Diverse Genotypes and Phenotypes of Three Novel Thyroid Hormone Receptor Alpha Mutations

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Background

Thyroid receptors are encoded by two genes: *THRA* and *THRB*

Classical thyroid hormone resistance is caused by *THRB* mutations. No mutation in *THRA* was reported until 2012.

The main features in the reported few cases with *THRA* mutations:

-delay in growth and development and constipation consistent with TRα1, one of the two products of *THRA,* being the chief thyroid hormone receptor in brain, bone, heart, and intestine.

-normal to high (F)T3, low to low-normal (F)T4, and normal to mildly elevated TSH levels. The latter is consistent with TRβ2, one of the two products of *THRB*, being the chief receptor in pituitary.

Aim

To determine the spectrum of clinical and functional consequences of 3 novel TRα mutations in the largest case series

Patients and Methods

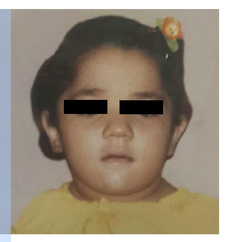
Three index patients with symptoms and signs suggestive of hypothyroidism associated with near-normal fT4 and TSH levels and their families were included (n=22).

Detailed information regarding developmental milestones and symptoms of hypothyroidism, physical examination, biochemical, imaging, genetic studies, and neurodevelopmental tests were collected.

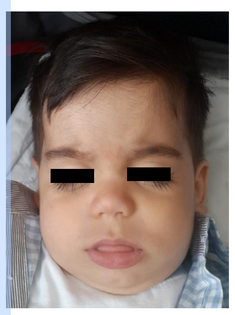
Functional characterization of TRα1 variants were done using JEG3 cells co-transfected with wild-type and mutant TRα1.

Results

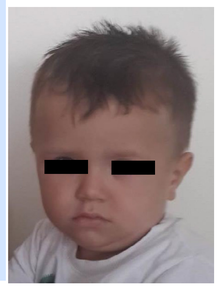
Index Cases



16 months; prominent delay in growth and development, constipation, hoarse cry, macrocephaly and macroglossia & normocytic anemia, high T3, low T4, normal TSH → L-thyroxine

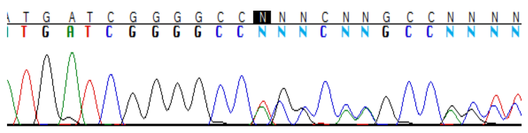


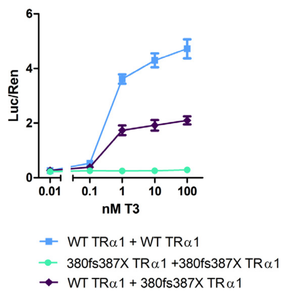
11 months; no significant delay in growth and development or constipation but macroglossia coarse facies, and macrocephaly & normocytic anemia, high fT3, low fT4 in the past, normal TSH, pericardial effusion, high CK, wormian bones in skull

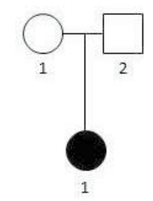


2 years 7 months; delay in eruption of tooth and closure of anterior fontanelle, constipation & low fT4 in the past, normal fT3 and TSH, wormian bones in skull, high CK

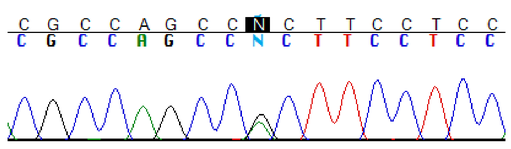
Heterozygous, p.C380fs387X

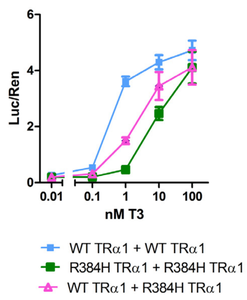


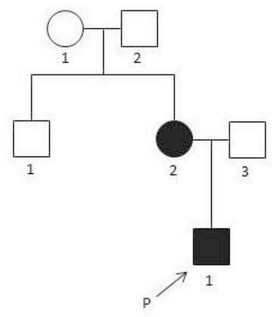




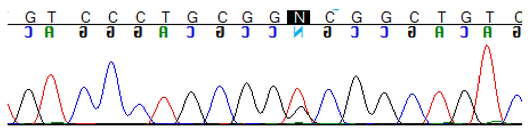
Heterozygous, p.R384H

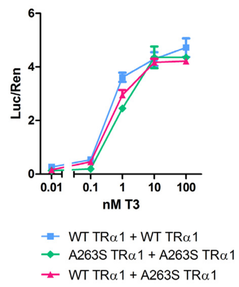


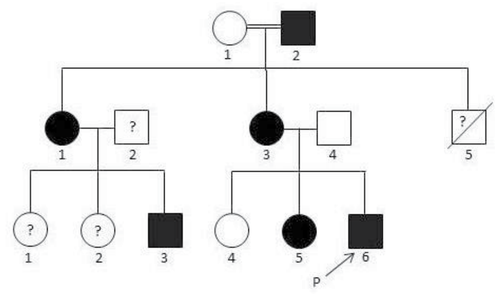




Heterozygous, p.A263S





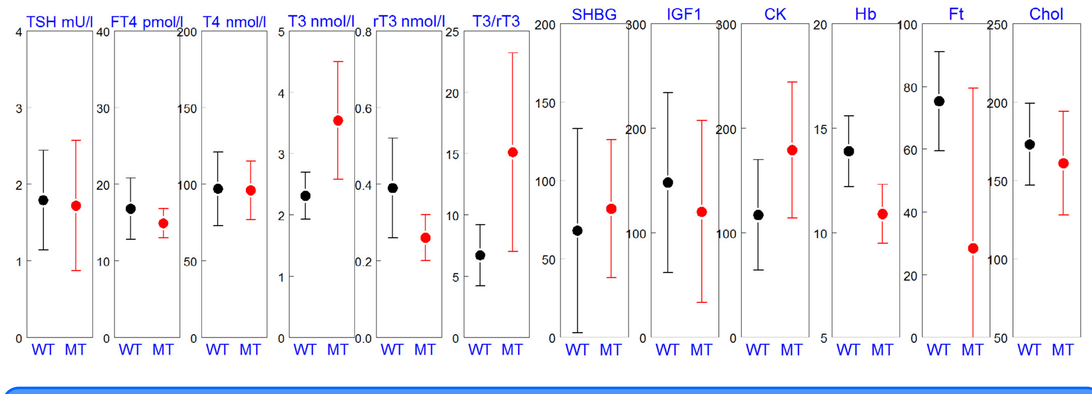


Characteristics of 9 Cases, 11 mo – 55 yrs

	Children (n=5)		Adults (n=4)		Total (n=9)	
	n	%	n	%	n	%
Female	2	40	3	75	5	56
Constipation	4	80	3	75	7	78
*Any developmental delay**	4	80	3	75	7	78
Macrocephaly	2	40	2	50	4	44
Disproportionate body ratio	2	40	1	25	3	33
Obesity	0	0	2	50	2	22
Short stature	1	20	1	25	2	22
No clinical clue	1	20	0	0	1	11
Wormian bones	5	100	4	100	9	100
Thickened skull	5	100	4	100	9	100
Frontal prominence	1	20	2	50	3	33

*Sitting, eruption of teeth, walking, talking, closure of anterior fontanelle.

Laboratory values, nonaffected vs affected



Conclusion

This is the largest case series reported which redefines the mildest and most severe ends of the clinical spectrum of THRA mutations.

High free or total T3, lateral cranial X-ray findings, normocytic anemia, and, particularly in children, high creatinine kinase levels strengthen the diagnosis when clinical signs of hypothyroidism are present along with near-normal fT4 and TSH.

References: 1. Visser WE et al. Different causes of reduced sensitivity to thyroid hormone: diagnosis and clinical management. Clin Endocrinol (Oxf) 2013; 79:595-605. 2. Bochukova E et al. A mutation in the thyroid hormone receptor alpha gene. N Engl J Med 2012; 366:243-249. 3. van Mullem A et al. Clinical phenotype and mutant TRalpha1 New Engl J Med 2012; 366;1451-1453.

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Thyroid.

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