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

Marta García 1, Jesús González de Buitrago 2, Mireia Jiménez-Rosés 3, Leonardo Pardo 3, Patricia M. Hinkle 4, José C. Moreno 1

1 Thyroid Molecular Laboratory, Institute for Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Autonomous University of Madrid, Spain. 2 Pediatric Endocrinology, San Pedro de Alcántara Hospital, Cáceres, Spain. 3 Computational Medicine Laboratory, Biostatistics unit, Autonomous University of Barcelona, Spain. 4 Pharmacology and physiology, University of Rochester Medical Center, Rochester, NY, United States.

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.

OBJECTIVE

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.

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 mutation decreased TRH affinity to TRHR and activation of the Gq-IP-PKC pathway. Accordingly with the molecular model, the I131T mutation disrupts TRHR-Gq coupling and decreases TRH binding at the extracellular site by an allosteric mechanism.