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

Maria Cristina Vigone1, Luca Saracco1, Gaia Vincenzi1, Silvana Caiulo1, Marianna Di Frenna1, Luca Persani2, Tiziana De Filippis2, Fabiana Guizzardi2, Maria Grazia Patricelli1, Ivana Spiga1, Giovanna Weber1

1Ospedale San Raffaele, Milan, Italy. 2Istituto Auxologico Italiano, Milan, Italy

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, DUOX2A, 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

<table>
<thead>
<tr>
<th>75 patients: NGS</th>
<th>56 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection criteria:</td>
<td>Selection criteria:</td>
</tr>
<tr>
<td>• phenotype mirrors previously reported cases with pathogenic variants</td>
<td>• patient underwent reevaluation at 3-5 years</td>
</tr>
<tr>
<td>• familiarity</td>
<td>• no morphological thyroid abnormalities</td>
</tr>
</tbody>
</table>

45/56 patients (80.36%) had a variant in the candidate genes
73 variants in 11 genes had been identified

| Variant | Pathogenic (24%) | Homozigous (6.15%) | Unknown (71%) | Reported (26.03%) | Novel (73.97%) |

N variants for patient: Diagnosis after re-evaluation:

• WT (19.64%)
• TG (28.57%)
• 1 variant (28.57%)
• 2 variants (32.14%)
• 3 or + (19.64%)

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.