Pop 023
First PreproTRH Mutation as a Cause of Central Congenital Hypothyroidism

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INTRODUCTION

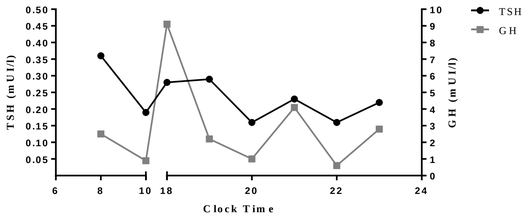
Isolated or syndromic congenital central hypothyroidism is a rare condition missed by neonatal screening programs based on TSH measurement. Several genes have been involved. Knock-out of preproTRH gene in mice leads to central hypothyroidism and diabetes mellitus

CLINICAL CASE

Inaugural ketoacidocis revealed a type 1 diabetes mellitus in a 4 years old girl, born to consanguinous turkish parents. During hormonal investigations central hypothyroidism was diagnosed, based on low free T4 : 7.4 pmole/l (11.1-18.1) and non elevated TSH : 2.2 mUI/L (0.65-5.1). No other hormonal abnormality was identified. TSH and Prolactin were normally responsive to TRH stimulation. No circadian TSH rhythm was documented. C-peptide was undetectable and was not stimulated by TRH injection. Islet Cell antibodies were positive. HLA genotype was DRB1*03/DQA1*05/DQB1*02.
Upon L-Thyroxine treatment, growth and development are unremarkable. There is no intellectual disability.

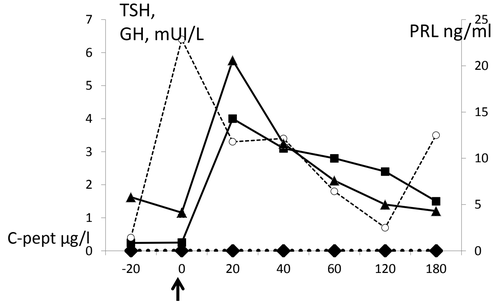
RESULTS

A panel of genes involved in the development or function of pituitary thyrotrophs was analysed by NGS. A homozygous duplication of one nucleotide at codon 54 in the preproTRH gene was identified in the patient (in heterozygous state in both parents), leading to a frameshift and a premature STOP codon. The STOP codon precedes the first of the 6 TRH coding sequences in the preproTRH polypetide, precluding TRH production anywhere in the body. No defect was found in the other genes involved in central hypothyroidism analysed by the same NGS Panel.

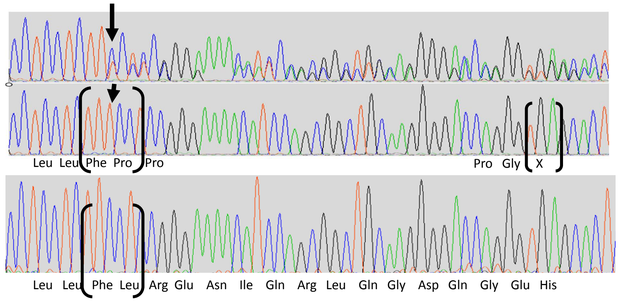


TSH (points) and GH (squares) circadian ryhthm

RESULTS

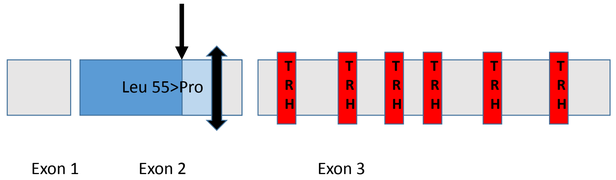


TSH (squares), Prolactin (triangles), GH (points) and c-peptide (diamonds) response to TRH



Nucleotide sequence of exon 2 of preproTRH gene. Top: parents, middle : patient, bottom: normal sequence. The T duplication is indicated by the arrow; the premature stop codon following frameshift is indicated by X

RESULTS



The mutation leads to a frameshift in the PreProTRH protein, and a premature stop codon preceeding the six GLU-HIS-PRO tripeptide (TRH)

CONCLUSION

This is the first case of inherited genetic defect of the preproTRH gene which illustrates the mild severity of congenital central hypothyroidism and the limited role of TRH in thyrotrophe's development. Diabetes mellitus is observed in preproTRH KO in mice although without autoimmunity documented. Surprisingly, considering the widespread extra hypothalamic production of TRH, the phenotype was limited to central hypothyroidism and autoimmune type 1 diabetes. This questions the relevance, in human, of the role of extra-hypothalamic TRH production proposed in animal models.