Central hypothyroidism and biallelic defect near the D/ERY motif of the *TRHR* gene

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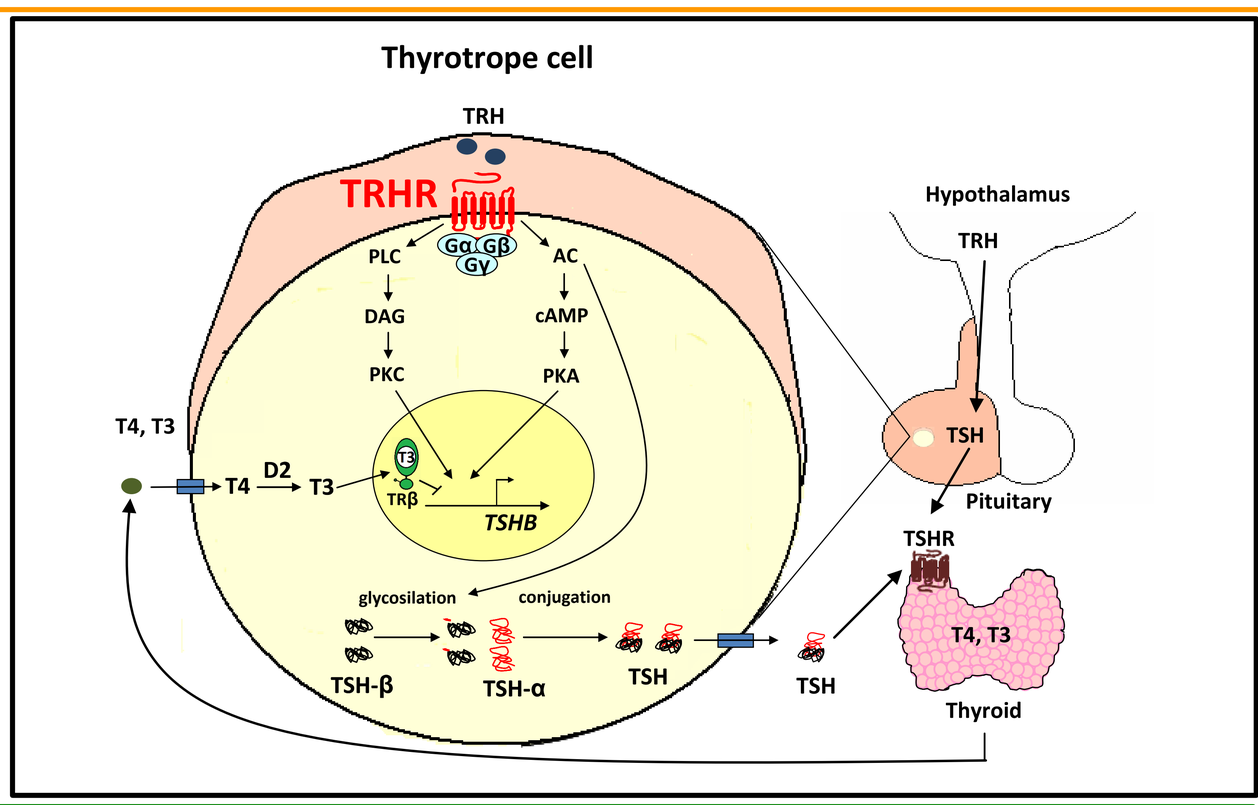
INTRODUCTION

The TRH receptor (TRHR) is a G-protein coupled receptor activated by hypothalamic TRH. In thyrotropes, TRH-TRHR signalling controls synthesis, secretion and bioactivity of TSH. Human TRHR gene defects are extremely rare, and only two cases are known showing central hypothyroidism and short stature as presenting features.

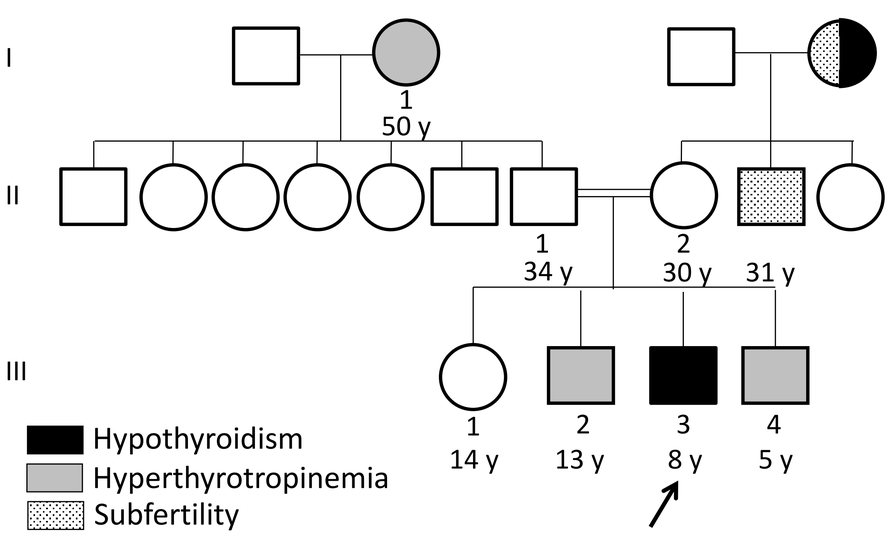
OBJETIVE Phenotypical characterization of a family with suspected central hypothyroidism and investigation of the molecular mechanism underlying the disorder.

PATIENTS AND METHODS

Mutation screening of the TRH, TRHR and TSHB genes in seven individuals of a consanguineous pedigree. Determination of membrane expression, ligand affinity and transactivation properties of a TRHR mutant using ELISA, ligand ([3H]MeTRH) binding and luciferase reporter assays, respectively.



CLINICAL RESULTS



Index patient (III.3): Central Hypothyroidism.

Not detected at the TSH-based neonatal screening.

Without hypothyroid symptoms.

Overweight: BMI 20,4 Kg/m^2 (1,64 SD).

Normal height: 122 cm (-0,58 SD).

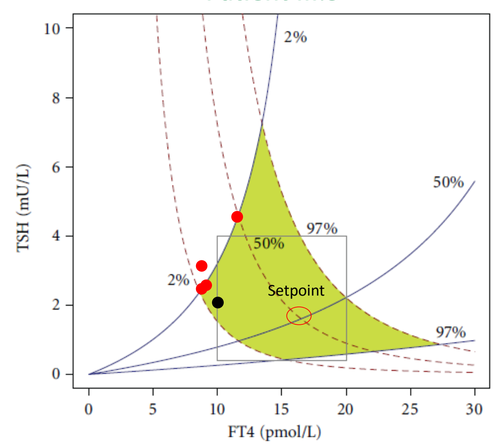
Familial hypercholesterolemia.

MRI: pituitary normal size and morphology.

Hormonal profile

Patient	TSH (mUI/L)	FT4 (ng/dl)	TSH/T4L
N.R.	0,27-4,2	0,85-2	0,35-1,67
I.1	**5,17**	Normal	-
II.1	1,3	1,08	1,20
II.2	3,89	1,17	**3,32**
III.1	2,95	1,38	**2,14**
III.2	**8,05**	1,06	**7,59**
III.3	2,61	**0,74**	**3,53**
III.4	**4,65**	0,97	**4,79**

Patient III.3

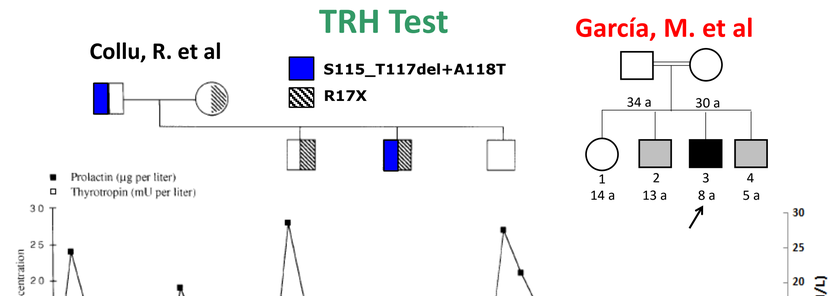


TSH and Thyrotropic agonists: Key actors in thyroid homeostasis. Dietrich, JW. et al. *J Thyroid Res. 2012*

Cases described in the literature (Collu, R. et al. JCEM 1997; Bonomi, M. et al. NEJM 2009; Koulouri et al. JCEM 2015)

Patient	Age	Neonatal screening	Hypothyroid symptoms	Hormonal profile	Stature
1	2 mo	Negative	Neonatal jaundice	N TSH, ↓T4	Normal
2	9 y		Lethargy Fatigue		Short
3	11 y				Short

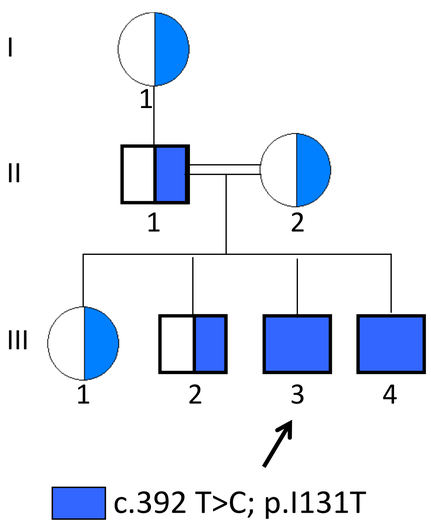
TRH Test

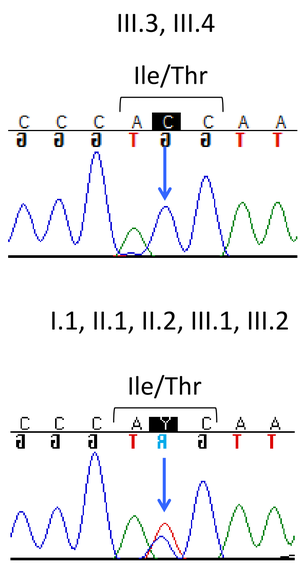


1. A novel mechanism for isolated central hypothyroidism: inactivating mutations in the Thyrotropin-Releasing Hormone Receptor Gene. Collu, R. et al. *JCEM*. 1997.

2. A family with complete resistance to thyrotropin-releasing hormone. Bonomi M. et al. *N Engl J Med* 2009.

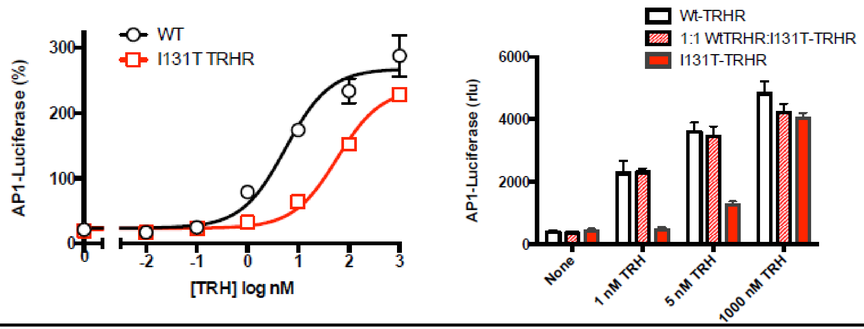
GENETICS AND FUNCTIONAL ASSAYS



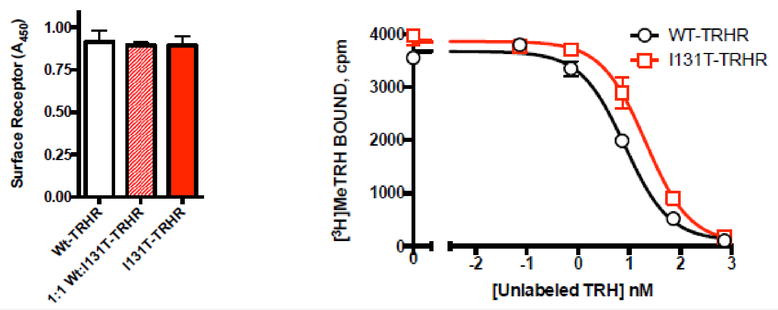


- The mutation localises in the 2nd intracellular loop of the TRHR, adjacent to the D/ERY motif involved in G protein activation.
- The mutation was in silico predicted as probably pathogenic.
- The amino acid is highly conserved in vertebrates.

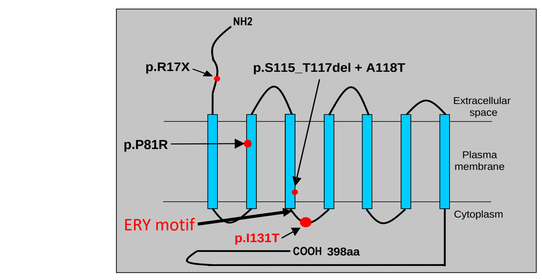
TRHR mutant in AP1- luciferase pathway activated by TRH

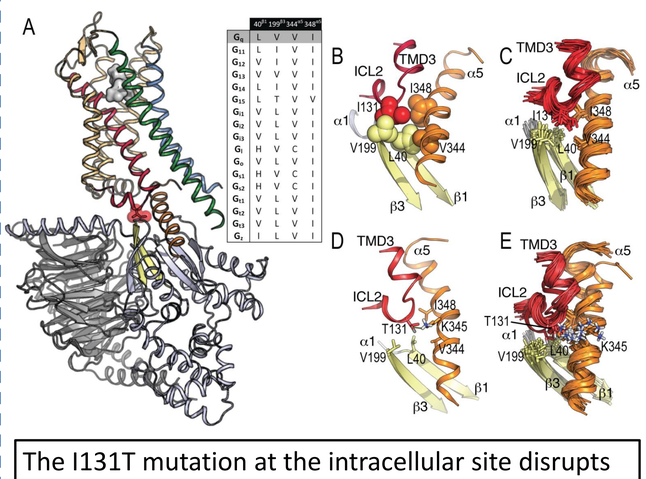


The I131T TRHR mutant impairs transactivation of an AP1-containing promoter by TRH.



The mutant does not interfere receptor trafficking to the membrane, but impairs signal transduction by decreasing its affinity to TRH.





The I131T mutation at the intracellular site disrupts TRHR-Gq coupling and decreases TRH binding at the extracellular site by an allosteric mechanism.

CONCLUSIONS

A novel defect in TRHR causes mild central hypothyroidism in the homozygous state but leads to hyperthyrotropinemia in heterozygotes, suggesting compensatory elevation of TSH with reduced biopotency. The I131T mutant decreased TRH ligand affinity to TRHR and activation of the Gq-IP-PKC pathway. Accordingly with the molecular model, the I131T mutation disrupts TRHR-Gq coupling and activation of the Gq-IP-PKC pathway and decreases TRH ligand affinity at the extracellular site by an allosteric mechanism.

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Thyroid

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