**TSH RECEPTOR GENE (TSHR) VARIANTS IN PEDIATRIC PATIENTS WITH NON AUTOIMMUNE HYPERTHYROTROPINEMIA**

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**METHODS**

- The whole coding sequence of TSHR gene (exons 1 to 10) and intronic flanking regions were amplified by PCR from genomic DNA and automatically sequenced.
- Different software tools were used for in silico prediction of gene variant effects:
  - PolyPhen 2 (http://genetics.bwh.harvard.edu/pph2/)
  - Mutation Taster (http://www.mutationtaster.org/)
  - SNAP (https://www.rostlab.org/services/snap/submit)
  - Exome Variant Server, NHLBI GO Exome Sequencing Project (ESP), Seattle, WA

**RESULTS**

- In two patients, two uncommon heterozygous missense variants were found in exon 10.
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**SUMMARY & CONCLUSIONS**

- All patients were responsive to TSH stimulation (Gq/11-dependent signaling pathway).
- Expression studies should also include the double expression of this novel variant is required to establish its role in thyroid pathogenesis.

PATIENT 1: p.Ile583Thr

**BACKGROUND**

TSH resistance is defined as reduced sensitivity to TSH, associated with molecular defects hampering the adequate transmission of TSH stimulatory signal into thyroid cells. Non-autoimmune hypothyropitropinemia (NAH) is a state of mild TSH resistance characterized by mildly elevated TSH associated to normal thyroid hormones serum levels, in the absence of anti-thyroid antibodies.

**AIM**

To assess the frequency of TSHR gene variants in a pediatric population with NAH.

**Subjects**

Children born SGA were younger and shorter at consultation and had significantly lower TSH and higher FT3 than AGA children.

**TSHR SEQUENCING: frequent SNPs (coding)**

<table>
<thead>
<tr>
<th>dbSNP database reference</th>
<th>Variant</th>
<th>Exon</th>
<th>MAP in our cohort</th>
<th>dbSNP 1000 Genome MAP</th>
<th>Exome Variant Server MAP</th>
<th>P (vs dbSNP)</th>
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</thead>
<tbody>
<tr>
<td>rs2234919</td>
<td>p.P407L/WT</td>
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<td>1</td>
<td>0.019</td>
<td>NS</td>
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<td>NS</td>
<td>0.004</td>
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<tr>
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<td>p.A459A/WT</td>
<td>5</td>
<td>2</td>
<td>0.019</td>
<td>NS</td>
<td>0.004</td>
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**TSHR SEQUENCING: uncommon variants**

Both variants were predicted as pathogenic by different bioinformatic tools.

**PATIENT 2: p.Pro407Leu**

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