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Phenotype and clinical course in three individuals with Multiple Endocrine Neoplasia Type 2A due to a RET gene mutation.

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Background:

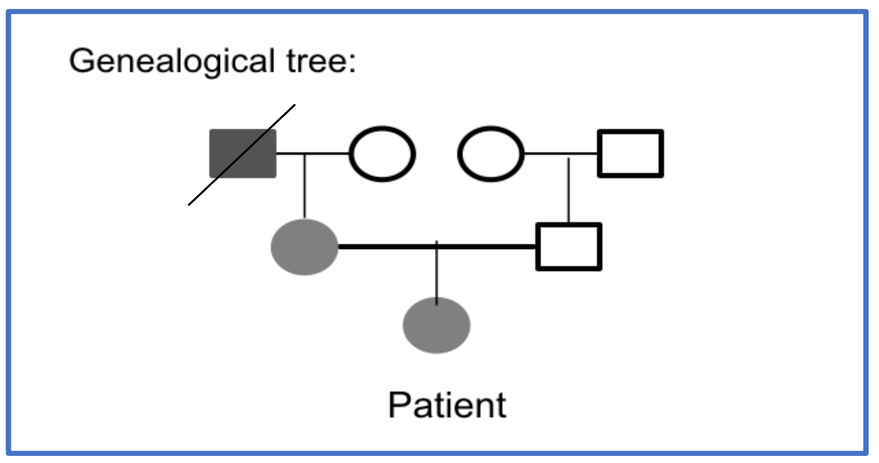
Mutations in the *RET* gene have been described in subjects with multiple endocrine neoplasia type 2 (MEN 2A). MEN 2A is a rare autosomal dominant disorder characterised by tumors of the C cells of the thyroid, adrenal medulla and parathyroid glands. Patients develop either C-cell hyperplasia or medullary thyroid cancer (MTC), pheochromocytoma, and in some cases hyperparathyroidism.

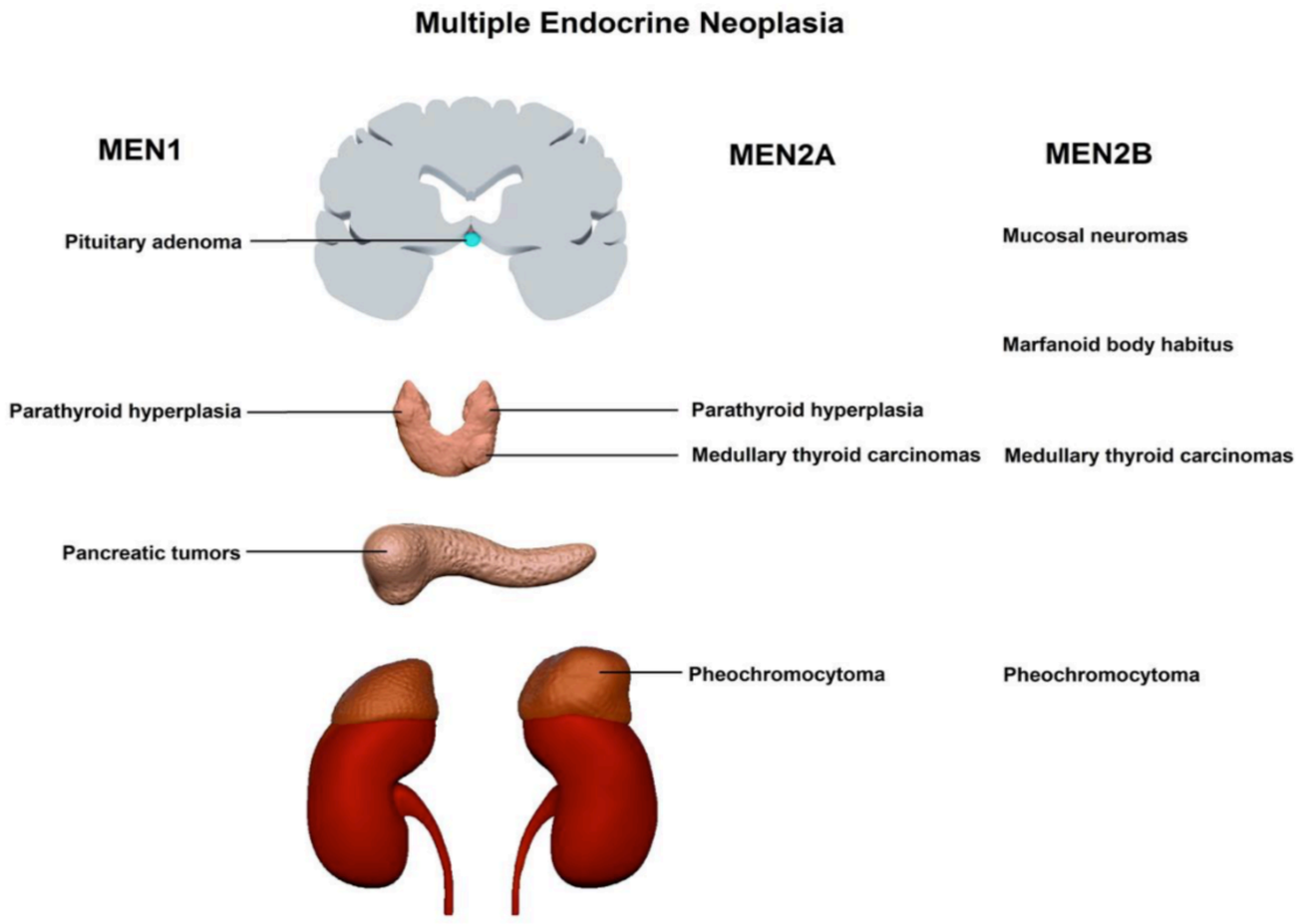
Objective:

To describe the phenotype and clinical course in three family members with MEN 2A syndrome. A *TGC/CGC RET* gene mutation (codon 634, exon 11) was identified in two of these subjects and was associated with their condition.

Methods/Results:

We report of three individuals diagnosed with MEN 2A syndrome. The proband was a 4-year-old girl, that has been followed-up in our department in the presence of a significant family history of MEN 2A syndrome.
Her mother, 31 years old, suffered from MEN 2A associated with a *TGC/CGC RET* (codon 634, exon 11) gene mutation. She had metastatic medullary thyroid cancer and had been treated with total thyroidectomy and surgical excision of cervical lymph node metastases as well as bilateral adrenalectomy for pheochromocytomas and radio frequency ablation of hepatic lesions. She now receives replacement treatment with levothyroxine, hydrocortisone and fluorohydrocortisone tablets.
The maternal grandfather was diagnosed with insulin dependent Diabetes mellitus and diabetic ophthalmopathy at 33 years of age. Further laboratory and imaging studies revealed MTC with multiple hepatic metastases and unilateral pheochromocytoma. He underwent total thyroidectomy and lateral adrenalectomy. Three years later he presented with a contralateral pheochromocytoma, which was inoperable, due to diffuse hepatic metastases and the patient died at 36 years of age.
The molecular genetic testing, that was performed by the 4-year-old female patient identified, that she harbored the same *RET* gene mutation as her mother. At the age of 5 years and 7 months the calcitonin levels were found increased and a prophylactic total thyroidectomy was performed due to her genetic risk. The histologic examination showed c-cell hyperplasia.
She presents regularly for evaluation, since she is in high risk of developing pheochromocytoma and hyperparathyroidism.





Conclusion:

Pheochromocytoma and thyroid cancer are indications for detailed clinical and genetic examination of all family members. Subjects with MEN 2A may exhibit a rapid progression and carriers of MEN 2A associated mutations need regular monitoring because of their genetic predisposition to tumor development.