

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

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Abbreviation: RTH, resistance to thyroid hormone.

1). 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 T_4 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

LEVEL OF THE DEFECT				
Commonly used name (References Are for first Reported Cases)	Synonyms	Gene Involved & Inheritance (OMIM)	Phenotype	
			Consistent (Pathognomonic)	Common
THYROID HORMONE CELL MEMBRANE TRANSPORT DEFECTS (THCMTD)				
Monocarboxylate transporter 8 (MCT8) defect (8,9)	Allan-Herndon-Dudley syndrome	MCT8 (SLC16A2) gene (300095) X-chromosome linked	High T ₃ , low rT ₃ and T ₄ , normal or slightly elevated TSH; low BMI; hypotonia, spastic quadriplegia; not walking or rarely ataxic gait; no speech or dysarthria, mental retardation	Hypermetabolism, paroxysmal dyskinesia, reduced muscle mass, seizures, poor head control, difficulty sitting independently.
Idiopathic & other THCMTDs		To be determined	Unknown	
THYROID HORMONE METABOLISM DEFECTS (THMD)				
Selenocysteine insertion sequence binding protein 2 (SBP2) defect (10)		SBP2 (SECISBP2) gene (607693) recessive	High T ₄ and rT ₃ , low T ₃ , normal or slightly elevated TSH; growth retardation	Azoospermia, immunodeficiency, photosensitivity, delayed bone maturation, myopathy, hearing impairment, delayed developmental milestones
Idiopathic & other THMDs		To be determined	Unknown	
THYROID HORMONE ACTION DEFECTS (THAD): nuclear receptor and other				
Resistance to thyroid hormone (RTH) ^a (1,2,3)	thyroid hormone unresponsiveness, generalized RTH, RTH beta; Refetoff syndrome	THRB gene (190160) dominant negative (rarely recessive)	High serum FT ₄ and non suppressed TSH.	High serum FT ₃ and rT ₃ , high thyroglobulin, goiter, attention deficit hyperactivity disorder (ADHD), tachycardia
nonTR-RTH ^b (13)		Unknown	Same as above	Same as above
RTH alpha1 ^c (11,12)	Congenital nongoitrous hypothyroidism 6	THRA gene (190120) dominant negative	Low serum T ₄ /T ₃ ratio; cognitive impairment, short lower limbs, delayed closure of skull sutures, delayed bone and dental development, skeletal dysplasia, macrocephaly; constipation; anemia	Low rT ₃ , seizures, placid behavior.
Hypersensitivity to thyroid hormone (HTH)		Unknown	Low FT ₄ and FT ₃ with normal TSH and no serum transport defects	Normal thyroid gland
Idiopathic & other THADs		To be determined	Unknown	

Abbreviations: FT₃, free T_3 ; FT₄, free T_4 ; BMI, body mass index.

^a Proposed future terminology: RTH beta.

^b RTH without mutations in the *THRB* gene.

^c A single case with a mutation involving both TR α 1 and TR α 2 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.

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