Classification and Proposed Nomenclature for Inherited Defects of Thyroid Hormone Action, Cell Transport, and Metabolism*


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Resistance to thyroid hormone (RTH) was first described in 1967 (1), and the first mutations in the \( THRB \) gene were identified in 1989 (2, 3), only 3 years after the cloning of the \( THR \) genes (4, 5). The cardinal features of this syndrome of reduced sensitivity to thyroid hormone are elevated serum levels of free thyroid hormone with nonsuppressed TSH, often with goiter and no clear symptoms and signs of thyrotoxicosis (6). In fact, signs of decreased and increased thyroid hormone action in different tissues may coexist.

During the First International Workshop on Resistance to Thyroid Hormone in Cambridge, United Kingdom in 1993, a consensus statement was issued to establish a unified nomenclature of \( THRB \) gene mutations in RTH (7), as defined above. In the ensuing years more than 3000 cases have been identified, 80% of which harbored mutations in the \( THRB \) gene. More recently, two syndromes with reduced cellular access of the biologically active thyroid hormone, \( T_3 \), were identified. These are caused by defects of thyroid hormone cell membrane transport (8, 9) and a defect reducing the intracellular metabolism generating \( T_3 \) from \( T_4 \) (10). To accommodate these new findings, it was proposed to broaden the definition of hormone resistance. Thus, the Fifth International Workshop on Resistance to Thyroid Hormone, which took place in Lyon, France, in 2005, saw the introduction of the term “reduced sensitivity to thyroid hormone (RSTH) to encompass all defects that can interfere with the biological activity of a chemically intact thyroid hormone secreted in normal or excessive amounts.”

Following the 10th International Workshop on Resistance to Thyroid Hormone and Action that took place in Quebec City, Canada, in 2012, a number of investigators took on the task to develop a nomenclature for inherited forms of impaired sensitivity to thyroid hormone (Table...
The term “impaired” was to substitute for “reduced” because nascent data indicate that syndromes of increased sensitivity may also exist. We are cognizant that no nomenclature can fit perfectly all aspects of the described syndromes because variability exists. Several aspects were taken into consideration: the already existing nomenclature, new findings, and anticipated putative discoveries. For example, in over 2000 publications “RTH” is used to define a phenotype of congenitally increased free T4 with nonsuppressed TSH, irrespective of the presence or absence of a THRB gene mutation (see non-TR-RTH). In view of the identification of THRA gene mutations that present a distinct phenotype (11, 12), we propose using the term “RTH α”, and in new publications to use “RTH β” when a THRB gene mutation is present in association with the RTH phenotype. This allows the naming of new gene defects in individuals with the RTH phenotype. The use of the abbreviation “THR” as a synonym for RTH is discouraged, not only because the hormone is not resistant, but also because this abbreviation is used to denote other circumstances. Indeed, a Medline search using THR yielded over 20,000 references, only a few related to resistance to thyroid hormone.

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### Table 1. Inheritable Forms of Impaired Sensitivity to Thyroid Hormone

<table>
<thead>
<tr>
<th>LEVEL OF THE DEFECT</th>
<th>Commonly used name (References Are for first Reported Cases)</th>
<th>Synonyms</th>
<th>Gene Involved &amp; Inheritance (OMIM)</th>
<th>Phenotype</th>
<th>Consistent (Pathognomonic)</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>THYROID HORMONE CELL MEMBRANE TRANSPORT DEFECTS (THCMTD)</td>
<td>Monocarboxylate transporter 8 (MCT8) defect (8,9)</td>
<td>Allan-Herndon-Dudley syndrome</td>
<td>MCT8 (SLC16A2) gene (300095); X-chromosome linked</td>
<td>Hypermetabolism, paroxysmal dyskinesia, reduced muscle mass, seizures, poor head control, difficulty sitting independently.</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Idiopathic &amp; other THCMTDs</td>
<td>Idiopathic &amp; other THCMTDs</td>
<td>To be determined</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THYROID HORMONE METABOLISM DEFECTS (THMD)</td>
<td>Selenocysteine insertion sequence binding protein 2 (SBP2) defect (10)</td>
<td></td>
<td>SBP2 (SECISBP2) gene (607693) recessive</td>
<td>Azoospermia, immunodeficiency, photosensitivity, delayed bone maturation, myopathy, hearing impairment, delayed developmental milestones</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Idiopathic &amp; other THMDs</td>
<td>Idiopathic &amp; other THMDs</td>
<td>To be determined</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THYROID HORMONE ACTION DEFECTS (THAD): nuclear receptor and other</td>
<td>Resistance to thyroid hormone (RTH) (1,2,3)</td>
<td>Iodothyronine unresponsiveness, generalized RTH, RTH beta; Refetoff syndrome</td>
<td>MTHFD gene (190160) dominant negative (rarely recessive)</td>
<td>High serum FT4 and non suppressed TSH.</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Non-TR-RTH (13)</td>
<td>Non-TR-RTH (13)</td>
<td>Unknown</td>
<td>Same as above</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTH alpha (11,12)</td>
<td>Congenital nongoutrous hypothyroidism 6</td>
<td>MTHFD gene (190120) dominant negative</td>
<td>Low serum FT3:FT4 ratio; cognitive impairment, short lower limbs, delayed closure of skull sutures, delayed bone and dental development, skeletal dysplasia, macrocephaly, constipation; anemia</td>
<td>Low FT3, seizures, placid behavior.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity to thyroid hormone (HTH)</td>
<td></td>
<td></td>
<td>Low FT3, and FT4, with normal TSH and no serum transport defects</td>
<td>Normal thyroid gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic &amp; other THADs</td>
<td>Idiopathic &amp; other THADs</td>
<td>To be determined</td>
<td>Unknown</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: FT3, free T3; FT4, free T4; BMI, body mass index.

a Proposed future terminology: RTH beta.

b RTH without mutations in the THRβ gene.

c A single case with a mutation involving both TRα1 and TRα2 presented a more complex phenotype, including severe bone malformations, hypercalcemia with hyperparathyroidism, and diarrhea rather than constipation. It is unclear whether all observed abnormalities are due to the THRA gene mutation alone.
References


13. Weiss RE, Hayashi Y, Nagaya T, et al. Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor α or β genes may be due to a defective cofactor. *J Clin Endocrinol Metab.* 1996;81:4196–4203.