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

Samuel Refetoff[a–c] J.H. Duncan Bassett[d] Paolo Beck-Peccoz[e, f] Juan Bernal[h] Gregory Brent[i] Krishna Chatterjee[j] Leslie J. De Groot[k] Alexandra M. Dumitrescu[a] J. Larry Jameson[l] Peter A. Kopp[m] Yoshiharu Murata[n] Luca Persani[e, g] Jacques Samarut[o] Roy E. Weiss[a, b] Graham R. Williams[d] Paul M. Yen[p]

Departments of [a]Medicine, [b]Pediatrics, and [c]Genetics, The University of Chicago, Chicago, Ill., USA; [d]Department of Medicine, Imperial College London, London, UK; [e]Department of Clinical Sciences and Community Health, University of Milan, [f]Fondazione Ca' Granda Policlinico, and [g]Istituto Auxologico Italiano, Milan, Italy; [h]Instituto de Investigaciones Biomédicas, Consejo Superior de Investigaciones Científicas-Universidad Autonoma de Madrid and Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain; [i]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Calif., USA; [j]Wellcome-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [k]Thyroidmanager and Endotext, South Dartmouth, Mass., [l]Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pa., [m]Division of Endocrinology, Metabolism, and Molecular Medicine and Center for Genetic Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Ill., USA; [n]Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan; [o]Ecole Normale Supérieure de Lyon, Lyon, France; [p]Laboratory of Hormone Action, Singapore Institute of Clinical Sciences, Singapore, Singapore

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 3,000 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

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Dr. Samuel Refetoff, MD
University of Chicago, Department of Medicine
5841 South Maryland Avenue
Chicago, IL 60637 (USA)
E-Mail refetoff@uchicago.edu

Table 1. Inheritable forms of impaired sensitivity to thyroid hormone

Commonly used name (references are for first reported cases)	Synonyms	Gene involved and inheritance (OMIM)	Phenotype	
			consistent (pathognomonic)	common
Level of the defect				
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 and 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 and other THMDs		to be determined	unknown	
Thyroid hormone action defects (THAD): nuclear receptor and other				
Resistance to thyroid hormone (RTH)[a] [1–3]	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
Non TR-RTH[b] [13]		unknown	same as above	same as above
RTH alpha[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 and other THADs		to be determined	unknown	

FT_3 = Free T_3; FT_4 = 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 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.

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 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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Disclosure Summary

The authors have nothing to declare.

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