, VitD

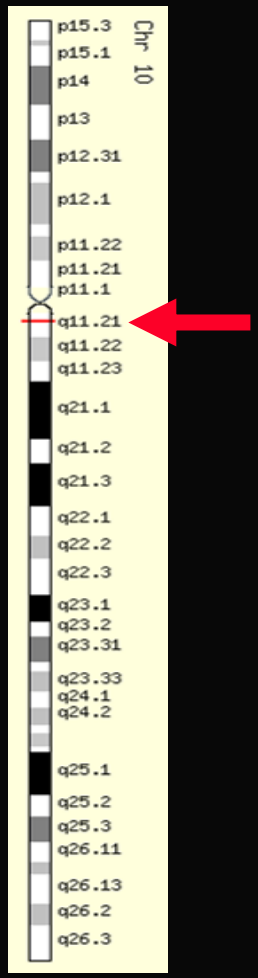
Rapid further investigation of any abnormality

MEN2 is caused by gain-of-function mutations in the *RET* proto-oncogene

(***RE***arranged during ***T***ransfection)

The *RET* proto-oncogene

Chr 10



Trans-membrane tyrosine kinase receptor
Expressed in cells derived from the neural crest

Chromosome 10

- 21 exons (1072-1114 amino acids)
- 3’ alternative splicing (RET9, RET43 and RET51)

Expression during embryogenesis

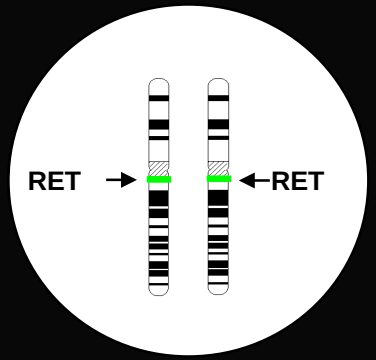
- Developing excretory system
- Peripheral nervous system
- CNS neurons
- C-cells of the thyroid

Essential function

- Development enteric nervous system
- Kidney organogenesis
- Spermatogenesis

RET mutation and tumour formation

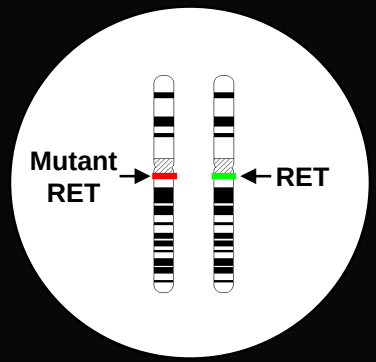
Normal Individual



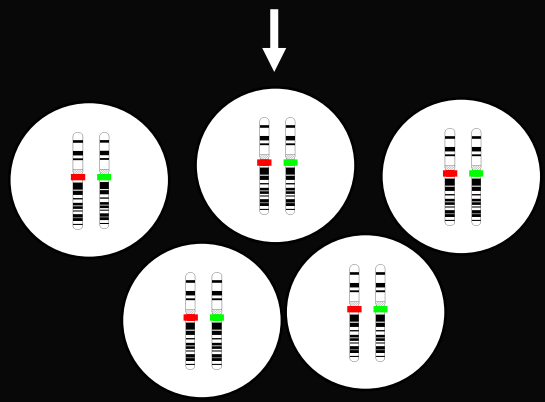
Susceptible cell with 2 normal RET alleles

Normal proliferation differentiation and survival

Mutant gene carrier



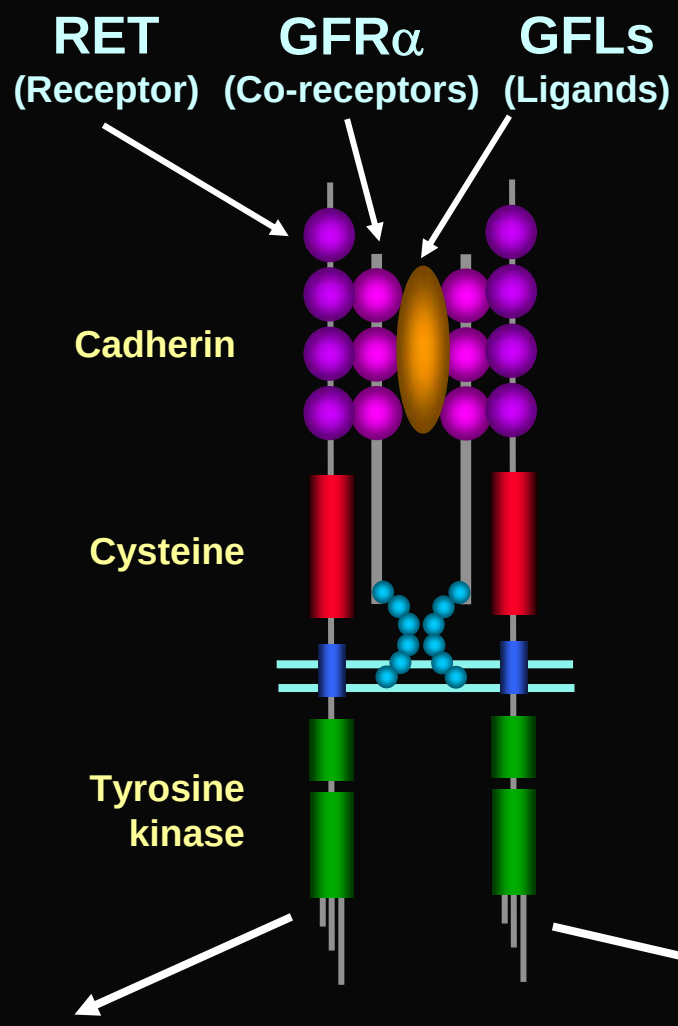
Susceptible cell with gain-of-function mutation in one RET allele



Abnormal proliferation differentiation and survival

The pattern of RET expression can explain the endocrine nature of associated tumours

Receptor for the glial cell-derived neurotrophic factor family of ligands (GFLs)



Ligands

GFLs: GDNF, neurturin, artemin, persephin

Co-receptor

GDNF receptor-α family (GFRα1 – GFRα4)

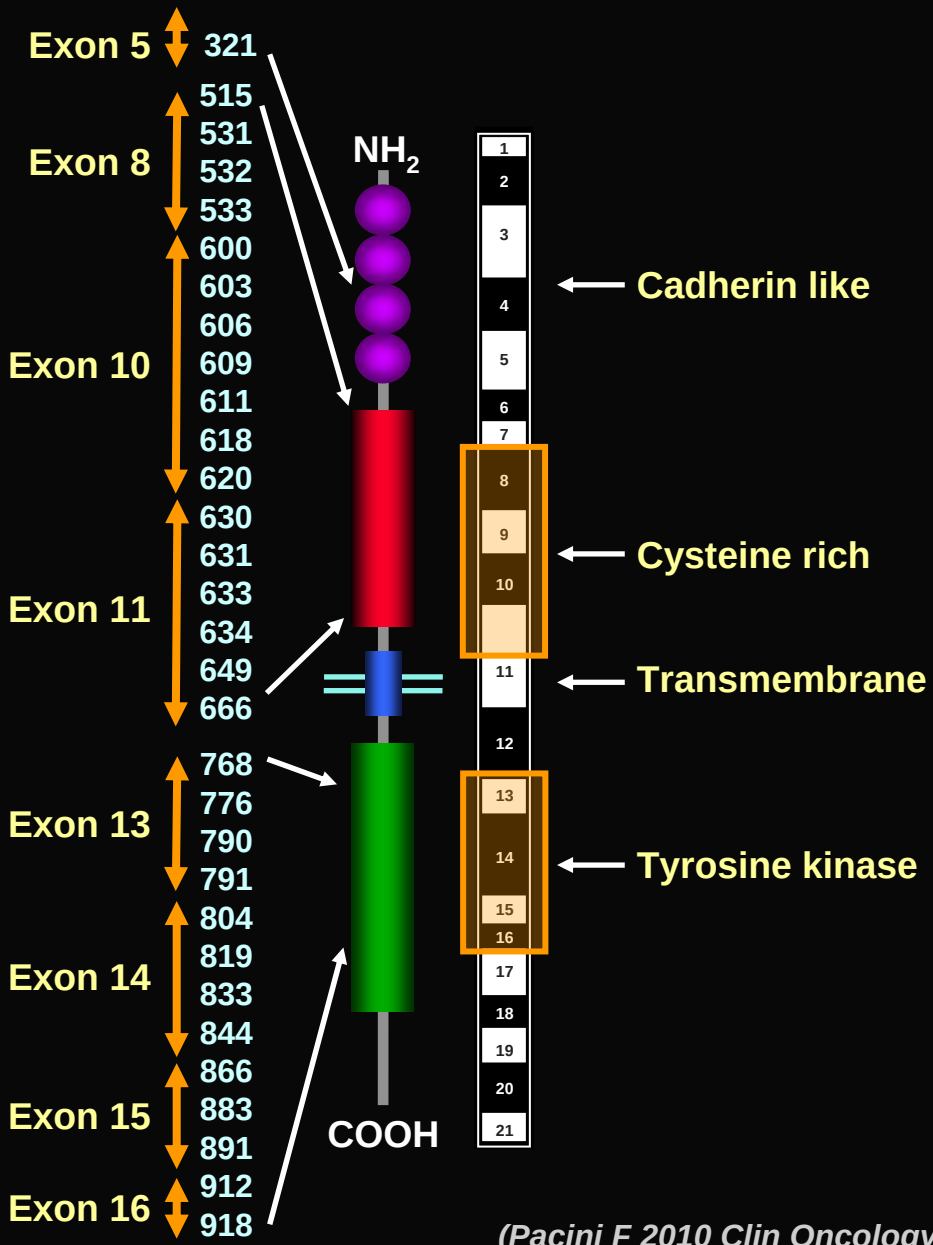
GDNF	GFRα1
Neurturin	GFRα2
Artemin	GFRα3
Persephin	GFRα4

Receptor tyrosine kinase

RET

(Plaza-Menacho I 2006 Trends Genet 22:627-636)

RET codons mutated in MEN2



95% of patients have RET mutations

138 different germ line mutations

Two hot spots

- Cysteine rich domain
- Tyrosine kinase domain

Mutations

- 95% missense mutations
- 5% in frame deletion/insertion

MEN2A and FMTC

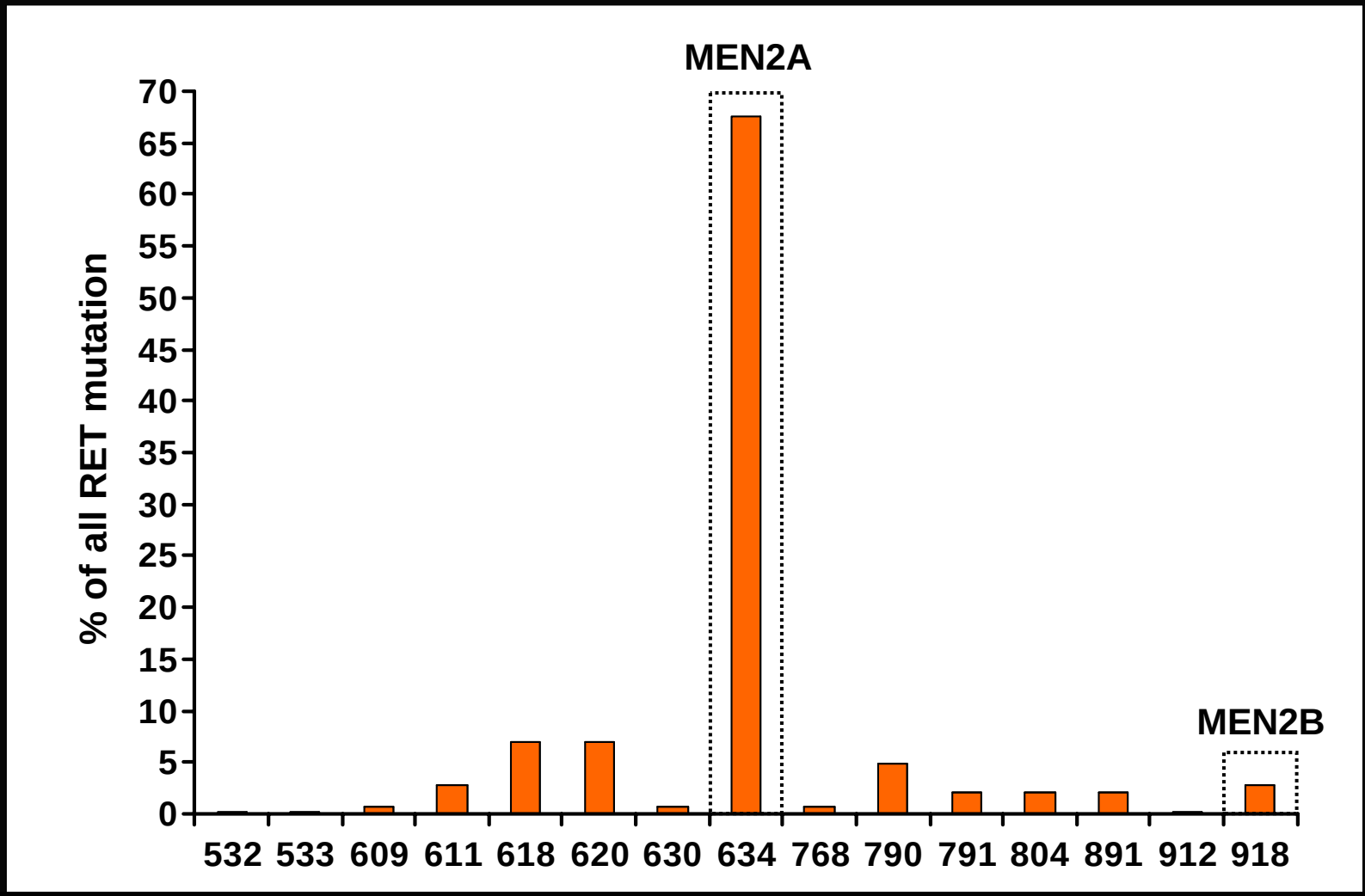
- 5-10% *de novo*

MEN2B

- 50% *de novo*

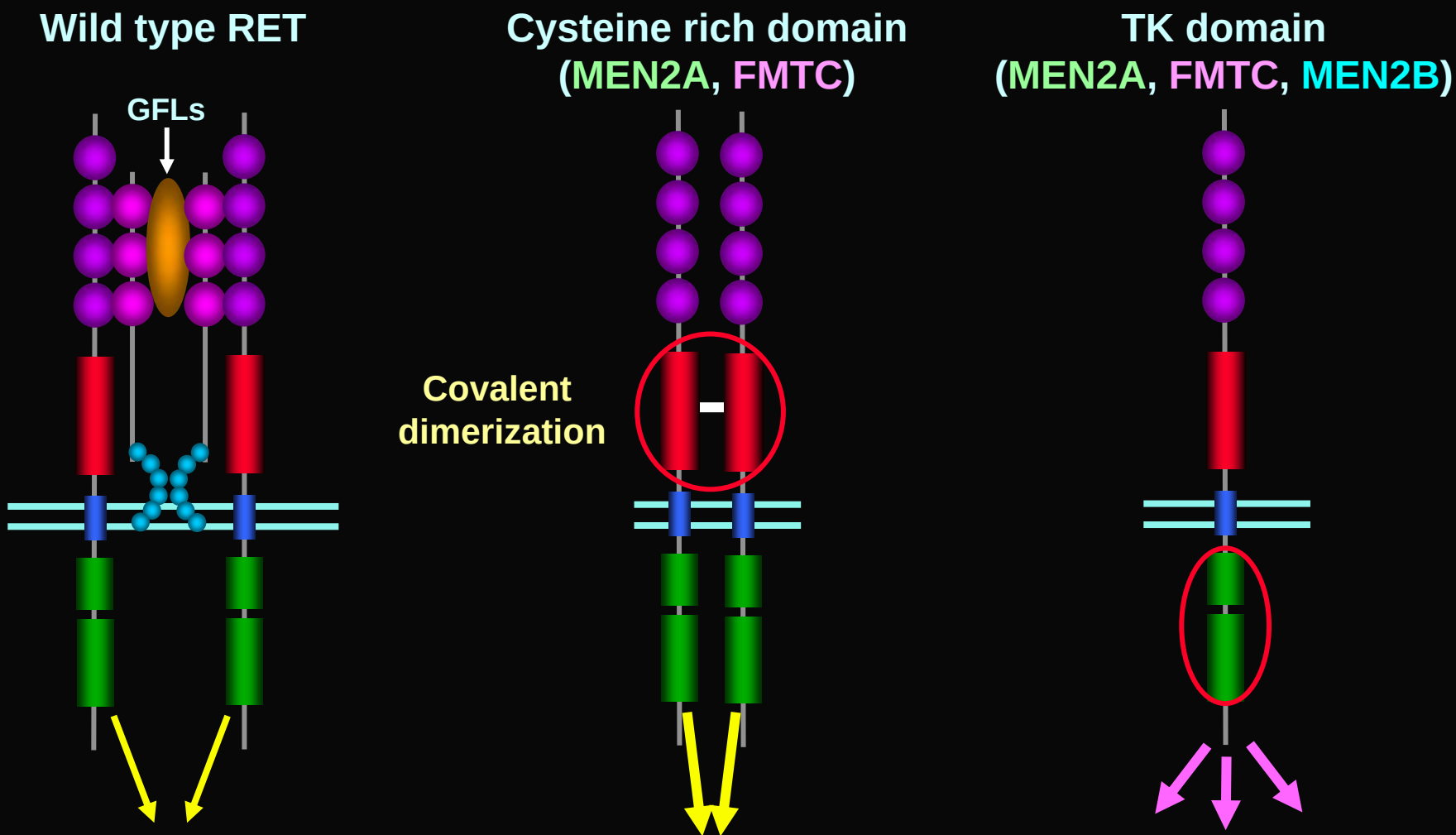
(Pacini F 2010 Clin Oncology 22:475-485; MEN2 mutation database, University of Utah)

Frequency of codon involvement in MEN2



(Machens A 2003 NEJM 349:1517-1525)

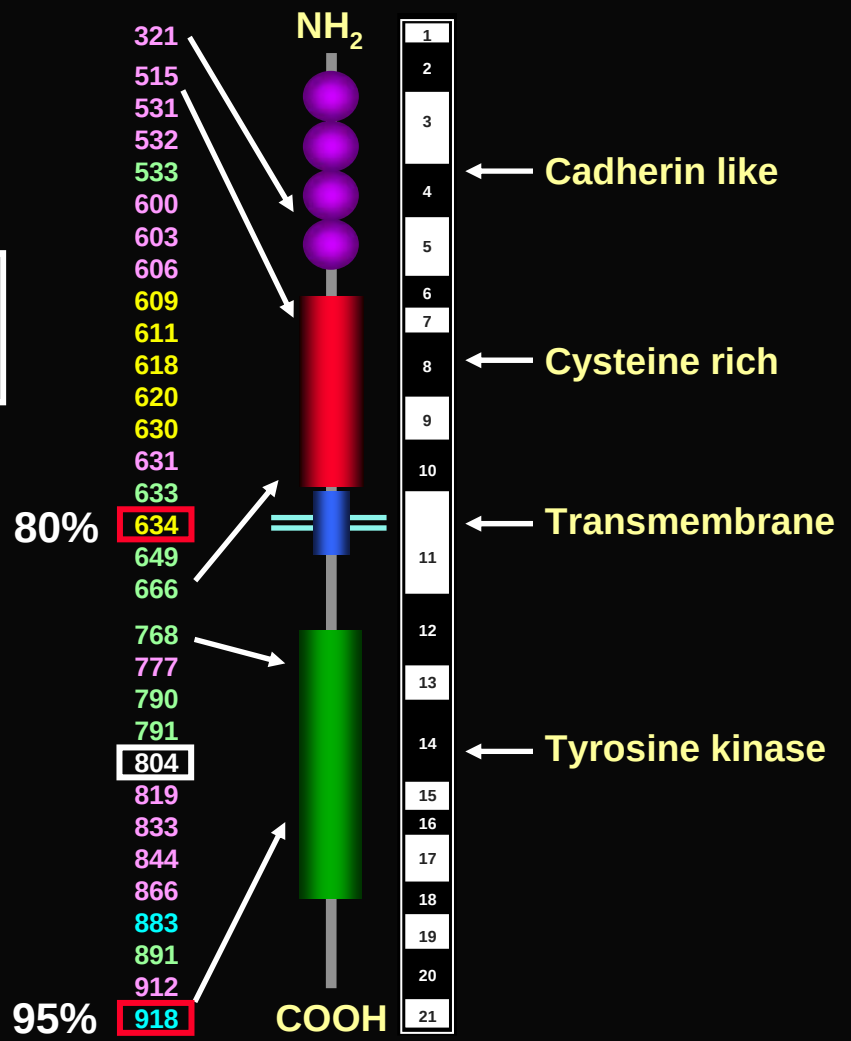
Mechanism of gain-of-function mutations



(Plaza-Menacho I 2006 Trends Genet 22:627-636)

Strong genotype phenotype correlation in MEN2

MEN2A or FMTC	FMTC?	MEN 2B
533	321	A883F
C609	515	V804M+E805K
C611	531	V804M+Y806C
C618	532	V804M+S904C
C620	600	M918T
C630	603	
633	606	
C634	631	
649	635	
666	777	
768	V804M+V778I	
790	819	
791	833	
804	844	
891	866	
	912	



Animal models of MEN2

Mouse models of MEN2A

Transgenic rCGRP/CT promoter driven RET9-C634R *(Michiels FM PNAS 1997 94:3330)*

- Multifocal bilateral MTC (similar to MEN2)
- From 3 weeks of age to 14 months (variable penetrance)

Transgenic hCALC promoter driven RET51-C634R *(Reynolds L 2001 Oncogene 20:3986)*

- MTC by 6 months, PTC and abnormal thyroid development
- MTC frequency increased with time and background dependent

Mouse models of MEN2B

Transgenic hCALC promoter driven RET9-M918T *(Acton DS 2000 Oncogene 19:3121)*

- C-cell hyperplasia from 8 months
- Bilateral MTC from 20 months (variable penetrance and latency)

RET M919T knock-in mouse *(Smith-Hicks CL 2000 EMBO 19:612)*

- RET(+/M919T) only CCH and pheochromocytoma at 12 months
- RET(M919T/M919T) more severe CCH and male infertility

Genetic background, *RET* dosage and *RET* isoform effect tumours
Additional oncogenic events are required for tumorigenesis

Genotype phenotype correlation and genetic testing in MEN2

Genetic testing in MEN2 and MTC

(Exeter, Oxford and Cambridge)

Genetic testing should be offered in all patents with MEN2 and MTC

Proband and then family members at 50% risk (<5y)

RET mutation screening is by direct exon sequencing

MEN2A/FMTC (exons 5,8,10,11,13,14,15 and 16)	**£245**
MEN2B (exons 15 and 16)	**£105**
Known RET mutation in family member	**£100**

If no common RET mutation and likely to be familial

Sequence all 21 exons	**£600**

(BTA/RCP 2007 Management of medullary thyroid cancer 41-48)

(Kloos RT 2009 ATA MTC Management Guidelines. Thyroid 19:565-612)

RET genetic testing

Probability of identifying a germline *RET* mutation

- **95% MEN2A and MEN2B**
- **88% of FMTC**
- **1-7% apparently sporadic MTC cases**

Benefits of *RET* genetic testing

- **Distinguish sporadic from familial MTC**
- **Early diagnosis of carrier state**
- **Guides timing of prophylactic thyroidectormy**
- **Directs surveillance for Phaeo, PHPT**
- **PREVENTS CANCER**

(BTA/RCP 2007 Management of medullary thyroid cancer 41-48)
(Kloos RT 2009 ATA MTC Management Guidelines. Thyroid 19:565-612)

A codon based approach risk stratification in MEN2

THYROID
Volume 19, Number 6, 2009

DOI: 10.1089/thy.2008.0403

Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association

The American Thyroid Association Guidelines Task Force*

Richard T. Kloos (Chair),[1] Charis Eng,[2] Douglas B. Evans,[3] Gary L. Francis,[4] Robert F. Gagel,[5] Hossein Gharib,[6] Jeffrey F. Moley,[7] Furio Pacini,[8] Matthew D. Ringel,[9] Martin Schlumberger,[10] and Samuel A. Wells Jr[11]

Risk stratification for MTC

American Thyroid Association risk levels (2009)

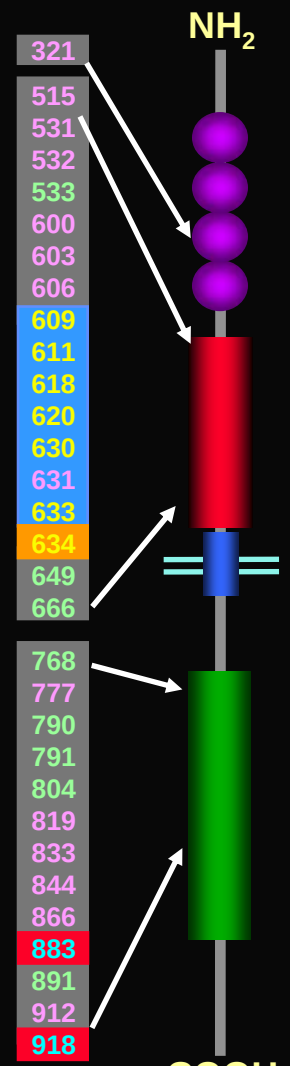
Level D: TTx ASAP but within the first year

Level C: TTx before 5 years

Level B: TTx by 5 years but may be delayed if normal U/S and CT

Level A: TTx may be delayed if normal U/S and CT<40pg/ml

MEN2A/FMTC	FMTC?	MEN 2B
533	321	A883F
609	515	M918T
611	531	
618	532	
620	600	
630	603	
633	606	
634	631	
649	635	
666	777	
768	819	
790	833	
791	844	
804	866	
891	912	

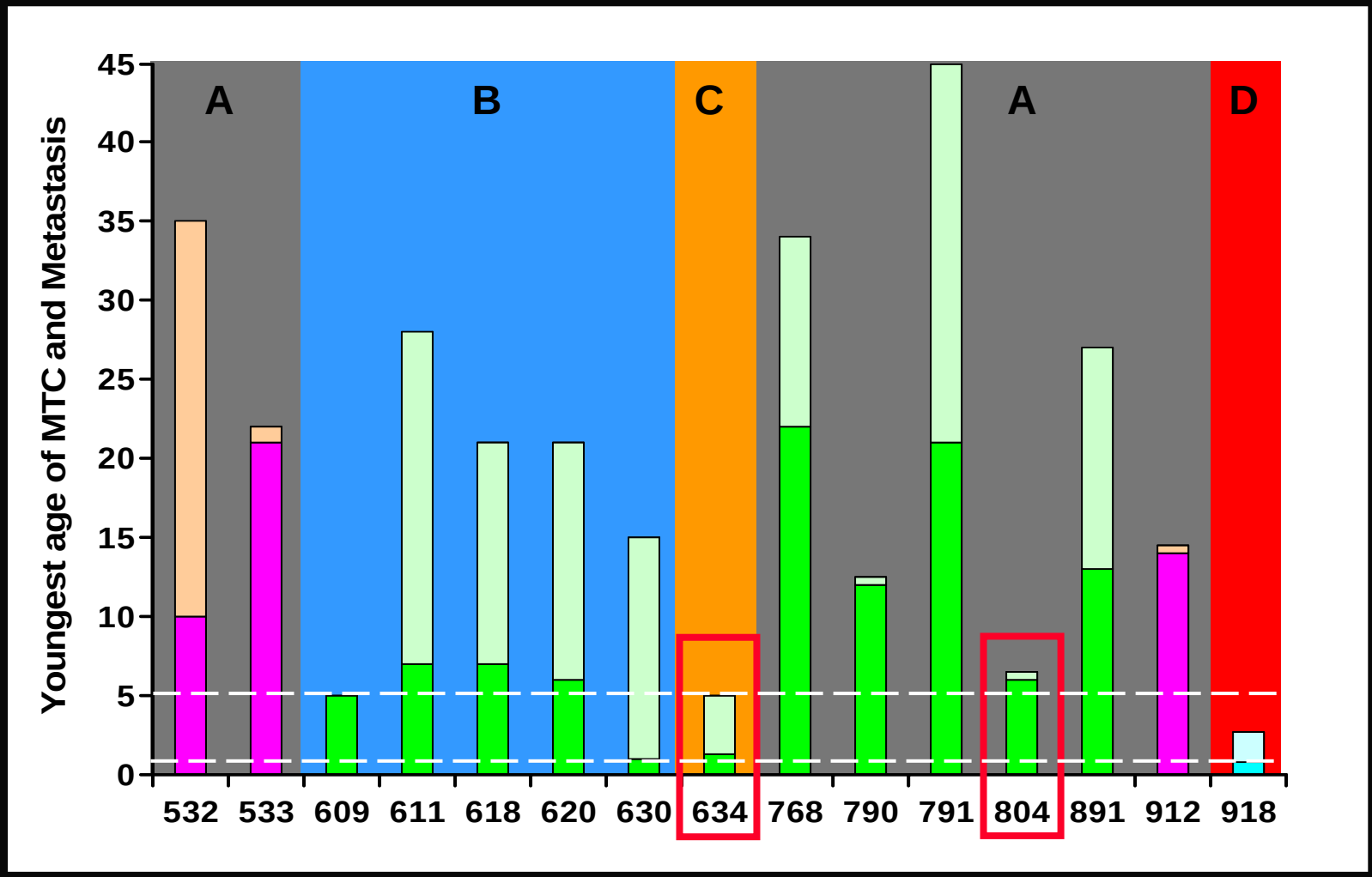


in vitro transforming ability

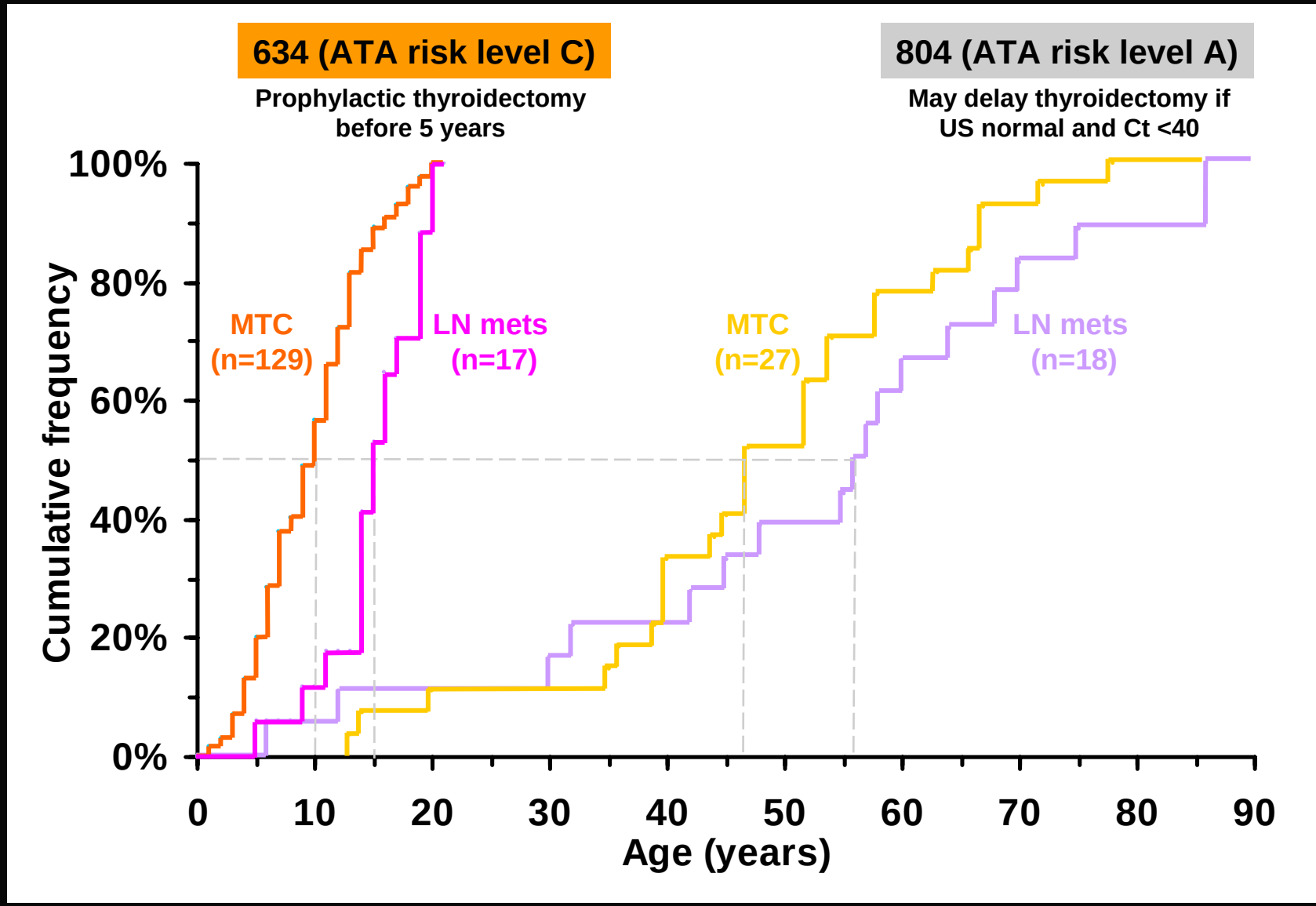
Mutant codon:	(768, V804M, 891)	(609, 611, 618, 620)	(630)	(A883F)	634	918
Transforming ability:	1x	2x	3x	7x	9x	10x

(Kloos RT 2009 thyroid 19:565-612)

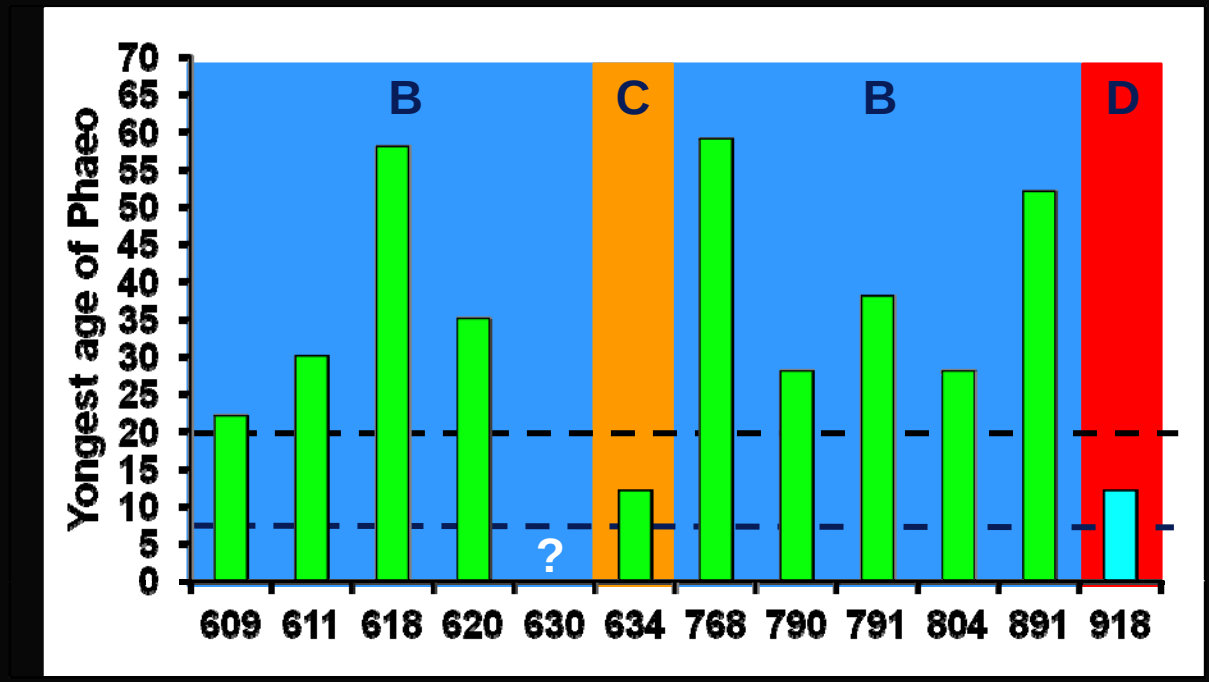
Youngest age of MTC and LN metastasis



RET Cys634 and Val804 mutations age of MTC and LN metastasis



Risk stratification for phaeochromocytoma

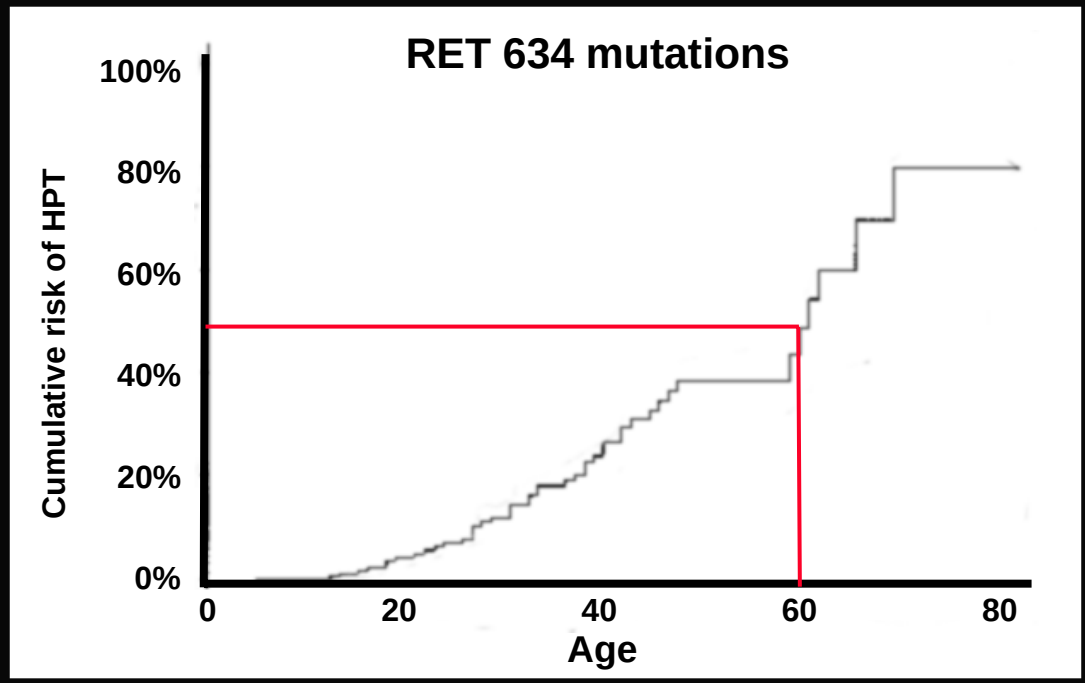


2009 ATA recommendation for phaeochromocytoma screening

Level D	883 and 918	Annual screening from 8 years of age
Level C	634	Annual screening from 8 years of age
Level B	630 Others	Annual screening from 8y Annual screening from 20 years
Level A		Periodical screening from 20 years

(Kloos RT 2009 thyroid 19:565)

Risk stratification for hyperparathyroidism



2009 ATA recommendation for 1^0HPT screening

Level D	883 and 918	Screening not required in MEN2B
Level C	634	Most frequently associated with 1^0HPT Annual screening from 8y
Level B	630 Others	Annual screening from 8y Annual screening from 20 years
Level A		Periodical screening from 20 years

(Kloos RT 2009 thyroid 19:565)

Limitations of a codon based approach to risk

Timing of thyroidectomy by mutant codon
- Earliest reported incidence of MTC
- Average age at which MTC occurs
- Earliest reported incidence of metastasis
- Average age at which metastasis occurs
- Role of annual US and calcitonin measurement

Limitations of codon based approaches
- Influence of genetic background and modifier genes
  - MEN2A and FMTC families have the same mutations
  - Phenotype of *RET* mutant mice is background dependent
  - Variation within families less than between families
- Additional stochastic events are required for tumour progression
- Lack of sufficient clinical data for many rare mutations

Early thyroidectomy in a specialist centre has low risk of complications and cures cancer

MEN2 Summary

- RET is a proto-oncogene and a receptor tyrosine kinase
  - Signalling via MAPK, AKT, JNK, PKC and JAK/STAT pathways
  - Roles in differentiation, proliferation, survival, motility and apoptosis
- Expression pattern explains clinical phenotype
- MEN2 caused by gain-of-function mutations
  - Mutations hotspots in cystine rich and TK domains
- Strong phenotype genotype correlation
  - *In vivo* and *in vitro*
- Genetic screening
  - Confirms diagnosis and identify mutant gene carriers
  - Guides clinical management and prevents cancer

- Target mutation in mice suggest that phenotype
  - Phenotype is depends on genetic background
  - Phenotype dependent on RET isoform and gene dosage
  - Additional somatic events required for tumour formation

Contrasting molecular genetics in MEN1 and MEN2

Multiple Endocrine Neoplasia Type 1 (MENIN)

- Loss-of-function mutations in a tumour suppressor gene
  - Further loss of the normal allele in tumours
- Highly conserved protein with no known homology
- Ubiquitously expressed but its function remains uncertain
- No phenotype genotype correlation
- Genetic screening
  - Confirms the diagnosis in the proband
  - Targets screening to mutant gene carriers
  - Does not prevent cancer

Multiple Endocrine Neoplasia Type 2 (RET)

- Gain-of-function mutations in a proto-oncogene
- Role as tyrosine kinase receptor already well established
- Expression pattern consistent with clinical phenotype
- Strong phenotype genotype correlation
- Genetic screening
  - Confirms diagnosis and identifies mutant gene carriers
  - Directs clinical management and prevents cancer