Diagnosis of the Resistance to Thyroid Hormone beta (RTHβ)
Japan Thyroid Association 2016

I. Clinical findings
1. A large number of cases show no clear clinical findings. However, some may exhibit signs of thyrotoxicosis or hypothyroidism, and sometimes both. *1
2. Mild diffuse enlargement of the thyroid gland and tachycardia is common.
3. No consistency is found between serum thyroid hormone levels and clinical findings. *2

II. Laboratory findings
1. Persistence of SITSH with elevated FT4 and normal-to-elevated TSH levels. *3, *4
2. Mutations of the *thyroid hormone receptor β* (*TRβ*) gene (*THRB*). *5

III. Supplementary findings
1. Normal response of serum TSH to the TRH test.
   Insufficient suppression of serum TSH levels after the administration of T3.
2. No elevation in the serum α subunit level or the ratio of the α subunit/TSH.
3. Family history.

IV. Exclusionary conditions
Thyrotropin-secreting pituitary adenoma (TSHoma) and Familial dysalbuminemic hyperthyroxinemia (FDH).

Diagnostic criteria
1) A patient is considered to have definite RTH if he/she satisfies the criteria for three Clinical findings and two Laboratory findings.
2) A patient is considered to have possible RTH if he/she satisfies the criteria for at least one of the three clinical findings and the first Laboratory finding (SITSH).

Genetic test for the TRβ gene

The genetic test should be performed after appropriate genetic counseling according to the guidelines. *6

The results of the *TRβ* gene with the below criteria indicate RTH.
1. SITSH is found in 1st degree relatives.
2. The mutation has already been reported and established as a cause of RTH.
3. A new mutation, if located in the three clusters of mutations of *TRβ* for RTH, is highly suggestive of disease-causing.
4. Mutations not consistent with the above three conditions should be proved to have abnormal function by an *in vitro* experiment.

Notes

*1. A case exhibiting severe thyrotoxicosis used to be known as the 'pituitary type', while others, the 'generalized type'. However, both types may have the same mutations of the *TRβ* gene.

*2. Laboratory tests reflecting hypermetabolism induced by thyroid hormone, including low cholesterol and CK or high ferritin and SHBG, should be considered.

*3. Since laboratory tests similar to SITSH are caused by different clinical conditions, true SITSH should be confirmed by measurements at different time points and with different assay systems.

*4. Some diseases other than SITSH show abnormal thyroid hormone levels.

Mutation of the thyroid hormone transporter (*monocarboxylate transporter 8*: *MCT8*) is associated with high T3, low T4, and normal-to-slightly elevated TSH levels.

Mutation of the *selenocysteine insertion sequence-binding protein 2* (*SBP2*), which plays a role in deiodinase activity, is associated with low T3, high T4, and normal-to-slightly elevated TSH levels.

Mutation of *TRα* is associated with normal to slightly elevated T3 and TSH, but normal-to-slightly low T4 levels.

*5. NonTR-RTH is defined as a probable case without a mutation of the *TRβ* gene.

*6. The following guidelines apply to genetic tests, which include: "Ethical Guidelines for Human Research" from three ministries of the Japanese government "Guidelines for Genetic Tests and Diagnoses in Medical Practice" from the Japanese Association of Medical Sciences, "Guidelines for Genetic Tests" from 10 Japanese academic societies, and "Ethical Guidelines for Human Genome and Genetic Sequencing Research" from three ministries of the Japanese government.

Degree of severity

Mild cases show no clear interference of daily activities.

Moderate cases show low-grade interference of daily activities due to tachycardia, palpitations, and irritability.

Severe cases show high-grade interference of daily activities due to severe tachycardia, atrial fibrillation, ADHD, mental retardation, and growth retardation.

It is noted that 50% of children inherit the disease, and that women with RTH frequently miscarry fetuses or deliver low-birth-weight infants whose genotypes are wild type.