

# A Case of Permanent Congenital Hypothyroidism with Compound Heterozygous Mutations of the Gene *DUOX2*

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## BACKGROUND

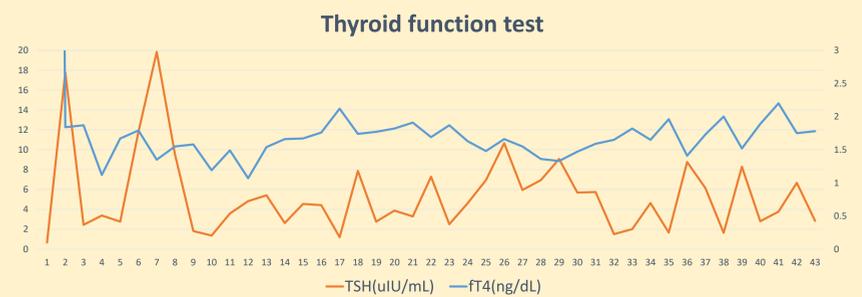
Congenital hypothyroidism is defined as thyroid hormone deficiency present at birth. It is the most common congenital endocrine disorder. Neonatal screening test for hypothyroidism can allow its early detection. The course of disease can be permanent or transient. Some permanent congenital hypothyroidism has been linked to defects in proteins involved in the synthesis of thyroid hormones. One of the critical steps in the synthesis of thyroid hormone is the generation of H<sub>2</sub>O<sub>2</sub> produced by dual oxidase at the apical membrane of follicular thyroid cells. This case report describes a permanent congenital hypothyroidism with heterozygous mutation in the *DUOX2* gene.

## CASE

An 12 years and 6 months boy was born at 37 weeks of gestational age by Caesarean section. Birth weight was 2.8 kg. He was transferred to Dankook University hospital due to low T4 and elevated TSH levels in neonatal screening test. On thyroid function test performed at 21 days, total T3 was 77.96 ng/dL with 0.66 ng/dL of free T4 and 34.55 uIU/mL of TSH. On physical examination, no major abnormality was found. Thyroid sonography showed normally positioned thyroid gland with normal echogenicity (Fig. 1). He has no family history of thyroid disease and other autoimmune disease. He was diagnosed with congenital hypothyroidism and levothyroxine supplement was started daily at 40 ug (11.1 ug/kg)(Table 1 & Fig. 2). He has been regularly followed up in outpatient clinic. His language development was somewhat slower than his peers until 3 years of his age, but showed normal development afterwards. Head circumference and height has been in normal range, but he is rather obese. During follow-up targeted exome sequencing which included 23 genes known to be associated with congenital hypothyroidism was performed and compound heterozygous mutations of the gene *DUOX2* were identified (Fig. 3). The sequences of DNA c.1462 guanine and c.2444 thymine were substituted by cytosine and adenine, respectively. As a result, amino acid was changed to Arginine and Proline instead of Glycine and Leucine, respectively. Same mutations were detected from his parents which showed paternal mutation on c. 1462G>A and maternal mutation on c.2444T>C (Fig. 3). Dosage of levothyroxine was adjusted based on the results of TFT and his weight. Recently his serum level of T3 was 158.8 ng/dL and freeT4 was 1.78 ng/dL. TSH was 2.85uIU/mL with daily thyroid hormone replacement of 137.5 ug (2.4 ug/kg/day)(Table 1).

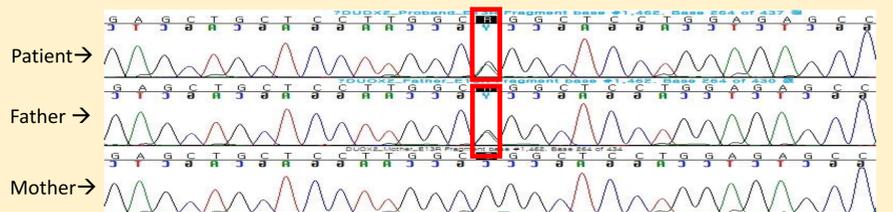
**Table 1. Thyroid function test and medication during follow-up**

	21 days	35 days	2 mos	1 y	2 y	4 y	6 y	8 y	10 y	12.6 y
T3 (ng/dL)	77.96	152.66	152.41	236.15	165.73	138	164.6	146.4	171.2	158.8
fT4 (ng/dL)	34.55	1.84	1.87	1.79	1.58	1.66	1.77	1.66	1.65	1.78
TSH (uIU/mL)	0.66	17.77	2.44	11.8	1.82	2.62	2.76	10.66	4.63	2.85
Tg (ng/mL)	2038.96					60				
Bwt (kg)	3.6	4.2	5.8	10.3	13.2	17.7	28.7	41.3	56.5	56.8
Ht (cm)			57.6		88.7	104.1	119.1	130.9	144.5	160.3
Levothyroxine	40 (ug/day)	40	40	40	60	75	75	75	100	137.5
	11.1 (ug/kg/d)	9.5	6.9	3.9	4.5	4.2	2.6	1.8	1.8	2.4

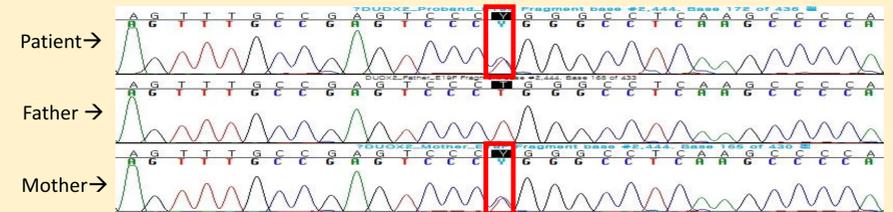


**Fig. 2. Thyroid function test during follow-up**

[C.1462G>A]

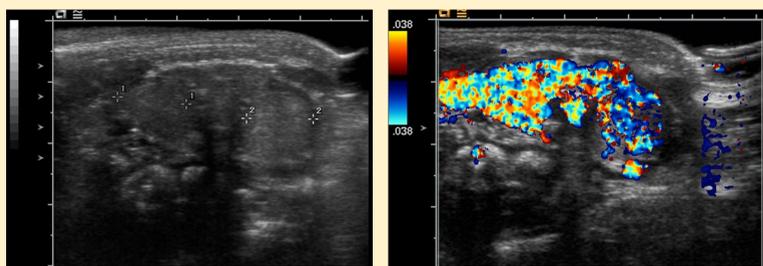


[C.2444T>C]



**Fig. 3. Result of gene study**

	Father	Mother
<b>DUOX2 exon 13 NM_014080.4: C.1462G&gt;A</b>	(+)	(-)
<b>DUOX2 exon 19 NM_014080.4: C.2444T&gt;C</b>	(-)	(+)



**Fig. 1. Initial thyroid sonography**

The initial thyroid imaging study showed no evidence of focal lesion in both thyroid lobe with normal echogenicity, except for the increased blood flow in thyroid gland in Doppler mode.

## CONCLUSION

We experience a case of permanent congenital hypothyroidism with compound heterozygous mutation of *DUOX2* gene. This case showed that c.2444T>C mutation could be thought as a likely pathogenic gene of congenital hypothyroidism.

