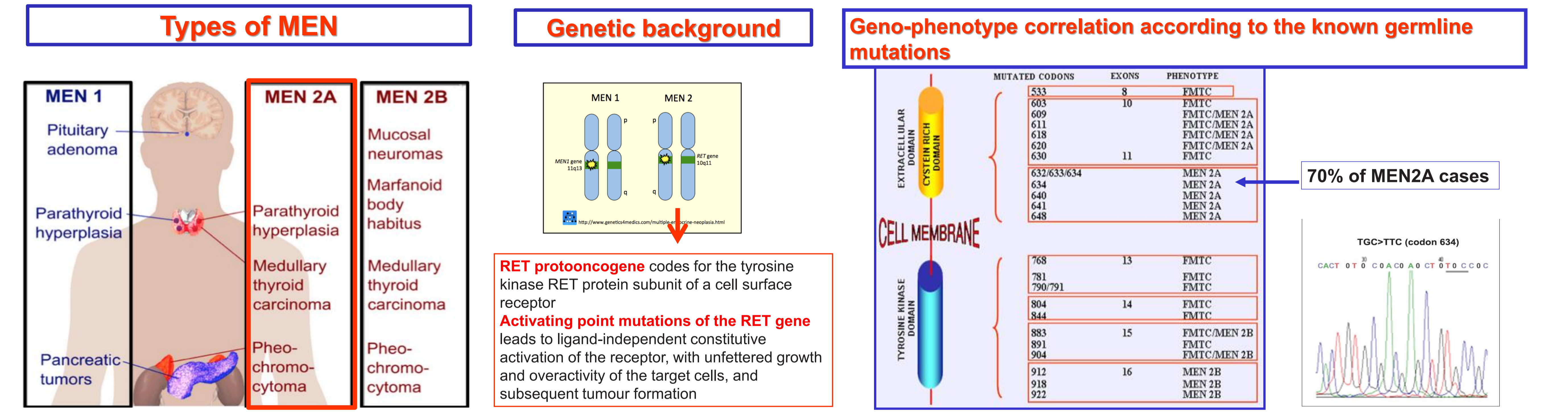


Abstract:

The case: The multiplex endocrine neoplasia 2A (MEN2A) syndrome is a monogenic disease caused by mutation of the RET protooncogene leading to medullary thyroid cancer (MTC), pheochromocytoma and primary hyperparathyroidism. The specific mutations determine the timing of the preventive thyroidectomy. In 2007, in a **26 year old female patient**, after detailed endocrine investigation, total thyroidectomy with both sided lateral neck lymph node dissection was performed because of suspicion of medullary thyroid cancer. The final histology proved the diagnosis. Three years later hypertensive peaks occurred, pheochromocytoma was found and removed by laparoscopic adrenalectomy. The family was screened for **MEN2A**. The **mutation TGC634TTC(Cys634Phe) of the codon 634** was found in the patient, in her father and one brother. After spontaneous conception and normal pregnancy in October 2012 she gave birth to a boy. The **son** was screened for MTC with calcitonin at the age of 11 and 13 months (15,6-18 pg/ml) and was proven to be RET positive. Preventive total thyroidectomy and partial parathyroidectomy was done at the age of 18 months. The final histology found no sign of medullary thyroid cancer or primary hyperparathyroidism. As the patient did not want to have another child affected by the disease, application of assisted reproductive technologies were recommended. After ovarian stimulation, **4 embryos were biopsied in trophoctoderm stage**. **Karyomapping (preimplantational genetic screening for chromosomal abnormalities and preimplantational genetic diagnostics for the specific mutation)** was performed revealing **one healthy and three MEN2A affected embryos, two of them with maternal aneuploidy** as well.

Conclusion: For the monogenic disease affected families, it is important to offer the possibility of preimplantation genetic diagnosis ensuring that the affected embryos are not transferred. Healthy children don't require lifelong endocrine follow-up and operations, and no psychological support.

Multiplex endocrine neoplasias (MEN): 2 or more endocrine tumors occur as a part of a defined MEN syndromes, in a single patient and there is evidence for either a causative mutation or hereditary transmission. Inheritance: **autosomal dominant**.



The family (hi)story

2007: MTC, pheo
Sep 2008: RET exon11:
TGC634TTC (cys634Phe)
2010: pheo → adrenalectomy
2011: HPTH (Ca:2,83mm/l)
2013: MTC, HPTH → total thyroidectomy and parathyroidectomy

Jan 2008: MTC → total thyroidectomy
Sep 2008: RET TGC634TTC

The first patient →
2007: Hashimoto's thyroiditis
MTC → total thyroidectomy
Sep 2008: RET TGC634TTC
2011: pheo → adrenalectomy

Calcitonin
Sep. 2013: 15.6 pg/ml
Nov. 2013: 18 pg/ml
Jan. 2014: 11,2 pg/ml
March 2014: RET TGC534TTC
May 2014: total thyroidectomy, partial parathyroidectomy (2ex)

• Date of birth
IVF: in vitro fertilization
HPTH: primary hyperparathyroidism
MTC: medullary thyroid cancer
PGD: preimplantational genetic diagnostics
PGS: preimplantational genetic screening
Pheo: pheochromocytoma

Planning the second pregnancy the patient (SA) decided herself for an IVF cycle during which preimplantational genetic diagnostics (PGD) for the ret mutation and preimplantational genetic screening (PGS) for chromosomal abnormalities could be done to exclude genetically affected embryos to be transferred.

The 1st hungarian karyomapping for MEN2A

Techniques for preimplantational genetic screening and diagnostics

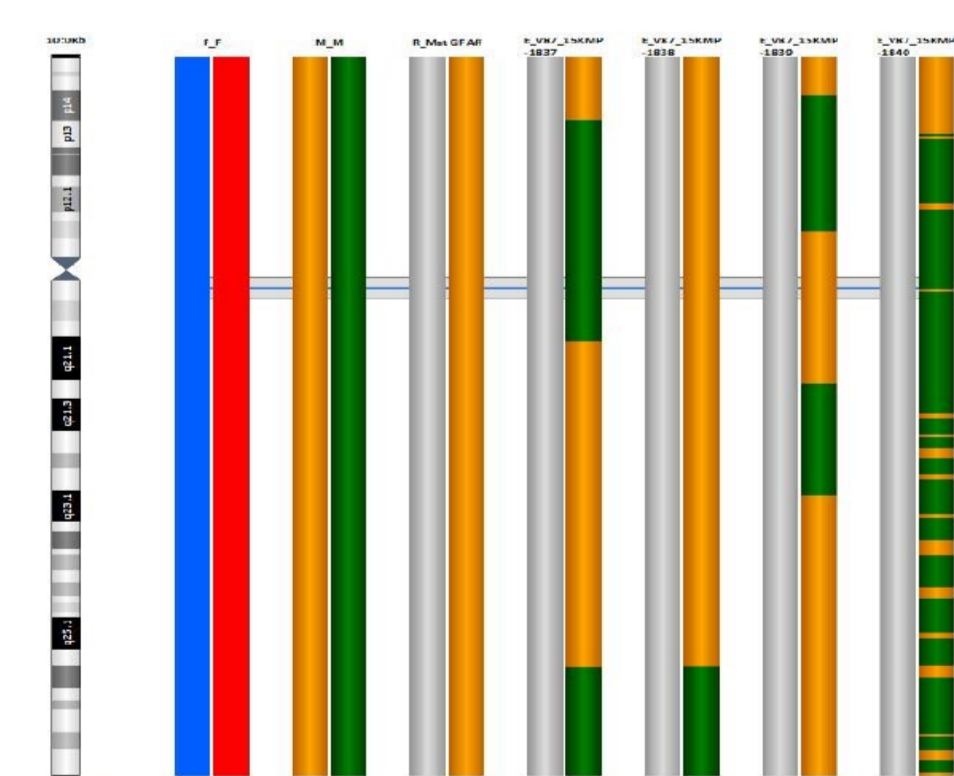
Comparative genomic hybridization (CGH): is a molecular cytogenetic method for analysing copy number variations (CNVs) relative to ploidy level in the DNA of a test sample compared to a reference sample. It compares two genomic DNA samples arising from two sources suspected to contain differences in terms of either gains or losses of either whole chromosomes or subchromosomal regions.

Karyomapping: uses genome-wide linkage-based analysis to determine the inheritance of single-gene defects from as little as a single embryonic cell. It enables all chromosomes to be screened, optimizes the likelihood that embryos with no identifiable genetic abnormalities are transferred during an IVF cycle.

Embryo-biopsy (trophoctoderm)



Karyomapping



Results

Protocol No.: V87/15KMP				
Date of birth: 17.12.1981		Date of embryo biopsy: 18.-19.4.2015		
embryo biopsy	genotype of RET gene	sex	additional findings	note
1837	non / non	XY	-----	-----
1838	c.1901G>T / non	XY	-----	MEN2
1839	c.1901G>T / non	XY	-8(mat)	MEN2, aneuploid
1840	c.1901G>T / non / non	XX	+3(mat), +10(mat)	MEN2, aneuploid

Estimation of genotyping accuracy: >99.5% for all embryos

Results:

Short GnRH ovarian stimulation protocol was used during which the patient produced 4 eggs. All were fertilized with ICSI (intracytoplasmic spermium injection). All four eggs reached the throphoctoderm stage and were biopsied. Karyomapping was performed revealing three embryos affected by the ret 634 codon mutation and two aneuploid ones. Only one embryo was healthy, which was transferred. Unfortunately, the pregnancy terminated on the 12th gestational week by a spontaneous abortion.

Conclusions:

Prenatal diagnostics is only applicable for determination of existing birth defect or inherited disease of the foetus in the early phase of pregnancy.

Preimplantational genetic screening (PGS) and diagnostics (PGD) is used for optimizing the likelihood that embryos with no identifiable genetic abnormalities (chromosomal abnormalities, germline mutations) are transferred during an in vitro fertilization (IVF) cycle.

In our case karyomapping revealed 75% genetically affected embryos, from which 75% were positive for ret 634 codon mutation and 50% were aneuploid.

Karyomapping allowed us to avoid genetically affected (MEN2A positive 3/- aneuploid 2) embryos to be transferred.

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References:

Christian Piolat et al.: Very early prophylactic thyroid surgery for infants with a mutation of the RET proto-oncogene at codon 634: evaluation of the implementation of international guidelines for MEN type 2 in a single centre, Clinical Endocrinology, Volume 65, Issue 1, pages 118–124, July 2006
Harper J et al.: Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy. Hum Reprod. 2014 Aug;29(8):1603-9.
Kang HJ et al.: Preimplantation genetic screening: who benefits? Fertil Steril. 2016 Apr 30. pii: S0015-0282(16)61124-X.
Altaregus G et al.: Preimplantation genetic diagnosis (PGD)—prevention of the birth of children affected with endocrine diseases. J Pediatr Endocrinol Metab. 2011;24(7-8):543-8.

