ANALYSIS OF HYPOTHYROIDISM NGS TEST IN KOREAN PATIENTS WITH CONGENITAL HYPOTHYROIDISM IN A SINGLE CENTER

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INTRODUCTION

Thyroid hormone is known as greatly influence on growth and development in fetuses and newborns. If the detection of the disease is delayed, hypothyroidism can cause irreversible damage, so early detection and treatment is very important. Hypothyroidism can be divided into permanent and temporary cases depending on the duration of treatment, but there is no predictor that can completely differentiate those two. However, as genes related to hypothyroidism are revealed, genetic analysis can help predicting whether hypothyroidism will be transient.

AIM

Analyzing causative genetic variations and clinical characteristics with congenital hypothyroidism.to predict disease persistence.

METHOD

- Subjects: 147 congenital hypothyroidism patients who want to implement the hypothyroidism NGS panel were enrolled (Male n=84, 57%).
- Period: 2017. 07 ~ 2020. 12
- Hypothyroidism NGS panel covers 30 genes; *DUOX2, DUOXA2, FOXE1, GNAS1, HESX1, IYD, LHX3, NKX2-1, NKX2-5, PAX8, POU1F1, PROP1, SLC16A2, SLC26A4, SLC5A5, TG, THRA, THRB, TPO, TRH, TRHR, TSHB, TSHR, LHX4, SOX2, GLIS3, OTX2, DUOX1, IGSF1, SOX3*.
- We retrospectively collected and analyzed the clinical data of those patients; Initial TSH, free T4, the last dose of levo-thyroxine, height/body weight, the results of hypothyroidism NGS panel.

RESULTS

Fig 1. (A) Proportion and frequency of known pathogenic variants. A total of 22 known pathogenic variants were identified in 20 patients.
(B) Proportion and frequency of likely-pathogenic variants. There were total 42 likely-pathogenic variants in 38 patients.

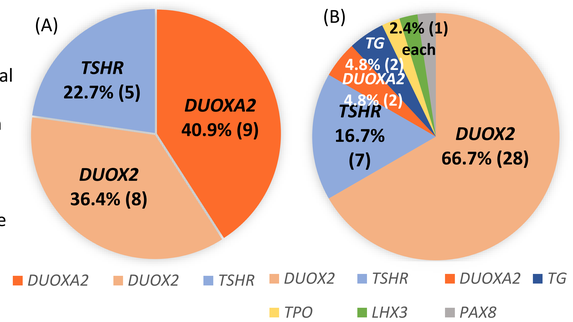

Table 1. Genes and the frequency which were detected as VOUS. 121 VOUS variants were identified in 90 patients.

Gene	Frequency (%)	Gene	Frequency (%)
DOUX2	40 (33.1%)	*PAX8*	3 (2.5%)
TG	27 (22.3%)	*DUOXA2*	2 (1.7%)
TPO	7 (5.8%)	*LHX4*	2 (1.7%)
GLIS3	6 (5.0%)	*OTX2*	2 (1.7%)
DUOX1	5 (4.1%)	*SLC26A4*	2 (1.7%)
IGSF1	5 (4.1%)	*HESX1*	1 (0.8%)
GNAS1	4 (3.3%)	*NKX2-1*	1 (0.8%)
LHX3	4 (3.3%)	*TRH*	1 (0.8%)
TSHR	4 (3.3%)	*IYD*	1 (0.8%)
TBL1X	3 (2.5%)	*THRA*	1 (0.8%)

Table 2. Clinical and the related genetic information of 15 transient congenital hypothyroidism patients who could stop medication at 1 year old.

Patient No.	Sex	Last dose of L-thyroxine (mcg)	Initial TSH (mIU/L)	Initial freeT4 (ng/dL)	ACMG classification	Gene	Nucleotide	Amino acid	Zygosity	Inheritance pattern
1	M	25	18.78	1.15	VOUS	*DUOX2*	c.3179C>T	p.Ala1060Val	Hetero	AD/AR
					VOUS	*TG*	c.426C>T	p.Asp142=	Hetero	AR
2	F	12.5	33.10	0.78	VOUS	*DUOX2*	c.2335G>A	p.Val779Met	Hetero	AD/AR
					VOUS	*TPO*	c.612G>A	p.Pro204=	Hetero	AR
3	F	25	na	na	-	-	-	-	-	-
4	M	20	77.16	0.5	VOUS	*TG*	c.3964T>C	p.Leu1322=	Hetero	AR
					VOUS	*TG*	c.4493C>T	p.Thr1498Met	Hetero	AR
5	F	15	na	na	VOUS	*GNAS*	c.58C>A	p.Leu20Met	Hetero	AD
6	M	12.5	na	0.98	VOUS	*TG*	c.2488C>G	p.Gln830Glu	Hetero	AR
					VOUS	*TG*	c.2035C>T	p.Pro1012Leu	Hetero	AR
7	M	30	na	na	-	-	-	-	-	-
8	M	20	na	na	-	-	-	-	-	-
9	M	25	20.03	1.06	-	-	-	-	-	-
10	M	15	37.11	0.69	-	-	-	-	-	-
11	M	12.5	45.65	1.98	-	-	-	-	-	-
12	F	12.5	7.28	1.30	VOUS	*THRA*	c.508A>G	p.Ile170Val	Hetero	AD
13	F	25	12.07	0.84	-	-	-	-	-	-
14	M	25	7.64	0.99	Pathogenic	*DUOXA2*	c.413dupA	p.Tyr138*	Hetero	AR
					VOUS	*IGSF1*	c.1603C>T	p.Arg535Trp	Hetero	XL
15	F	10	na	na	-	-	-	-	-	-

Table 3. Clinical and the related genetic information of 18 transient congenital hypothyroidism patients who could discontinue the treatment after 3 years old.

Patient No.	Sex	Age of discontinuation (yr)	Last dose of L-thyroxine (mcg)	Initial TSH (mIU/L)	Initial freeT4 (ng/dL)	ACMG classification	Gene	Nucleotide	Amino acid	Zygosity	Inheritance pattern
16	M	3	37.5	28.56	1.34	-	-	-	-	-	-
17	M	3	20	37.74	1.79	Likely pathogenic	*DUOX2*	c.1462G>A	p.Gly488Arg	Hetero	AD/AR
						Likely pathogenic	*DUOX2*	c.3329G>A	p.Arg1110Gln	Hetero	AD/AR
18	F	3	na	na	na	Likely pathogenic	*DUOX2*	c.2181del	p.Ala728Profs*22	Hetero	AD/AR
						VOUS	*DUOX2*	c.2654G>T	p.Arg885Leu	Hetero	AD/AR
19	F	3	25	na	na	Pathogenic	*DUOXA2*	c.738C>G	p.Tyr246*	Hetero	AR
20	F	3	25	26.00	0.68	Likely pathogenic	*DUOX2*	c.1462G>A	p.Gly488Arg	Hetero	AD/AR
						Likely pathogenic	*DUOX2*	c.1883delA	p.Lys628Argfs*11	Hetero	AD/AR
						VOUS	*PAX8*	c.1028A>G	p.Asn343Ser	Hetero	AD
21	F	3	20	10.09	1.17	VOUS	*DUOX1*	c.3107G>A	p.Arg1036His	Hetero	AR
22	M	3	37.5	na	na	Likely pathogenic	*DUOX2*	c.1871del	p.Gly624Alafs*15	Hetero	AR
						VOUS	*DUOX2*	c.2635G>A	p.Glu879Lys	Hetero	AR
						VOUS	*DUOX1*	c.415C>A	p.Arg139Ser	Hetero	
23	M	3	25	48.19	0.79	Likely pathogenic	*DUOX2*	c.1871delG	p.Gly624Alafs*15	Hetero	AR
						VOUS	*DUOX2*	c.3442A>G	p.Asn1148Asp	Hetero	AR
24	M	3	32.5	3.40	0.62	VOUS	*OTX2*	c.406A>G	p.Ser136Gly	Hetero	AD
						VOUS	*TG*	c.3197G>A	p.Arg1066His	Hetero	AR
						VOUS	*TG*	c.4493C>T	p.Thr1498Met	Hetero	AR
25	M	3	25	>150	na	-	-	-	-	-	-
26	F	3	12.5	17.60	0.88	VOUS	*DUOX2*	c.3116G>A	p.Arg1039Gln	Hetero	AR
27	F	4	37.5	27.12	0.82	VOUS	*TG*	c.4435G>A	p.Gly1479Arg	Hetero	AR
28	F	5	37.5	255.16	<0.40	VOUS	*DUOX2*	c.3442A>G	p.Asn1148Asp	Hetero	AR
29	M	5	37.5	na	na	Pathogenic	*DUOXA2*	c.738C>G	p.Tyr246*	Hetero	AR
						Likely pathogenic	*DUOX2*	c.214G>T	p.Ala72Ser	Hetero	AR
30	M	5	37.5	>100	0.33	Pathogenic	*DUOX2*	c.1588A>T	p.Lys530*	Hetero	AD/AR
						Likely pathogenic	*DUOX2*	c.1462G>A	p.Gly488Arg	Hetero	AD/AR
31	M	5	50	na	na	Likely pathogenic	*DUOX2*	c.1462G>A	p.Gly488Arg	Hetero	AR
						VOUS	*DUOX2*	c.2291G>A	p.Arg764Gln	Hetero	AR
32	F	7	50	93.88	0.41	VOUS	*GLIS3*	c.2213C>T	p.Ser738Phe	Hetero	AR
33	M	9	50	na	na	Pathogenic	*DUOX2*	c.3329G>A	p.Arg1110Gln	Hetero	AR
						VOUS	*DUOX2*	c.2104_2106del	p.Gly702del	Hetero	AR

Among 147 patients, 50 patients (34.0%) had known pathogenic or likely pathogenic genes and 33 patients (22.4%) had none of related mutations.
There were 9 ectopic thyroid, 4 agenesis, 1 hemiplasia patient and 33 patients could stop treatment until now.

CONCLUSIONS

It is expected that causative genetic analysis of congenital hypothyroidism will be helpful in actively stopping the treatment of congenital hypothyroidism according to the clinical condition of the patient, except when the disease is estimated due to pathogenic or likely pathogenic genes.

CONTACT INFORMATION

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