Genetic Evaluation of Congenital Hypothyroidism with Gland-in-Situ using Targeted Exome Sequencing

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Introduction

Congenital hypothyroidism (CH)

Most common congenital endocrine disorder

Leading to permanent mental retardation if not treated early

Incidence: 1:3000-4000 newborns, in worldwide

1:1283 in Korea newborn screening

Molecular basis of CH with gland-in-situ(GIS)

- 7 genes of Hormone biosynthesis
  DUOX2, DUOXA2, TPO,TG, SLC26A4, SLC5A5,IYD
- *TSHR* gene medicates some cases
- Next-generation sequencing (NGS) technologies enable to screen multiple genes simultaneously

The aim of this study

-To analyze the genetic cause of congenital hypothyroidism by targeted gene panel sequencing in pediatric patients with congenital hypothyroidism with thyroid gland-*in-situ* (GIS)

Methods

20 patients with eutopic thyroid gland

- Diagnosed with congenital hypothyroidism
- Undergone thyroid image (evidence of goiter or normal size)
- L-thyroxine (L-T4) treatment for 3 years
- Re-evaluation after the age 3, after L-T4 therapy withdrawal
- Based on Thyroid function test, thyroid ultrasound, scintigraphy

Patients' subgroup after re-evaluation

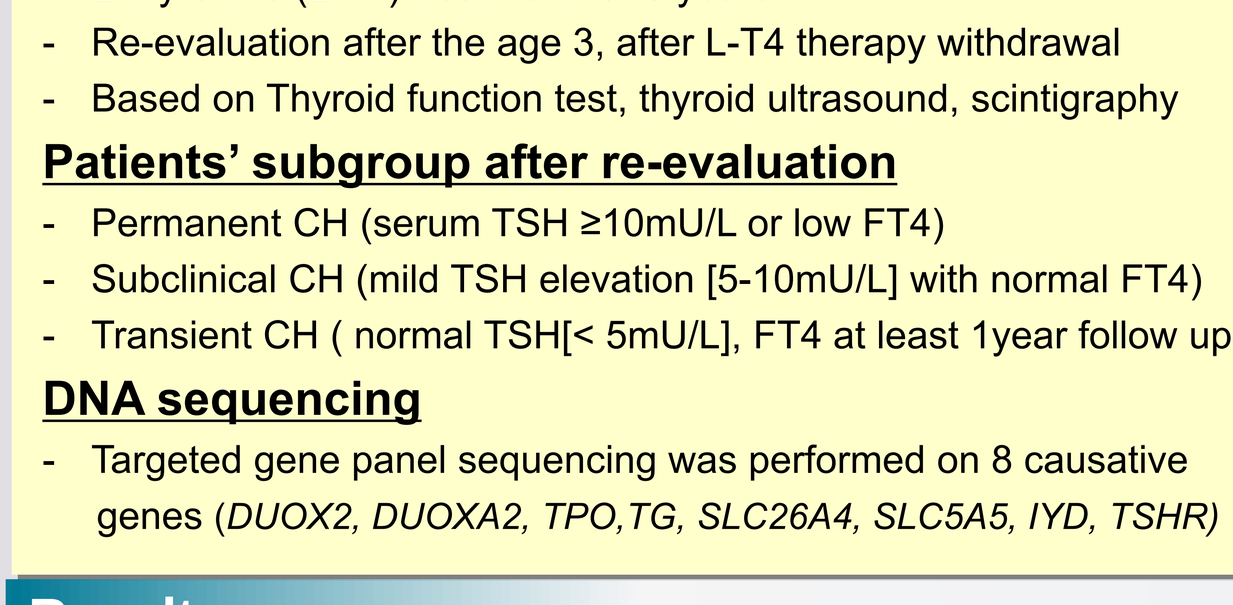
- Permanent CH (serum TSH ≥10mU/L or low FT4)
- Subclinical CH (mild TSH elevation [5-10mU/L] with normal FT4)
- Transient CH (normal TSH[< 5mU/L], FT4 at least 1year follow up)

DNA sequencing

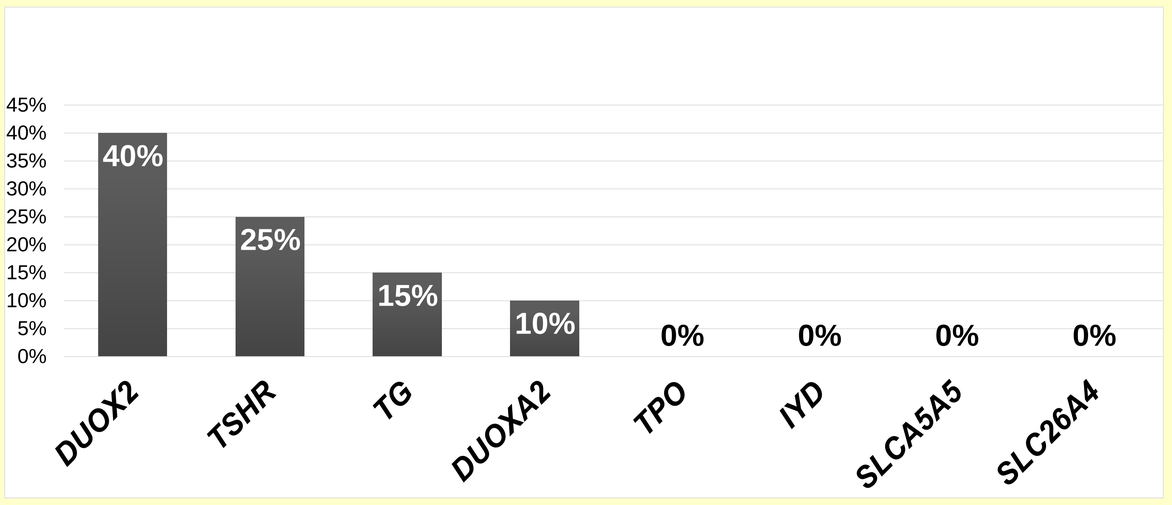
- Targeted gene panel sequencing was performed on 8 causative genes (*DUOX2, DUOXA2, TPO,TG, SLC26A4, SLC5A5, IYD, TSHR)*

Results

Distributions of mutation in the patients with CH and GIS



Mutation frequency



Spectrum of mutations identified in this study

Gene	ID	cDNA change	Protein change	classification	type	zygosity
DUOX2	F1	c.3693+1G>T		LPV	Permanent	Hetero
	F4	c.1588A>T	Lys530*	LPV	Permanent	Hetero
	F6	c.1588A>T	Lys530*	LPV	Subclinical	Hetero
	F7	c.2000del	Leu667Argfs*9	LPV	Permanent	Hetero
	F8-1-1	c.1462G>A	Gly488Arg	LPV	Permanent	Compound hetero
	F8-1-2	c.127A>T	Asn43Tyr	LPV	Permanent	
	F15	c.2654G>A	Arg885Gln	LPV	Permanent	Hetero
	F19-1-1	c.243G>A	Pro81=	VUS	Permanent	Compound hetero
	F19-1-2	c.605_621del	Gln202Argfs*93	PV	Permanent	
	F20-1-1	c.567C>T	His189=	VUS	Subclinical	Compound hetero
	F20-1-2	c.1462G>A	Gly488Arg	LPV	Subclinical	
TSHR	F2	c.1349G>A	Arg450His	LPV	Permanent	Hetero
	F9-1	c.1349G>A	Arg450His	LPV	Permanent	Compound hetero
	F9-2	c.1522T>C	Ser508Pro	VUS	Permanent	
	F16	c.1349G>A	Arg450His	LPV	Permanent	Hetero
	F17-2	c.733G>A	Gly245Ser	VUS	Permanent	Hetero
	F20-2	c.611C>T	Ala204Val	VUS	Subclinical	Hetero
TG	F10-1-1	c.5998T>G	Cys2000Gly	VUS	Transient	Compound hetero
	F10-1-2	c.6709C>T	Pro2237Ser	VUS	Transient	
	F11	c.379G>A	Ala127Thr	VUS	Subclinical	Hetero
	F17-1-1	c.7666G>A	Val2556Ile	VUS	Permanent	Compound hetero
	F17-1-2	c.733G>A	Gly245Ser	VUS	Permanent	
DUOXA2	F12	c.758C>A	Thr253Lys	VUS	Permanent	Hetero
	F13	c.495C>A	Ser165Arg	VUS	Permanent	Hetero

Conclusion

Of 20 patients, permanent CH, subclinical CH, and transient CH was found in 15(75%), 3(15%), 2(10%) patients , respectively. Targeted gene panel sequencing on 8 genes identified 24 variants among 16 patients : *DUOX2*-11variants in 8 patients; *TSHR*-6 variants in 5 patients; *TG*-5 variants in 3 patients; and *DUOXA2*- 2 variants in 2 patients. Among these 24 variants, 10 were novel variants. Two Patients showed trialleic (digenic) mutations.

Based on the findings, the genetic causes of congenital hypothyroidism by targeted gene panel sequencing in patients with thyroid gland *in situ* were identified in 60% of the cases, with *DUOX2* and *TSHR* gene mutation being the most common causes. As there were many novel variants, and the frequency of cases where the genetic mutations were unidentified was high (45%), Additional studies on genetic causes of congenital hypothyroidism Is warranted.

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