Thyroid dyshormonogenesis: a case report of two siblings with a heterozygous variant in the *TPO* gene.

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INTRODUCTION

Congenital hypothyroidism (CH) is an inborn disease with an incidence rate of 1 case per 3,600 newborns of which 15-20% cases are associated with thyroid dyshormonogenesis. The ***TPO* gene** encodes thyroid peroxidase - an enzyme which plays a central role in thyroid gland function. Disease associated with this gene is usually transmitted in an autosomal recessive mode. Hypothyroidism-associated TPO variants are usually biallelic, limited evidence for cases in patients with heterozygous variants exists.

AIM

to study clinical and genetic characteristics of CH in this family.

METHOD

- ✓ Thyroid imaging was performed using ultrasound (US) and scintigraphy (Tc99m).
- ✓ Serum thyroglobulin (TG) was detected by ELECSYS immunoassay method, TSH and free T4 were measured by ARCHITECT test system.
- ✓ Genetic data was obtained with targeted gene panel including 23 genes associated with CH using Illumina MiSeq System in patient 1 and the regions of interest were analyzed with Sanger sequencing

RESULTS

Patient 1 (proband): girl 13 yrs. with CH.

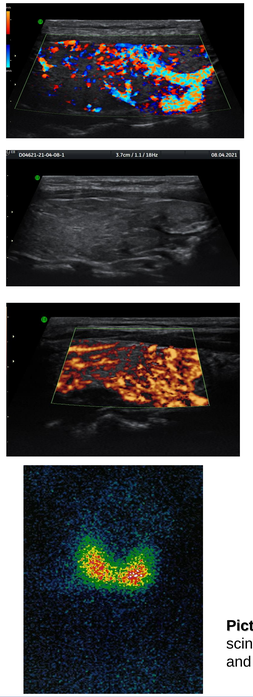
- Neonatal **TSH at 200 mU/l.**
- US scan and scintigraphy showed *in situ* thyroid gland with extremely **high blood flow and increased radiotracer** uptake up to 3.3% (0.8-1.7), pict. 1
- **TG ↑ to 445 ng/ml**.

*All of these studies were conducted after discontinuation of l-thyroxine therapy for two weeks at the age of 13.

Patient 2: 10 yrs. The sister with normal thyroid.

Patient 3: 8 yrs. The brother with CH and high level of neonatal TSH up to 180 mU/l. Clinical analysis results are similar to that of the proband in 8 yrs. age - **increased ultrasound blood flow, radiotracer uptake** to 3.9% and **TG up to 273.4 ng/ml.**

Patient 4: 3 yrs. The brother with normal thyroid.



Patient 1 13 yrs Proband	Patient 2 10 yrs Healthy sister	Patient 3 8 yrs Brother with CH	Patiient 4 3 yrs Healthy brother	Mother	Father
NGS (Panel CH)	Region of interest (Sanger)	Region of interest (Sanger)	Region of interest (Sanger)	Region of interest (Sanger)	Region of interest (Sanger)
TPO gene c.1188 1193delCGCCAGins10p. (Ala397Profs*76)	*TPO gene* c.1188 1193delCGCCAGins10p. (Ala397Profs*76)	*TPO gene* c.1188 1193delCGCCAGins10p. (Ala397Profs*76)	No	*TPO gene* c.1188 1193delCGCCAGins10p. (Ala397Profs*76)	No

The heterozygous known pathogenic variant in the *TPO* gene c.1188 1193delCGCCAGins10p. (Ala397Profs*76) was found in proband and confirmed by the mother, 10 yrs. old healthy sister and 8 yrs. old brother with CH.

The heterozygous *SLC5A5* gene variant c.1 192T>A p. Cys398Ser with an unknown clinical significance was detected in proband, mother, healthy 10 yrs. old sister and 3 yrs. old healthy brother. The father did not have any of those variants. Increased radiotracer uptake in proband's thyroid excluded the role of the variant in the *SLC5A5 (NIS*) gene in the etiology of CH in this family.

Pict.1 Thyroid US and scintigraphy imaging Patient 1 and Patient 3

CONCLUSIONS

The variant in the *TPO* gene might play the main role in the etiology of patient's 1 and patient's 3 CH. We are going to analyze proband's TPO gene with Sanger sequencing that may identify a new intron variant and verify the etiology of CH in this family.

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