

# Thyroid Stimulating Immunoglobulins (TSI) Assay

## TO CONFIRM A DIAGNOSIS OF GRAVES DISEASE

### Disease Overview

Hyperthyroidism is a medical condition that is defined by overproduction of thyroid hormone. Hyperthyroidism is most commonly caused by autoantibodies to the thyroid stimulating hormone receptor (TSHR), a condition known as Graves disease, but can also be caused by thyroid nodules, thyroid tumors, or excessive administration of thyroid hormone.

### Pathophysiology

- TSHR is a G-protein coupled receptor that has structural homology with other glycoprotein hormone receptors.<sup>1</sup>
- Binding of TSH to the TSHR activates both the adenylate cyclase/cyclic adenosine monophosphate (cAMP) and the phospholipase C signaling pathways.<sup>1</sup>
- Adenylate cyclase and cAMP regulate I<sup>-</sup> uptake and transcription of thyroglobulin (Tg), thyroid peroxidase (TPO), and sodium/iodide symporter (NIS), while the phospholipase C pathway regulates I<sup>-</sup> efflux, H<sub>2</sub>O<sub>2</sub> production, and Tg iodination.<sup>1</sup>
- Increased cAMP levels have been used as a biomarker for physiological conditions that cause stimulation of the TSHR, such as thyroid stimulating immunoglobulins (TSI).
- Autoantibodies to the TSHR may be stimulating, blocking, or neutral.<sup>2</sup> Stimulating antibodies mimic the action of TSH and cause hyperthyroidism (Graves disease), whereas blocking antibodies block the binding of TSH and cause hypothyroidism.<sup>2</sup> Both stimulating and blocking antibodies usually occur together in any given patient and may change over time.<sup>3</sup>

### Epidemiology

- Prevalence of hyperthyroidism is approximately 2–3 percent of the general population.
- The majority of hyperthyroidism, 60–80 percent, occurs as a consequence of Graves disease.

### Indications for Ordering

Subsequent to a diagnosis of hyperthyroidism (below normal TSH levels or elevated free T<sub>4</sub> levels), this assay would be used to confirm TSI involvement.

### Methodology

- ARUP Laboratories has recently developed an ectopically expressing TSHR cell line for use in this assay. These cells also fuse the alpha subunit of the appropriate G protein (GNAS) to the TSHR to yield greater sensitivity. In addition, the method using the improved cells demonstrates better precision compared to the previously offered TSI assay.

- Ectopically expressing TSHR-GNAS cells are seeded into microplates, grown for two days, then incubated with a dilution of patient serum and subsequently lysed.
- Levels of cAMP are measured using a commercially available kit (DiscoverX<sup>®</sup>).
- Results are reported as a percent of normal control.

### Interpretation

- Using a cutoff of 114 percent of normal yields an 82.1 percent sensitivity and a 98.4 percent specificity for serum samples considered to be autoimmune hyperthyroid vs. normal serum.
- Results between 114 percent and 127 percent of normal are considered indeterminate, as serum samples from both autoimmune and nonautoimmune hyperthyroid patients can yield results in this range.
- Results that are 128 percent of normal and above are considered positive for the presence of TSI.

### Limitations

- The TSHR expressed in the assay cells is the native form and will bind to all anti-TSHR antibodies (i.e., stimulating, blocking, and neutral). Consequently, even though a serum sample contains stimulating antibodies, the presence of blocking antibodies may obscure the results from the stimulating antibodies.<sup>2,4-5</sup> However, this net response most closely represents the physiological one.
- Serum levels of TSH at or above 76mU/L are known to stimulate cAMP levels in the assay and accentuate stimulation as a result of TSI.

### Related Tests

- Thyroid Stimulating Hormone Receptor Antibody (TRAb) (2002734)
- Thyroid Peroxidase (TPO) Antibody (0050075)
- Thyroglobulin Antibody (0050105)

## References

1. De La Vieja A, et al. Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. *Physiol Rev* 2000;80:1083–105.
2. Michalek K, et al. TSH receptor autoantibodies. *Autoimmun Rev* 2009;9:113–6.
3. Demers LM and Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol* 2003;58:138–40.
4. Evans M, et al. Monoclonal autoantibodies to the TSH receptor, one with stimulating activity and one with blocking activity, obtained from the same blood sample. *Clin Endocrinol* 2010;73:404–12.
5. Kohn LD and Harii N. Thyrotropin receptor autoantibodies (TSHRabs): epitopes, origins, and clinical significance. *Autoimmunity* 2003;36:331–7.

## Test Information

0099430

### Thyroid Stimulating Immunoglobulin

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

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