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New Case of Thyroid Hormone Resistance α Caused by a Mutation of *THRA*/TRα1

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We found a sporadic case of mental retardation associated with short stature and constipation. We investigated the possible genetic origin of the syndrome. Clinical and biochemical investigations were conducted. Exome sequencing was used to search for pathogenic variations. A *de novo* mutation (c.1183G>T, p.E395X) was found in one allele of the *THRA* gene. The mutation creates a stop codon, which eliminates the C-terminal helix of the TRα1 receptor for thyroid hormone. The patient has typical symptoms for the resistance to thyroid hormone α (RTHα) genetic disease, but has a normal head circumference. There are now 21 known mutations in *THRA*. All mutations that alter the C-terminal helix of TRα1 lead to severe forms of RTHα.

Freeform/Key Words: thyroid hormone, nuclear receptor, genetic disease

T3 is essential for normal development and metabolism. Its action is mediated by its binding to the nuclear receptors TRα1 and TRβ1/2, which are ligand-dependent transcription factors encoded by the *THRA* and *THRB* genes. *THRA* germline mutations cause a rare genetic disease called RTHα, first reported in 2012 [1, 2]. The variety of symptoms, their variable severity, and the absence of reliable biochemical markers make the diagnosis difficult [3, 4]. Only 20 missense and frameshift mutations have been reported to date, in 31 patients (Table 1). From this small group of patients and analysis of animal models, researchers have determined the disease severity correlates with the inability of the receptor to release transcription corepressors in the presence of T3 [13]. This can result from either a decrease in the affinity of TRα1 for T3 or from an alteration of its C-terminal helix, which normally recruits transcription coactivators upon T3 binding, releasing corepressors.

1. Case Report

We report on a patient with RTHα in China. The patient is the only child of healthy, unrelated parents. This boy was born at full term by vaginal delivery. His birth weight was 4 kg. His developmental milestones were delayed: He walked at 18 months and knew only two words at age 2 years ("mama" and "baba"). Poor coordination and clumsiness were noted. At 2 years

Abbreviation: RTHα, resistance to thyroid hormone α.

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Table 1. Known *THRA* Mutations

Position	DNA Mutation	Mutation Type	Amino Acid	No. of Cases	Country	Skeletal	Brain	Other Traits	First Author
207	Unknown	Missense	G207E	2	Belgium	Nd	Nd	Nd	Unpublished
211	632A>G	Missense	D211G	2	Netherlands	SS, MC	ES, DM	hBMI	van Gucht[5]
263	788 C>T	Missense	A263V	3	United Kingdom	BM	DM	AN, CP	Moran [6]
263	789 G>T	Missense	A263S	7	Turkey	SS, MC, WB	DM	CP, AN, hBMI, ST	Demir [7]
274	821T>C	Missense	L274P	1	United Kingdom	SS, BM, WB	DM	AN, BF	Moran [6]
348	1044G>T	Missense	A348S	1	India	Nd	ASD	Nd	Kalikiri [8]
351	1053C>G	Missense	H351Q	1	India	Nd	ASD	Nd	Kalikiri [8]
359	1075C>G	Missense	N359Y	1	France	SS, BM		CP, AN	Espiard [9]
367	1099C>A	Missense	L367M	1	India	Nd	ASD	Nd	Kalikiri [8]
380	1137ins.4nt	Frameshift	C380fs387X	1	Turkey	SS, BM, MC	DM	CP, BF, AN, hBMI	Demir [7]
382	1144G>C	Missense	A382P	1	India	Nd	ASD	Nd	Kalikiri [8]
382	c1144delG	Frameshift	A382PfsX7	1	United Kingdom	SS, MC	ES, DM	CP, hBMI, ST, BF, AN	Moran [10]
384	Unknown	Missense	R384C	1	Canada	Nd	ASD	Nd	Yuen [11]
384	1151 G>A	Missense	R384H	2	Turkey	SS, MC, WB	DM	AN, CP, hBMI	Demir [7]
395	c.1183G>T	Nonsense	E395X	1	China	SS	DM	AN, CP	Present study
397[a]	insert 1nt	Frameshift	F397fs406X	2	Greece	SS, MC	DM	AN, CP	van Mullem [2]
398	1193C>G	Missense	P398R	1	Poland	SS, MC, BM	DM	AN, CP	Tylki-Szymańska [12]
401	1202T>C	Missense	F401S	1	India	Nd	ASD	Nd	Kalikiri [8]
403	1207G>A	Missense	E403K	2	Poland	SS, MC, BM	DM	AN, CP	Tylki-Szymańska [12]
403	1207G>T	Missense	E403X	1	United Kingdom	SS, MC, WB	DM	CP, hBMI	Bochukova [1]
403	1207G>T	Nonsense	E403X	1	Poland	SS, MC, BM	DM	AN, CP	Tylki-Szymańska [12]
405	1213T>C	Missense	F405L	1	India	Nd	ASD	Nd	Kalikiri [8]

Abbreviations: AN, anemia; ASD, autism spectrum disease; BF, broad face; BM: long bones malformation, dysgenesis or hyperostosis; CP, constipation; DM, delayed milestones; ES, epileptic seizures; hBMI, high body mass index; MC, macrocephalia; Nd, not determined; SS, short stature, ST, skin tags; WB, Wormian bones.

[a]AA 397-410 constitutes the C-terminal helix of TRα1.

old, he underwent the Denver Developmental Screening Test, which result of which was abnormal. The child had chronic constipation.

On examination at age 2 years, the patient's height was 80 cm (reference range, 82.1 to 95.3 cm). At 3 years, his skeletal growth remained retarded (83.5 cm; reference range, 89.7 to 104.1 cm). He was disproportionately short, with a short arm span (78 cm). The patient's heart rate was low (85/min; reference range, 100 to 120/min). His skin was thick without skin tags. The face and nasal bridge were broad, but there was no macroglossia.

The patient underwent multiple thyroid function tests (Table 2). Although T4 and TSH levels remained within reference ranges, his T3 level was slightly elevated. This resulted in a marked reduction of the T4-to-T3 ratio. Consistent with the patient's slow body growth, his IGF-1 level was low. Muscle creatine kinase levels were also elevated, possibly because of the elevated T3 level. The patient's Hb level was low, indicative of mild anemia. Results of the screening tests for metabolic defects, including analyses of blood and urine amino acids and urinary organic acid were normal. Routine karyotyping (G-bands) showed 46,XY.

We evaluated the thyroid gland function by measuring serum thyroglobulin level, which was slightly elevated. We searched for antibodies directed against thyroid peroxidase, or thyroglobulin, which were absent at this early stage. Observations on ultrasonic cardiogram and thyroid pelvic ultrasound were normal. Head and pituitary MRI appeared normal. Overall, the function of the pituitary–thyroid gland axis appeared close to normal, in contrast with the severe symptoms evocative of hypothyroidism. Radiographic studies showed a normal morphology of the vertebral column and no sign of hip dislocation. Wormian bones were absent. At 3 years old, the patient's head circumference was within normal range (51 cm; reference range, 45.7 to 52.2 cm). After obtaining the patient's informed consent (2016034), we performed DNA sequencing using target region sequencing and Sanger sequencing. This revealed that the patient was heterozygous for a *THRA* mutation (c.1183G>T,p.E395X), which was absent in his parents.

The initial dose of 25 μg/d levothyroxine was ordered. The child was irregularly taking medication. Approximately 6 months later, his motor coordination remained poor and clumsiness was visible, but his parents rejected further examination. After then, he was lost to follow-up.

Table 2. Patient's Biochemical and Metabolic Measurements Before Treatment

		Age (Mo)			
Variable	**Reference Values for Children**	**24**	**37**	**37**	**38**
T4	51.83–122.49 ng/mL	77.8	67.7	79.1	
fT4	1.20–1.73 ng/dL	0.91	1.01	0.87	
T3	0.99–2.27 pg/mL	2.18	2.25	2.30	
fT3	2.75–4.68 pg/mL	5.23	5.28	5.25	
TSH	0.38–7.31 μIU/mL	1.38	1.53	1.38	
TPO Ab	0–60 IU/mL			47.8	
Tg	0–35 ng/mL			43.6	
TgAb	0–60 IU/mL			<15	
Hb	110–140 g/L	86	90		87
MCV	80–100 fL	88	87		89
MCH	27–34 pg	30.2	29.6		28.8
MCHC	320–360 g/L	343	342		325
CK	25–225 U/L	981.6	404.9		
CK-MB	0.0–3.7 ng/mL	8.6	7.4		
IGF-1	40–189 ng/mL	33.7	36.3		

Abbreviations: Ab, antibody; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; fT3, free T3; fT4, free T4; MCH, mean corpuscular Hb; MCHC, mean corpuscular Hb concentration; MCV, mean corpuscular volume; Tg, thyroglobulin; TgAB, thyroglobulin antibody; TPO, thyroid peroxidase.

2. Discussion

The E395X mutation eliminates the C-terminal helix of TRα1 and, thus, is expected to display consequences similar to that of C392X, F397fs406X, and E403X mutations, which exert a strong dominant-negative influence in heterozygous cells. Our observations confirm that, for this type of mutation, levothyroxine-T4 treatment provides little benefit, and the manifestations of RTHα are severe.

Our findings also indicate the variability in RTHα manifestations; RTHα remains difficult to recognize even in its severe form. In the patient described here, constipation, small stature, mild anemia, and mental retardation were typical traits of the disease that were reported also for the aforementioned similar cases. The T4 and TSH levels also remained within normal range, and T3 was slightly elevated, which fits the general trend of observing a low T4-to-T3 ratio in these patients. The moderate decrease in IGF-1 and the increase in muscle creatine kinase level are also consistent with previous case reports [3]. By contrast, the slight elevation in thyroglobulin level was not typical of the disease. Perhaps more importantly, the patient's head circumference was normal, whereas it is elevated in all patients with mutations altering the C-terminal helix 12 of the receptor (Table 1). Therefore, our data confirm that RTHα diagnosis cannot rely on a single clinical trait and that the manifestation of the disease varies even for patients with seemingly equivalent mutations.

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