Clinical course in a girl with two hTPO mutations - homozygous c.1268G>A (p.Gly393Arg) and heterozygous c.208C>G (p.Ala70Pro):
27 years of follow up

INTRODUCTION
Of the several genetic defects responsible for thyroid dyshormonogenesis, mutations in TPO gene are the most prevalent causes of inherited defects in congenital hypothyroidism (CH). Prevalent mutations are in exons 8-11 (catalytic site).

CLINICAL CASE
Girl, born at 16d after term, before the nationwide introduction of the neonatal screening, with asphyxia and BL 55 cm, BW 4 kg. Because of insufficient weight gain, feeding difficulties, prolonged jaundice she was referred to a pediatric endocrine clinic with high suspicion for CH. At d 42 all classical clinical signs of CH were fully present, the clinical diagnosis was confirmed by the hormonal constellation (Table 1) and a gland in situ was present as well (no data on the volume before L-T4 introduction).

<table>
<thead>
<tr>
<th>Age</th>
<th>NTSH mU/l (Delfia)</th>
<th>TSH mU/l</th>
<th>T4 nmol/l</th>
<th>Tg ng/ml (Delfia)</th>
<th>TT4 pmol/l (Delfia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42d</td>
<td>ND</td>
<td>&gt;200</td>
<td>33</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>11yrs</td>
<td>107</td>
<td>139</td>
<td>&lt;20</td>
<td>22.6</td>
<td>&lt;1.2</td>
</tr>
</tbody>
</table>

TREATMENT
L-thyroxin treatment was introduced, the dosages increased gradually up to 75 mcg/d. At 11 years the treatment was discontinued by the mother and permanent primary CH with an eutopic thyroid: normo-hypoechogenic parenchyma, volume 9.6 ml were reconfirmed (Figure 1). The therapeutic strategy changed (gradual increment of L-T4, not until “toxic” dosages), a stable euthyroid situation was achieved, the adherence of the patient and the family improved.

CONCLUSIONS
Early molecular genetic studies are important for patients with primary CH and eutopic thyroid glands because of refining the treatment and follow up strategy - the increased risk for thyroid cancer should be kept in mind.

MOLECULAR DIAGNOSIS
A homozygous mutation c.1268G>A (p.Gly393Arg) and a heterozygous missense c.208C>G (p.Ala70Pro) were found by Sanger sequencing. The homozygous mutation is new, undescribed in the databases. A stop-gain mutation, with the functional consequence of a protein lacking the catalytic site and therefore inability of effective thyroid hormone synthesis (p.Gly393*), on the same position has been described. The missense heterozygote c.208C>G (p.Ala70Pro) in exon 4 is a rare variant (Exac MAF=0.007) with unknown clinical significance and may also contribute to the phenotype as it is predicted as possibly damaging and deleterious by Polyphen and SIFT prediction programs.

REFERENCES