Targeted next-generation sequencing for congenital hypothyroidism with positive neonatal TSH screening results

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Introduction

Congenital hypothyroidism (CH) is mostly detected with neonatal newborn screening (NBS). CH is the most common neonatal endocrine disorder, however the molecular etiology is sill poorly understood, considering pathogenic variations in candidate genes have been found only in 10-20 % of CH.

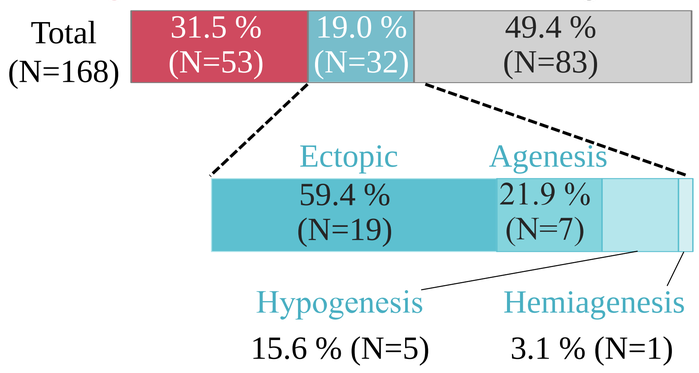
Subjetcs / Method

Subjects

Number（male; female）	**168** (75; 93)
Age (yr)	**9.0** (0.2-26.2)*
NBS-TSH（μIU/mL）	**15.6** (1.1-275.3)*
NBS-FT4（ng/mL）	**1.59** (0.11-3.32)*
Age for starting LT4（days）	**22** (7-2301)*
Dose of staritng LT4（μg/kg）	**6.3** (1.9-15.6)*

* median (range)

Disease-type diagnosis



Targeted next-generation sequencing

NGS panel	Haloplex
Target region	**22 genes** *NKX2-1, FOXE1, PAX8, NKX2-5, GLIS3, TSHR, JAG1, TG, TPO, DUOX2, DUOXA2, DUOX1, SLC5A5, SLC26A4, IYD, SLC16A2, SECISBP2, GNAS, DIO1, DIO2, DIO3, CDCA8* All exons and exon-intron boundaries (10bp) of these genes

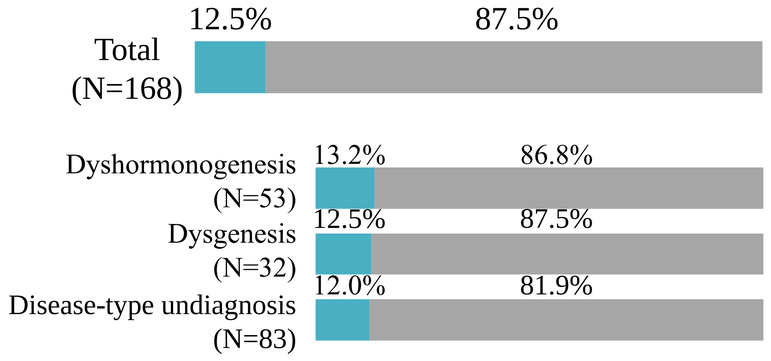
* Called variants were confirmed by Sanger sequence.
* In silico tools (polyphen-2, SIFT, M-CAP) were used for interpretation of variants.
* All available parents were performed with Sanger sequencing of the patient's variants.

Results 1

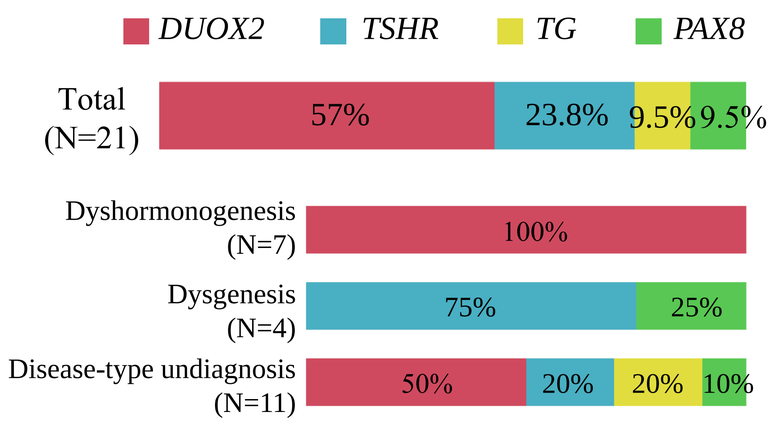
Single gene disorders

- **A single gene known as candidate genes of CH**
- **Autosomal dominant or autosomal recessive**

Overall detection rate



Detected genes

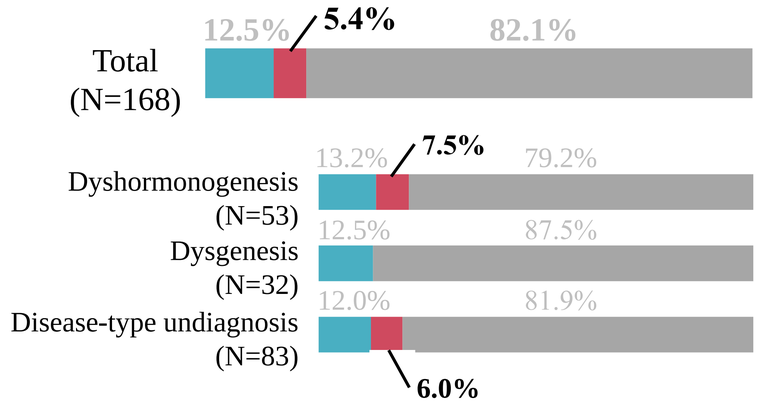


Results 2

Oligogenic inheritance

- **Patients found to carry two or more heterozygous pathogenic variants in different CH candidate genes**

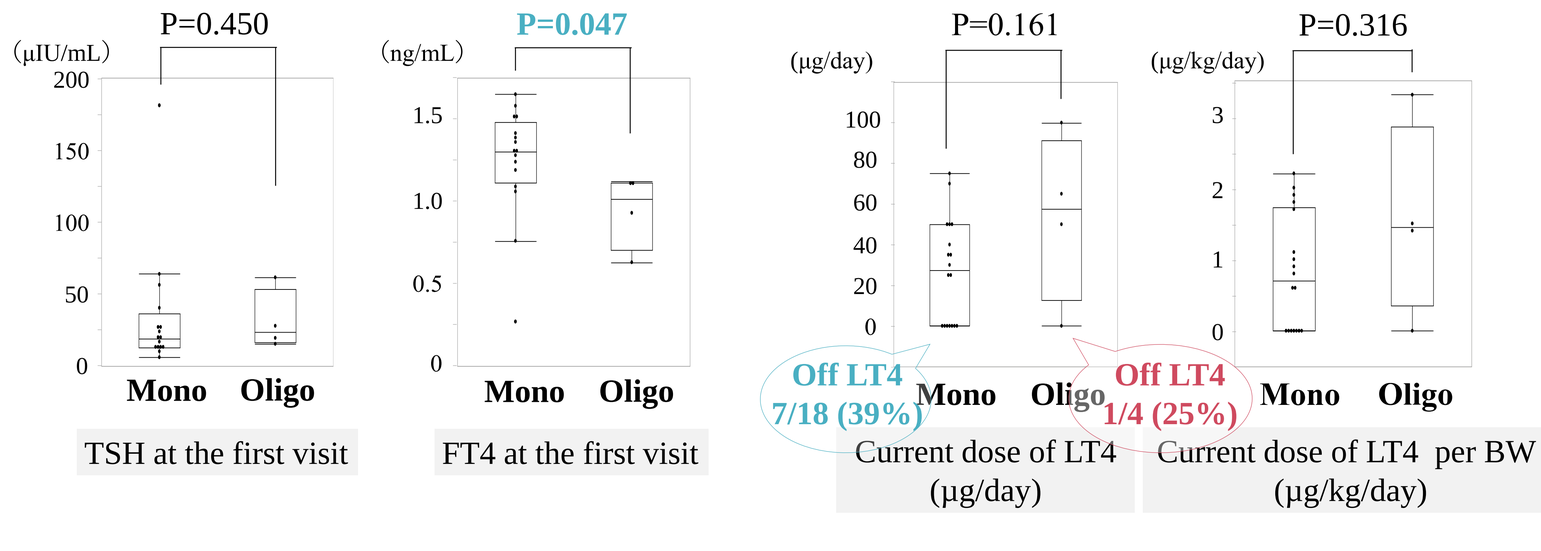
Detection rate



Mutated genes detected hetelozygously (nine cases)

	Dyshormonogenesis				Disease-type undiagnosis				
	1	2	3	4	5	6	7	8	9
DUOX2	■	■	■		■	■			
TG	■			■	■				■
TSHR		■		■			■		
DUOXA2			■				■		
GLIS3								■	
TPO									■
SECISBP2						■			
SLC26A4								■	

Monogenic (carrying one mutation) vs Oligogenic (carrying two or more mutations)



Discussions / Conclusions

✔ The overall detection rate of NGS was 12.5 % of single gene disorders in NBS-positive CH, which is similar result as previously reported.

✔ Moreover, our study showed 5.4 % in CH patients having oligogenic defects, and the number of carrying mutations tended to correlate with CH severity.

✔ The role of oligogenicity in etiology of CH remains unclear, however it is reported that frequent occurrence of several mutations in two or more candidate genes suggest the contribution of oligogenic variants.

✔ The systematic NGS analysis is useful in determining an underlying moleculer etiology of CH.

References

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