Multiple endocrine neoplasia type 2 (MEN2)

Sophie Giraud

Laboratoire de Génétique, Hôpital E. Herriot, 69437 Lyon cedex 03, France (SG)

Published in Atlas Database: January 2001
Online updated version : http://AtlasGeneticsOncology.org/Kprones/MEN2ID10009.html
DOI: 10.4267/2042/37740

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2001 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Alias
Sipple syndrome
Gorlin syndrome (not to be confused with the Gorlin-Goltz/naevoid basal cell carcinoma syndrome).

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.

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 0.1/10^5/year. It is generally assumed that 20 to 25% of medullar thyroid carcinomas (MTC) are heritable.

Clinics

Phenotype and clinics

Three subtypes have been described:
MEN2A (Sipple syndrome) is the most frequent form, characterized by MTC in 95% of cases, pheochromocytoma 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 pheochromocytoma 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 lethal by hypertension episodes but prognosis is essentially dependant from MTC.

Genes involved and proteins

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 amino acids. There is a cleavable signal sequence of 28 amino acids, 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 amino acids 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.

**References**


Höppner W, Dralle H, Brabant G. Duplication of 9 base pairs in the critical cysteine-rich domain of the RET proto-oncogene causes multiple endocrine neoplasia type 2A. Hum Mutat. 1998;Suppl 1:5128-30


Ponder BA. The phenotypes associated with ret mutations in the multiple endocrine neoplasia type 2 syndrome. Cancer Res. 1999 Apr 1;59(7 Suppl):1736s-1741s; discussion 1742s

