TSHR Gene

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thyroid stimulating hormone receptor

genes

1. Normal Function

The *TSHR* gene provides instructions for making a protein, known as a receptor, that attaches (binds) to a hormone called thyroid stimulating hormone (TSH). This receptor spans the membrane of certain cells (called follicular cells) in the thyroid gland, a butterfly-shaped tissue in the lower neck. A large part of the receptor sits on the outer surface of the cell (extracellular), and a small portion is retained inside the cell (intracellular). Thyroid stimulating hormone binds to the extracellular portion of the receptor like a key fitting into a lock, activating a series of reactions that control development of the thyroid gland and its functions. Among its functions, the thyroid gland produces iodine-containing hormones (thyroid hormones), which help regulate growth, brain development, and the rate of chemical reactions in the body (metabolism).

2. Health Conditions Related to Genetic Changes

2.1. Congenital Hypothyroidism

Several *TSHR* gene mutations have been identified in people with congenital hypothyroidism, a condition characterized by abnormally low levels of thyroid hormones starting from birth. *TSHR* gene mutations change one of the protein building blocks (amino acids) used to make the thyroid stimulating hormone receptor. Some of these mutations prevent the receptor from properly spanning the membrane, and in some cases the entire receptor is retained inside the cell. As a result, the receptor cannot interact properly with thyroid stimulating hormone. Other mutations impair the receptor's ability to bind with thyroid stimulating hormone, even though the receptor correctly spans the membrane.

Without properly functioning receptors, thyroid hormone production is not stimulated. The body tries to correct the blocked stimulation by producing more thyroid stimulating hormone. In some cases, the increased levels of thyroid stimulating hormone compensate for receptors with minor defects, and the thyroid functions normally. In other cases, thyroid hormone levels remain low, causing mild to severe congenital hypothyroidism. Impaired thyroid stimulating hormone receptors may also disrupt thyroid development, and as a result, the gland is smaller than

normal. Cases of congenital hypothyroidism caused by *TSHR* gene mutations are sometimes classified as thyroid dysgenesis because development of the thyroid gland is impaired.

2.2. Graves Disease

2.3. Other Disorders

TSHR gene mutations can cause disorders associated with hyperthyroidism. These mutations change one of the amino acids used to make the thyroid stimulating hormone receptor. As a result, the receptor is continuously activated and overstimulates the production of thyroid hormones. *TSHR* gene mutations can lead to an enlarged thyroid gland (goiter) and symptoms of hyperthyroidism, such as a rapid heartbeat. Hyperthyroidism that is present from birth is called nonautoimmune congenital hyperthyroidism (or sporadic toxic thyroid hyperplasia). Onset of hyperthyroidism that begins in childhood or adulthood is known as nonautoimmune autosomal dominant hyperthyroidism (or hereditary toxic thyroid hyperplasia).

2.4. Tumors

Sometimes gene mutations are acquired during a person's lifetime and are present only in certain cells. This type of mutation is called somatic, and it is not inherited. Somatic mutations in the *TSHR* gene have been identified in thyroid tumors. These mutations are found only in the tumor cells.

Somatic *TSHR* gene mutations have been reported in many cases of noncancerous (benign) thyroid tumors, called nodules or adenomas, which are associated with an overactive thyroid (hyperthyroidism). Somatic mutations have also been identified in some cancerous (malignant) thyroid tumors known as thyroid carcinomas. As a result of these somatic mutations, the thyroid stimulating hormone receptor is continuously activated, which could prompt the overgrowth of thyroid cells.

3. Other Names for This Gene

- LGR3
- thyrotropin receptor
- TSH Receptors
- TSHR_HUMAN

References

1. Abramowicz MJ, Duprez L, Parma J, Vassart G, Heinrichs C. Familial congenital hypothyroidism due to inactivating mutation of the thyrotropin receptor causingprofound hypoplasia of the thyroid gland. J Clin Invest. 1997 Jun15;99(12):3018-24.
2. Baş VN, Cangul H, Agladioglu SY, Kendall M, Cetinkaya S, Maher ER, Aycan Z.Mild and severe congenital primary hypothyroidism in two patients by thyrotropin receptor (TSHR) gene mutation. J Pediatr Endocrinol Metab. 2012;25(11-12):1153-6.doi: 10.1515/jpem-2012-0211.
3. Biebermann H, Schöneberg T, Krude H, Schultz G, Gudermann T, Grüters A.Mutations of the human thyrotropin receptor gene causing thyroid hypoplasia andpersistent congenital hypothyroidism. J Clin Endocrinol Metab. 1997Oct;82(10):3471-80.
4. Cangul H, Aycan Z, Saglam H, Forman JR, Cetinkaya S, Tarim O, Bober E, CesurY, Kurtoglu S, Darendeliler F, Bas V, Eren E, Demir K, Kiraz A, Aydin BK,Karthikeyan A, Kendall M, Boelaert K, Shaw NJ, Kirk J, Högler W, Barrett TG,Maher ER. TSHR is the main causative locus in autosomal recessively inheritedthyroid dysgenesis. J Pediatr Endocrinol Metab. 2012;25(5-6):419-26.
5. Cangul H, Saglam H, Saglam Y, Eren E, Dogan D, Kendall M, Tarim O, Maher ER,Barrett TG. An essential splice site mutation (c.317+1G>A) in the TSHR gene leadsto severe thyroid dysgenesis. J Pediatr Endocrinol Metab. 2014Sep;27(9-10):1021-5. doi: 10.1515/jpem-2014-0048.
6. Castro I, Lima L, Seoane R, Lado-Abeal J. Identification and functionalcharacterization of two novel activating thyrotropin receptor mutants in toxicthyroid follicular adenomas. Thyroid. 2009 Jun;19(6):645-9. doi:10.1089/thy.2009.0002.
7. Davies TF, Ando T, Lin RY, Tomer Y, Latif R. Thyrotropin receptor-associateddiseases: from adenomata to Graves disease. J Clin Invest. 2005Aug;115(8):1972-83. Review.
8. Gozu H, Avsar M, Bircan R, Sahin S, Ahiskanali R, Gulluoglu B, Deyneli O, OnesT, Narin Y, Akalin S, Cirakoglu B. Does a Leu 512 Arg thyrotropin receptormutation cause an autonomously functioning papillary carcinoma? Thyroid. 2004Nov;14(11):975-80.
9. Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J Med Genet.2005 May;42(5):379-89. Review.
10. Refetoff S. Resistance to thyrotropin. J Endocrinol Invest. 2003Aug;26(8):770-9. Review.
11. Russo D, Costante G, Bruno R, Sponziello M, Tamburrano G, Dima M, Sacco R,Giacomelli L, Durante C, Filetti S. TSH receptor extracellular region mutationsin thyroid functioning nodules: further evidence for the functional role of this region in the receptor activation. Endocrine. 2011 Dec;40(3):492-4. doi:10.1007/s12020-011-9525-7.