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Severe Hyperthyroidism in an infant revealed a Familial Non Autoimmune Hyperthyroidism with novel stimulating thyrotropin receptor germline mutation

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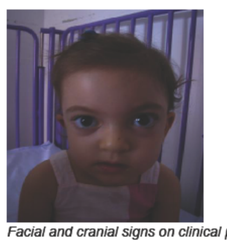
Nothing to disclose

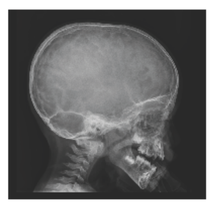
Introduction

The Familial Non Autoimmune Hyperthyroidism (FNAH) is a hereditary disease caused by stimulating mutations of the TSH receptor (TSHR) gene and is rare in the pediatric population. We report 2 young patients, from the same family, which conducted to identify a novel stimulating thyrotropin receptor germline mutation.

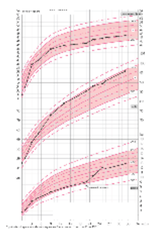
Patient 1

A 20-month girl was referred for **tachycardia** (180/mn).
In personal history, she was delivered at 35 weeks of gestation by caesarean for **fetal tachycardia**; she had been hospitalized at 1 and 5 months for **diarrhea** and tachycardia was noticed. Clinically she presented with **advanced growth** (+2 SD) and **bone age** (5 years), **hypotrophy**, **scaphocephaly** and **craniostenosis**, **hyperactivity**, motor delay by proximal **amyotrophy**. Discrete **ophthalmopathy** without inflammatory sign was observed.
Minor mitral insufficiency with **mitral prolapse** on cardiac ultrasonography was identified.





Facial and cranial signs on clinical presentation and X ray.



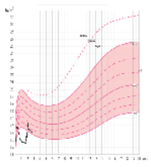


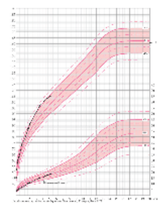
Fig 1&1': Head circumference, Height, Weight and BMI growth charts at diagnosis and after treatment.

Thyroid function tests revealed severe hyperthyroidism (table 1). No anti-TSH receptor antibody was identified.

Ultrasonography showed diffuse enlargement of thyroid gland (volume: 4 cm^3, normal for age < 2.5 cm^3).

Patient 2

Because of same history of advanced growth, her 5-year old sister was tested.



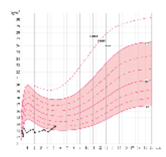
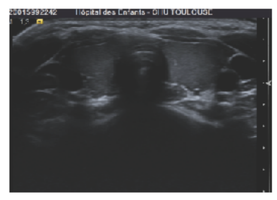


Fig 2 &2':Height, Weight and BMI growth charts at diagnosis and after treatment.

She presented less severe clinical presentation, with same mitral prolapse, and similar hormonal and ultrasonography (thyroid volume 5.5 cm^3; normal for age <3 cm^3) exploration.



Evolution: For the two sisters, a treatment with thiamazole was administered (1 mg/kg/d) and hyperthyroidism was partially controlled after 3 months (see table 1).
Total thyroidectomy was then performed.

		D 0	D 21	D 75	D100	M6	M9	M12
Patient 1	T3L pg/ml (2- 4.2)	>20	9.8	6.1	4.9	5	4.5	5
	T4L pg/ml (7.5-16)	52	33.3	27.8	37.1	19.8	17.2	15.8
	TSH µui/ml (0.4-4.4)	0.005	0.009	<0.005	<0.005	0.005	0.005	0.005
	Thiamazole mg/kg/d	0.55	1	0.9	0.9	1	1	1
Patient 2	T3L pg/ml (2- 4.2)	15.3	7.6	4.39	5.9	2.5	2.72	3.1
	T4L pg/ml (7.5-16)	39.9	30.2	24.3	20.9	7	10.5	7.1
	TSH µui/ml (0.4-4.4)	0.006	0.009	<0.005	<0.005	0.1	0.32	0.57
	Thiamazole mg/kg/d	0.65	0.65	0.6	0.75	0.75	0.75	0.75

Table 1:Hormonal tests evolution during first-year thiamazole treatment, before thyroidectomy for the 2 children.

Genetics

In familial history**, father and father's mother** have been treated for hyperthyroidism: the father had total thyroidectomy and histopathology revealed **papillary micro carcinoma**, while the grandmother had **voluminous and recurrent benign goiter after partial thyroidectomy** (fig 3)

We identified in the patient, her sister, father and grandmother a germline mutation in the exon 10's seventh transmembrane segment of the TSH-R gene; **mutation C672W resulting for a cysteine to tryptophan substitution**.

This 672 cysteine amino acid has been previously described[1] to be changed into another amino acid of the aromatic family. However, tryptophan presents a larger aromatic ring than the tyrosine residue previously explored that should modify more deeply the steric hindrance of the amino acid.

Interestingly, association with mitral valve prolapse has yet been once described[2] in mutation of the sixth transmembrane segment of TSH-R.

[1].Duprez & Al. Nature Genetics. 94; 7; 396-401
[2].Khoo & Al. JCEM 99; 4: 1459-62

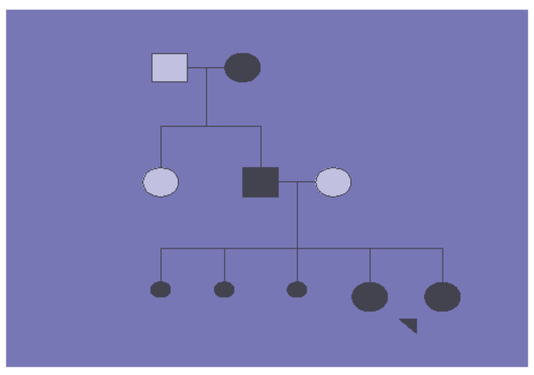
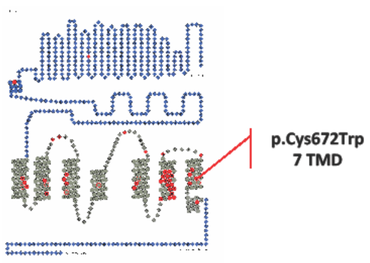


Fig 3: Pedigree of the family.
The arrow identifies patient 1. Solid square and circles indicate members with hyperthyroidism and mutation.



Germline mutation in exon 10 of the TSHR gene

Conclusion: **We report a French family with severe FNAH caused by a new germline mutation in TDM7 of TSH receptor gene.**

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