P1-199

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New p.Ser237Asn Activating Mutation At The TSHR Receptor, Causing Familial Non- Autoimmune Hyperthyroidism.

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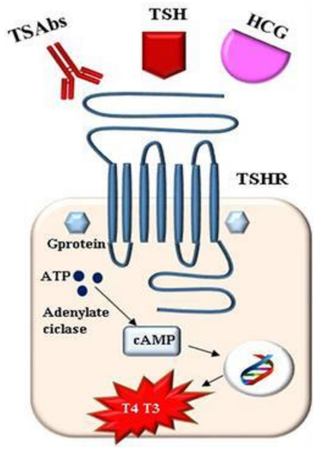
INTRODUCTION

Thyroid-stimulating hormone (TSH) is the main regulator of thyroid growth and function in the adult. The lack of TSH or its action due to inactivating TSH receptor (TSHR) mutations impairs the thyroid function leading to hypothyroidism. In contrast, pathologically elevated serum TSH levels, TSHR stimulating antibodies or constitutively activating TSHR mutations stimulate thyroid hormone production and thyroid growth, resulting in hyperthyroidism and goiter. TSH regulates the thyroid function via its G protein-coupled TSHR. Data from patients with TSHR mutations, *in vitro* and *in vivo* studies have shown that TSH preferentially couples to the alpha-subunit of the stimulatory guanine-nucleotide–binding protein (Gαs) that activates adenylate cyclase and increases the intracellular cyclic AMP (cAMP). However, higher TSH concentrations can also activate Gq-mediated signaling, resulting in the activation of phospholipase C, and an increase in intracellular calcium levels. This signaling pathway, has been suggested to play a role in some phenotypes of patients with TSH resistance or in murine goiter development, but unlike demonstrated in some other GPCRs the exact physiological impact of the biased G protein signaling of TSHR remains unclear.

In humans, the TSHR is involved in a wide range of diseases. It acts as a target of thyroid-stimulating or blocking antibodies, which can be detected in Graves' disease or autoimmune hypothyroidism. The mutations in *TSHR*, either somatic or germline, can present gain-of or loss-of-function and lead to nonautoimmune hyperthyroidism (NAH) with dominant inheritance or a variable degree of TSH resistance (RTSH), respectively. The gain-of function due to a constitutively activating mutation (CAM) in the *TSHR* presents the most common cause for NAH. The TSHR CAMs can be identified from a spectrum of hyperthyroid phenotypes including familial nonautoimmune autosomal dominant hyperthyroidism (FNAH), sporadic congenital nonautoimmune hyperthyroidism (SNAH), and up to 80% of toxic thyroid nodules or toxic multinodular goiters. To date, almost 40 families and 23 sporadic cases with CAMs of *TSHR* have been published. These *TSHR* CAMs typically lead to an increased basal production of cAMP and occasionally also to a simultaneous increase in inositol phosphate production in thyrocytes. This ligand-independent *TSHR* activity increases thyroid hormone synthesis and leads to hyperthyroidism, which is usually persistent and requires ablative therapy to avoid relapses. Therefore, it is recommended that all patients with non-autoimmune familial hyperthyroidism should be evaluated for the *TSHR* activating mutations.



Ines Ines; Cesidio Giuliani; Giorgio Naplitano; Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance; Front. Endocrinol., 2017

INTRODUCTION

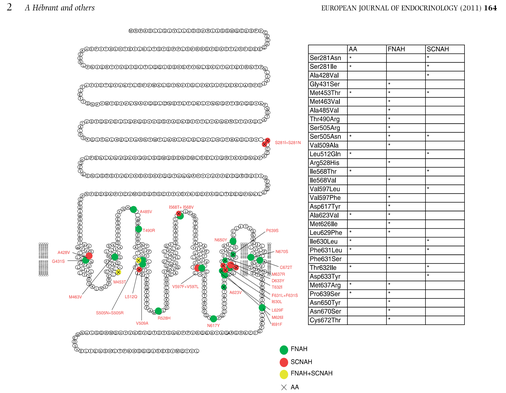


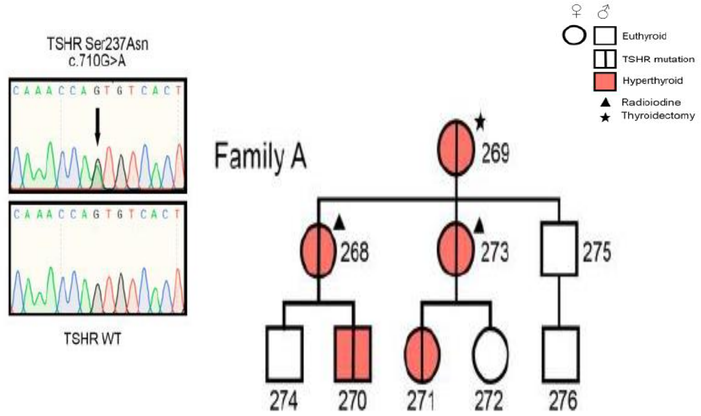
Figure 1 Activating mutations on *TSHR* gene in the various genetic hyperthyroidism syndromes. Comparison of amino acid structure of the TSHR and locations of gain-of-function mutations found in FNAH (green), in SCNAH (red), or in FNAH and SCNAH (yellow). TSHR mutations also found in AA are encircled in blue. TSHR mutations found in AA only are not indicated.

	AA	FNAH	SCNAH
Ser281Asn	*		*
Ser281Ile	*		*
Ala428Val		*	
Gly431Ser		*	
Met463Thr	*	*	*
Met463Val		*	
Ala485Val		*	
Thr490Arg		*	
Ser505Arg		*	
Ser505Asn	*	*	*
Val509Ala		*	
Leu512Gln	*		*
Arg528His		*	
Ile568Thr	*		*
Ile568Val		*	
Val597Leu		*	*
Val597Phe		*	
Asp617Tyr		*	
Met626Val	*	*	*
Met626Ile		*	
Leu629Phe	*	*	
Ile630Leu	*	*	*
Phe631Leu	*		*
Phe631Ser		*	
Thr632Ile	*		*
Asp633Tyr			*
Met637Arg	*	*	
Pro639Ser	*	*	
Asp650Tyr		*	
Asn670Ser		*	
Cys672Tyr		*	

Target site in *TSHR*	Forward primer	Reverse primer	Ta
p.Val233Met (c.697G>A)	5'- AGT CCC CAA ACT CTA GTC CCC -3'	5'- GGT AAG AAA GGT CAG CCC GTG -3'	65 □C
p.Ser237Asn (c.710G>A)	5'- AGT CCC CAA ACT CTA GTC CCC -3'	5'- GGT AAG AAA GGT CAG CCC GTG -3'	65 □C
p.Ala485Val (c.1454C>T)	5'- -3'	5'- -3'	□C
p.Leu629Phe (c.1887G>C)	5'- GTC AGT ATC TGC CTG CCC AT -3'	5'- CTG AGC CTG GCG TTT ACA GA -3'	64 □C
p.Tyr601Asn (c.1801T>A)	5'- CCG AGA CCC CTC TTG CTC TG-3'	5'- CCA GCA AGA TTT TGG AGT TGC T -3'	63 □C
p. Asp633His (c.1897G>C)	5'- CCG AGA CCC CTC TTG CTC TG -3'	5'- CCA GCA AGA TTT TGG AGT TGC T -3'	63 □C
p.Ile640Val (c.1918A>G)	5'- GTC AGT ATC TGC CTG CCC AT -3'	5'- CTG AGC CTG GCG TTT ACA GA -3'	64 □C

Variants of the activating mutation of the TSHR receptor (chromosome 14q31)

FAMILY WITH NAHT



HORMONAL DATA

ID	268	269	270	271	273	272, 274 - 276
p. Ser237Asn c. 710G>A	HET	HET	HET	HET	HET	WT
TSH mU/L ref. 0.28 - 4.3	<0.05	0.02	0.005	0.01	<0.01	0.9 - 2.1
fT4 (pmol/L) ref. 11.6 - 21.8	69.0	74.5	35.4	29.5	37.3	na
fT3 (pmol/L) ref. 4.0 - 8.3	26.1	13.7	11.7	14.1	17.6	na
Age (years)	26	40	13	10	14	-

CONCLUSIONS

1/ In the event of non-autoimmune hyperthyroidism in a patient, it is worthwhile to deepen the family history and perform genetic tests to identify a possible gene mutation in the TSHR receptor.

2/Proper diagnosis determines the application of effective radical treatment.

3/The diagnosed of activating mutation at the TSH receptor will allow for careful observation of the patient and possible early implementation of appropriate treatment.

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