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, DUOX2, TPO, TG, SLC26A4, SLC5A5, IYD
- TSHR gene mediates 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 1 year follow up)

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

Results

Distributions of mutation in the patients with CH and GIS

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: DUOX2-11 variants in 8 patients; TSHR-6 variants in 5 patients; TG-5 variants in 3 patients; and DUOX2-2 variants in 2 patients. Among these 24 variants, 10 were novel variants. Two patients showed triallelic (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.