

## Multiple Endocrine Neoplasia type 2 (MEN2)

### Identity

**Note** Multiple Endocrine Neoplasia type 2 (MEN2) is defined by the association of C-cell tumors of the thyroid ( medullar thyroid carcinoma), tumors of the adrenal medulla ( [pheochromocytoma](#)) and parathyroid hyperplasia or adenoma in a single patient or in close relatives

Other names

Sipple syndrome

Gorlin syndrome (not to be confused with the [Gorlin-Goltz/naevoid basal cell carcinoma syndrome](#))

**Inheritance** MEN2 is an autosomal dominant disorder with a high penetrance. Expressivity is variable but phenotype-genotype correlations have been described. Incidence is estimated at 0.1/10<sup>5</sup>/year. It is generally assumed that 20 to 25% of medullar thyroid carcinomas (MTC) are heritabl

### Clinics

**Phenotype and clinics** Three subtypes have been described:  
MEN2A (Sipple syndrome) is the most frequent form, characterized by MTC in 95% of cases, phaeochromocytoma in 50% and parathyroid hperplasia or adenoma in 25%.  
In familial MTC (FMTC), MTC is the only clinical manifestation.  
MEN2B (Gorlin syndrome) is the least frequent variant defined by predisposition to MTC and phaeochromocytoma and marfanoid habitus, mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract. C-cells secrete the hormon calcitonin which is a valuable marker for early diagnosis and for following the later course of the disease. There is no obvious syndrome of calcitonin overproduction.  
Pheochromocytoma secrete adrenaline and noradrenaline which are responsible of hypertension but could be undetected and lead to fatal hypertensive episodes.  
Parathyroid hyperplasia or adenoma lead to hyperparathyroidism; they are often clinically silent but could be revealed by symptomatic hypercalcemia or renal stones.

**Neoplastic risk** MTC is a malignant tumor, metastasizing at first locally within the neck and then to distant sites. Usually pheochromocytoma is non malignant; parathyroid hyperplasia or adenoma are benign

**Treatment** Total thyroidectomy with bilateral radical lymph node dissection is the treatment of MTC. Thyroidectomy is recommended for carriers of mutations, in the first years of life in MEN2A and MEN2B families, as soon as elevation CT during pentagastrin test in FMTC families. Pheochromocytoma, hyperplasic parathyroid or adenoma should be surgically removed.

**Prognosis** Pheochromocytoma could be letal by hypertension episodes but

prognosis is essentially dependant from MTC.

## Genes involved and Proteins

**Gene Name** [RET](#)

Location 10q11.2

### DNA/RNA

Description 21 exons; genomic sequence of 55kb

### Protein

Description Three main 3' alternatively spliced forms of 1072 to 1114 aminoacids. There is a cleavable signal sequence of 28 aminoacids, a glycosylated extracellular domain formed of a region of cadherin homology and another cystein-rich region, a transmembrane domain and an intracellular tyrosine kinase domain.

Expression RET is expressed predominantly in the developing central and peripheral nervous system, the excretory system and the migratory neural-crest cells during embryogenesis.

Function Receptor tyrosine kinase

### Mutations

Germinal In MEN2A and FMTC, mutations are located in the sequence encoding the juxtamembrane cystein-rich domain and involved aminoacids C609, C611, C618, C620, C630, D631 and C634. Most of these mutations result in the substitution of the cystein for a different amino acid. MEN2A is predominantly associated with a mutation of C634, highly predictive for the development of pheochromocytoma and hyperparathyroidism. Until today three duplications in the cystein-rich domain have been published.

MEN2B is caused by germline mutations of the tyrosin kinase domain: substitution M918T in more than 95% of cases, A883F in less than 4% of those. Rare mutations at aminoacids 912, 922 and an association of V804M/Y806C have been described.

Other mutations of the tyrosin kinase domain have been identified in FMTC families and unusually in MEN2A patients: E768D, L790F, Y791F, V804M, V804L and S891A.

Some families with MEN2 and Hirschsprung disease have been described: each of them has a mutation in either C618 or C620. Families with Hirschsprung disease alone have mutations overspread in all the coding region of RET.

## External links

[OMIM](#) [164761](#)

[Orphanet](#) [Multiple endocrine neoplasia type 2](#)

[HGMD](#) [120346](#)

Other database [NEM2 - SFE](#)

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