The genetic and clinical characteristics of pediatric patients with congenital hypothyroidism gland in-situ

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INTRODUCTION

The underlying genetic causes of congenital hypothyroidism with gland in-situ (CH GIS) and hyperthyrotropinemia (HT) remain largely a mystery. Thanks to NGS, genetic screening is now finding many novel variants. The challenge is to correctly identify which genes and which variants lead to CH and which cause only a transient HT.

OBJECTIVES

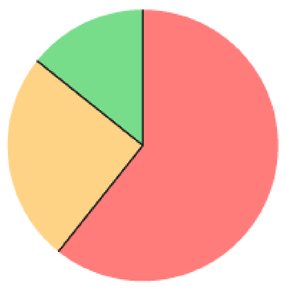
Our objectives were to evaluate the presence of variants in 14 candidate genes (*TG,DUOX2*, *DUOXA2, TPO*, *TSHR*, *PAX8, GLIS3*, *SLC5A5*, *SLC26A4, NKX2-1, NKX2-5, JAG1, IYD*, FOXE1) using NGS in patients diagnosed with CH GIS and clinically reevaluated later in life. We wanted to compare the clinical data of the patients with their genotype.

MATERIALS and METHODS

CH GIS patients in follow-up at the OSR Pediatric Thyroid Clinic → 75 patients: NGS → **56** patients

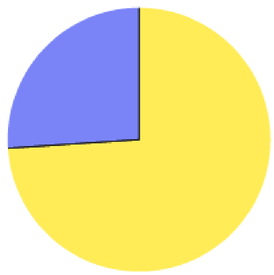
Selection critera:
- phenotype mirrors previously reported cases with pathogenic variants
- familiarity

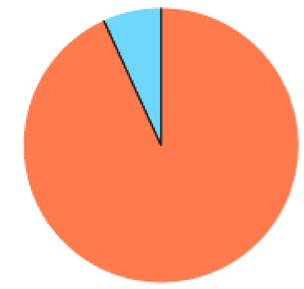
Selection criteria:
- patient underwent reevaluation at 3-5 years
- no morphological thyroid abnormalities

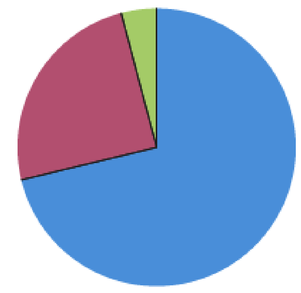


RESULTS

45/56 patients (**80,36%**) had a variant in the candidate genes
73 variants in 11 genes had been identified





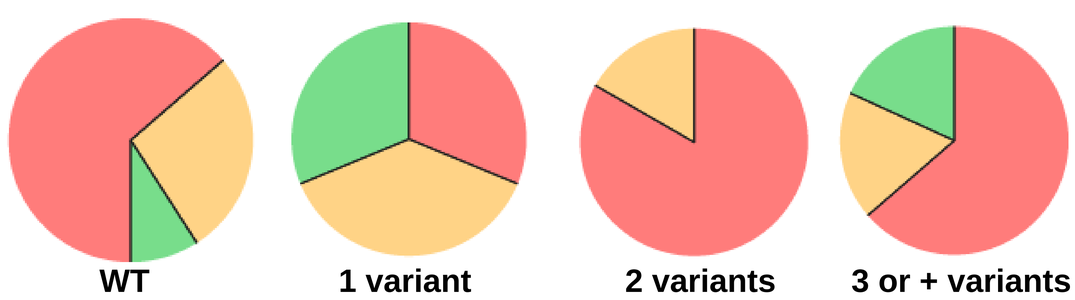


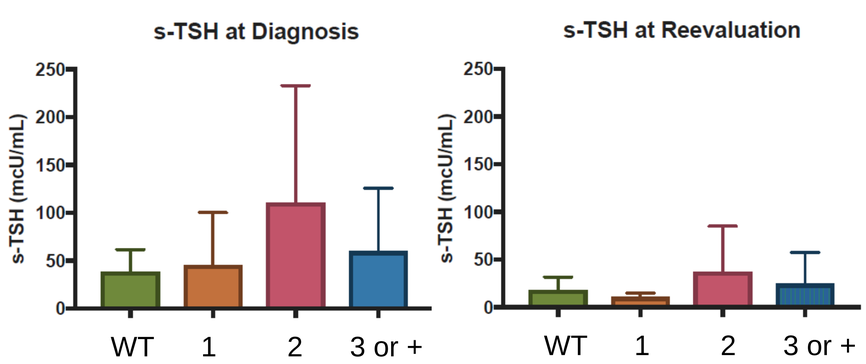
- **TG** - 21 variants (17 novel)
- **DUOX2** - 21 variants (12 novel)
- **TPO** - 8 variants (7 novel)
- **TSHR** - 6 variants (2 novel)
- **PAX8** - 4 variants (3 novel)
- **GLIS3** - 6 variants (all novel)
- **SCL5A5** - 3 variants (all novel)
- **SLC26A4** - 1 variants (novel)
- **NKX2-1** - 1 variants (novel)
- **JAG1** - 1 variants (novel)
- **IYD** - 1 variants (novel)
- DUOXA2, FOXE1 and NKX2-5 - none

N variants for patient:

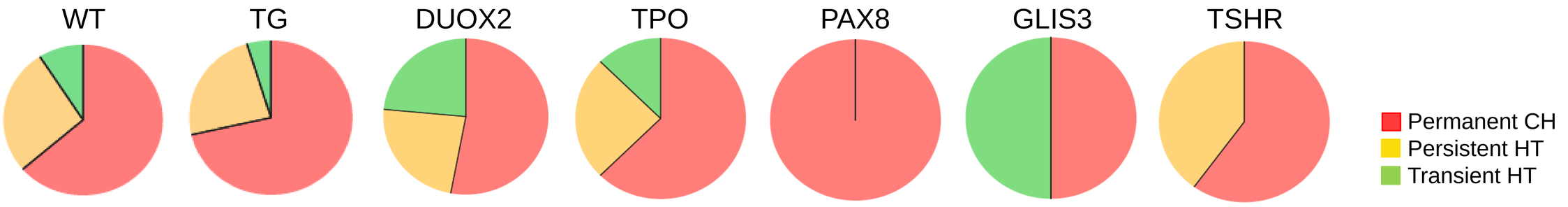
- **WT** (19,64%)
- **1** (28,57%)
- **2** (32,14%)
- **3 or +** (19,64%)

Diagnosis after re-evaluation:





Variant-phenotype relation:



CONCLUSIONS

Although a genetic screening program for CH GIS patients is still a long way off, information from studies utilizing NGS is giving clinicians a clearer picture of the underlying causes. While the etiology is mostly still unclear, studies such as this one help identify possible pathologic variants and lead to a better understanding of CH GIS