A Nonsense Thyrotropin Receptor Gene Mutation (R609X) is Associated with Congenital Hypothyroidism and Heart Defects

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Background

Congenital hypothyroidism, one of the most important preventable causes of mental retardation, is a clinical condition characterized by thyroid hormone deficiency in newborns.

Objective and hypotheses

Congenital hypothyroidism is most often caused by defects in thyroid development leading to thyroid dysgenesis. Thyrotropin receptor (TSHR) is the main known gene causing thyroid dysgenesis in consanguineous families with Congenital hypothyroidism. In this study, we aimed to determine the genetic alteration in a case with congenital hypothyroidism and heart defects coming from a consanguineous family

Case

Five days old male newborn was referred with complaints of jaundice which did not require any treatment

Family history showed parental consanguinity, where the parents were second-degree relatives (children of an aunt and uncle)

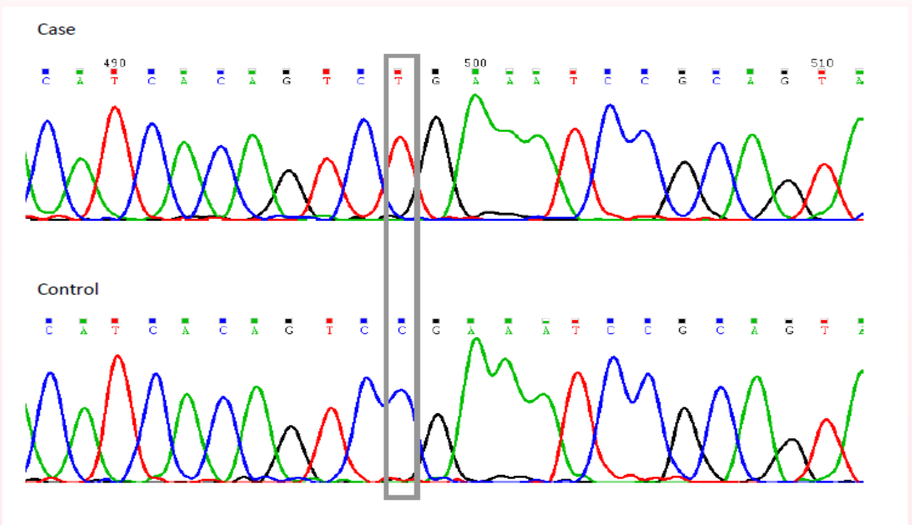
Physical examination revealed anterior fontanelle 3x3 cm, posterior fontanelle 1x1 cm,

grade II/VI systolic, ejection-type murmur in the pulmonary area,

As no normal thyroid tissue was observed in thyroid ultrasonography, and there was no activity involvement in thyroid scintigraphy, the patient was diagnosed with athyreosis and L-thyroxine at 10 mcg/kg/day was introduced.

Echocardiography revealed pulmonary stenosis (valvular) and atrial septal defect.

In the last control visit, patient was 8 years old, grade II/VI systolic, ejection-type murmur in the pulmonary area; patient had no mental retardation (IQ= 95 points) with Tanner stage 1 (bilateral testicular volumes were 2 ml) of puberty. No thyroid gland was detectable during ultrasonography examination performed on two different times. Echocardiography revealed only pulmonary stenosis (valvular). The dose of thyroid hormone was adjusted according to weight and TSH levels during follow-up.



Molecular analysis of the *TSHR* gene revealed a homozygous cytosine to thymine transition at position 609 (C→T) in exon 10. Molecular analysis of the patients' DNAs identified a homozygous mutation at codon R609X (CGA to TGA) in the exon 10 of the *TSHR* gene. Also this mutation has also been previously identified.

C.A. (d,y,m)	TSH (mU/L) (N:0.5-5.6)	FT4 (ng/dl) (N:0.9-2.3)	FT3 (pg/ml) (N:2-5)	BA (y, m)	Height (cm) (SDS)	Weight (kg) (SDS)	H.C. (cm) (p)	L-thyroxine dose (mcg/kg/day)
5 d	>150	< 0.1	1.8		49	2.95	34 (25)	12,5
3 m	1.75	1.9	4,2		57 (-1.4)	5.8 (-0.6)	40 (25)	10
1 y	4.2	1.9	3.4	9 m	73(-1.2)	10.4 (0.2)	45.8(10-25)	7.5
2 y	3.7	1.7	3.8	1 y 6 m	84.5 (-1)	12.8 (0)	48.3(25)	6
3 y	8.2	0.8	1.9	2y 6 m	93 (-0.9)	15(0)		5
4 y	3.9	1.6	3.8	3 y 6 m	99.5(-0.8)	16.5 (-0.1)		4.5
5 y	2.6	1.1	3.6	4 y 6 m	106.5 (-0.8)	17,3 (-0.5)		4.7
6 y	4.8	1	2.8	5 y 6 m	112 (-0.9)	19 (-0.6)		4.3
7 y	2.1	1.5	3.9	6 y 6 m	118.5 (-0.6)	21.5 (-0.6)		3,8
8y	3.6	1.4	3.5	7 y	125 (0.6)	23 (-0.1)		3.5

Conclusions

In conclusion, this study emphasizes the role of detailed genetic analyses in definitive diagnosis and accurate classification of familial CH and suggests that the nonsense R609X mutation in the TSHR gene could be accompanied by cardiac malformations. Cardiac malformations are not uncommon in sporadic congenital hypothyroidism, here they are reported for the first time with R609X mutation in a familial case.