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Gene Section
Review

TSHR (thyroid stimulating hormone receptor)

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Identity

Other names: CHNG1; LGR3; MGC75129; TSH-R; hTSHR-I

HGNC (Hugo): TSHR

Location: 14q31.1

Local order: Telomeric to NMNATP (nicotinamide nucleotide adenylyltransferase pseudogene); centromeric to GTF2A1 (general transcription factor IIA, 1, 19/37 kDa).

Note: Belongs to the rhodopsin-like G-protein coupled receptor superfamily (GPCR) and leucine-rich repeat containing GPCR family (LRG).

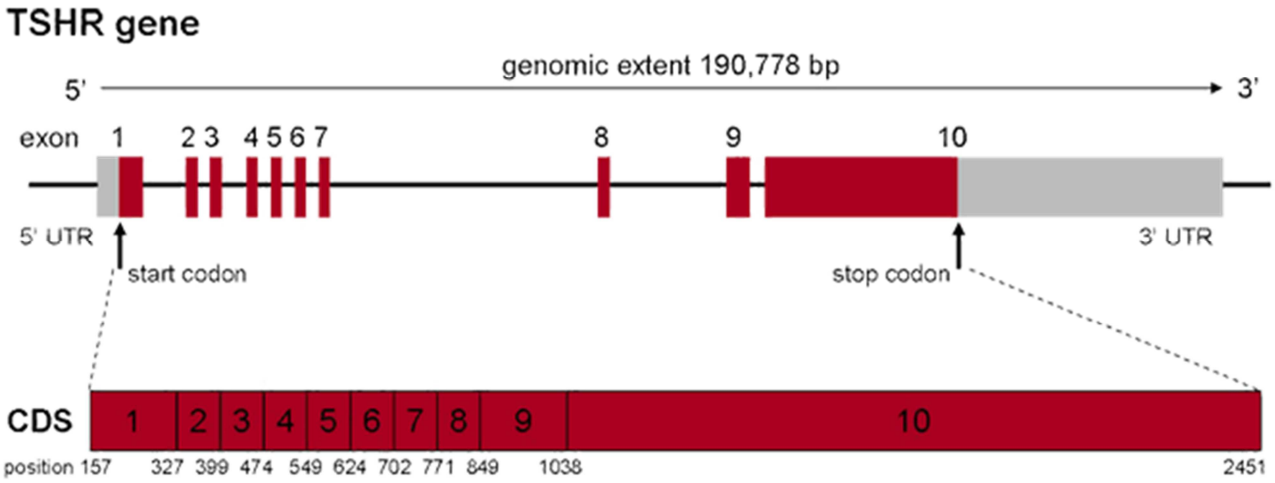
DNA/RNA

Description

Spans 190,778 bp, contains 10 exons. Kakinuma and Nagayama (2002) identified 13 exons, but most findings relate to the 10-exon pattern.

Transcription

Regulated by a TATA-less promoter containing binding sites for GABP, TTF1, CREB, ATF2, TR/RXR, SSBP and ICER.
Major transcript (TSHR isoform 1 precursor, NM_000369.2) encoded by 10 exons, transcript length 4410 bp, 2295 bp ORF, ~100 bp 5' UTR and



Structure of the TSHR gene and coding sequence (CDS). Boxes represent exons numbered 1 to 10 and proportional to length, red representing the coding sequence, grey representing untranslated regions (UTR); the horizontal line joining exons represents introns, shrunk to minimal length. Positions below the CDS are numbered relative to the transcription start.

1.6 kb 3' UTR; the coding region spans positions 157-2451 bp, with a signal peptide at 157-216 bp, mature peptide from 217 to 2448 bp, poly-A signal at 4371-4376. Encodes the canonical protein, 764 aa.
NCBI Entrez Gene describes two alternatively spliced variants, TSHR isoform 2 precursor (NM_001018036.1) and TSHR isoform 3 precursor (NM_001142626.1). Additional transcripts are possible; according to NCBI/Aceview, there are 10 alternatively spliced variants, based upon cDNAs deposited in GenBank derived from normal and neoplastic human tissues and cell lines. There are 3 probable alternative promoters, 6 non overlapping alternative last exons and 6 validated alternative polyadenylation sites. The mRNAs appear to differ by truncation of the 5' end, truncation of the 3' end, overlapping exons with different boundaries, alternative splicing or retention of 2 introns. There is no evidence for protein expression of splice variants.

Transcription variant *	Exons in CDS	mRNA	Predicted protein	Protein evidence
a; *isoform 1 precursor*	10	4570 bp	764 aa	yes
b; *isoform 3 precursor*	9	1089 bp	274 aa	no
c; *isoform 2 precursor*	9	1281 bp	253 aa	no
d	8	1184 bp	231 aa	no
e	9	901 bp	229 aa	no
f	2	699 bp	167 aa	no
g	6	1018 bp	160 aa	no
h	6	445 bp	141 aa	no
i	3	561 bp	106 aa	no

Table 1: TSHR transcript variants. *Letters refer to NCBI Aceview nomenclature as of April 2007; names in italics refer to NCBI Entrez Gene nomenclature.

Protein

Description

G-protein coupled receptor (GPCR), 764 aa membrane glycoprotein. Predicted MW 84.5 kDa; apparent MW of glycosylated protein 95-120 kDa.
Consists of two subunits:
(i) A or α subunit: encoded by exons 1-8 of TSHR gene; glycosylated extracellular ectodomain containing 9 leucine-rich repeats (LRR) and the N-terminus; binds TSH and other ligands (hCG and LH),
(ii) B or β subunit: encoded by exons 9-10 of TSHR gene; consists of 7 trans-membrane domains (TMD) connected by extracellular loops (important for basal and activated function) and intracellular loops (important for G protein coupling), and an intracellular C terminus.
A and B subunits are produced by posttranslational proteolytic cleavage of single-chain TSHR at the cell surface, with removal of a 50 aa peptide, and subsequent joining of A and B subunits by disulfide bridges. The B subunit is thought to be constitutionally active, and interaction with the A subunit ectodomain maintains the B subunit in an inactive state.

Expression

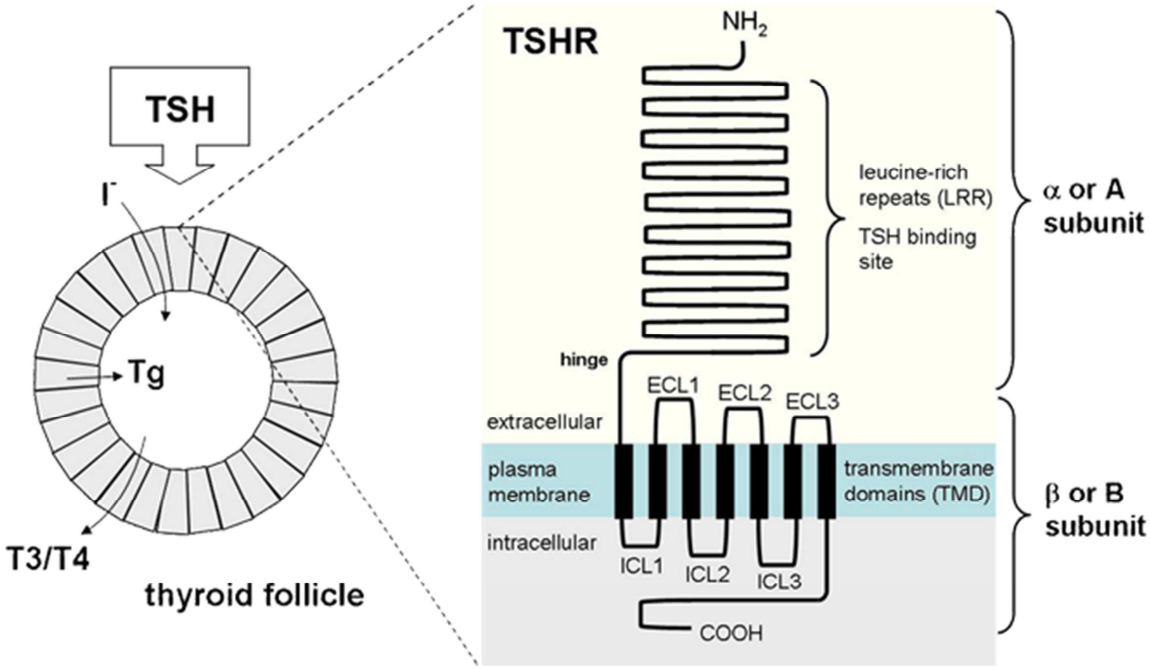
Thyroid follicular epithelial cells; to a lesser degree in thymus, pituitary gland, lymphocytes, testis, retro-ocular fibroblasts, adipocytes, brain, heart and kidney.

Localisation

Plasma membrane.

Function

Regulation of thyroid metabolism.
TSHR is the receptor for thyrotropin (thyroid stimulating hormone or TSH), a member of the glycoprotein hormone family. TSH is released by the anterior pituitary gland and is the main regulator of thyroid gland growth and development. Binding of TSH to TSHR stimulates thyroid epithelial cell proliferation, and regulates the expression of differentiation markers such as thyroglobulin, thyroperoxidase and the sodium iodide symporter (NIS), necessary for the synthesis of thyroid hormones.
TSHR is coupled to heterotrimetric G proteins, regulatory proteins associated with the inner surface of the plasma membrane. Binding of TSH to TSHR causes a conformational change in TSHR, provoking the GTP-dependent dissociation of the Gα subunit from GβGγ dimers. Gα activates distinct signal transduction pathways to stimulate gene transcription and cell proliferation.
Two G protein-dependent pathways are activated by TSHR:
(i) Gαs activates adenylate cyclase to increase cAMP levels; cAMP activates protein kinase A (PKA) causing translocation of its catalytic subunit to the nucleus; PKA phosphorylates, among others, the transcription factor CREB thereby increasing its transcriptional activity.
(ii) Gαq activates phospholipase C to increase phosphoinositide turnover, releasing inositol triphosphate (IP3) and diacylglycerol (DAG); DAG activates protein kinase C, which promotes proliferation via the RAF/MEK/ERK pathway.
Complex cross-talk occurs between these pathways and other signaling pathways including the PI3/Akt, PKC/NFkB and JAK/STAT pathways (for reviews see García-Jiménez and Santisteban (2007) and Latif et al. (2009)).



TSHR localization and structure. Left, thyroid follicle where the TSH-stimulated synthesis of thyroid hormone (T3 and T4) occurs following iodide uptake and organification into thyroglobulin (Tg). Right, TSHR protein structure, showing the A subunit composed of leucine-rich repeats (LRR) and the N-terminus, and the B subunit composed of 7 transmembrane domains (TMD), the intracellular and extracellular loops (ICL and ECL respectively) and the C-terminus.

TSHR is also activated by other members of the glycoprotein hormone family, including human chorionic gonadotropin (hCG), luteinizing hormone (LH) and thyrostimulin (a heterodimer composed of A2 and B5 glycoprotein hormone subunits).

Homology

LHCGR (Luteinizing Hormone, Choriogonadotropin receptor) 51% amino acid identity; FSHR (Follicle Stimulating Hormone receptor) 48% amino acid identity.

Mutations

Note

Over 90 naturally occurring TSHR mutations have been identified, and are catalogued in the GRIS database and TSHR mutation database. Mutations are gain-of-function resulting in constitutional activation of the receptor independently of TSH, or loss-of-function resulting in loss of TSH sensitivity.

Polymorphisms: Coding missense SNPs: Pro27Thr, Glu34Lys, Asp36His, Pro52Thr, Thr574Ser, Tyr601His, Val721Phe, Glu727Asp, Asn 744Lys.

Germinal

Germinal TSHR mutations include missense mutations, nonsense mutations, insertion/deletions, and exon skipping due to alternative splicing. Germinal activating mutations are associated with hereditary or sporadic congenital hyperthyroidism, whereas germinal inactivating mutations are a cause of TSH resistance associated with congenital hypothyroidism and euthyroid hyperthyrotropinaemia.

Somatic

Somatic TSHR mutations include missense mutations and in-frame deletions. Activating mutations have been identified in hyperfunctioning thyroid adenoma and toxic multinodular goiter; few cases are associated with thyroid carcinoma. No somatic inactivating mutations have been described so far.

Implicated in

Thyroid adenoma

Disease

Somatic activating TSHR mutations are a major cause of hyperfunctioning thyroid adenomas, benign neoplasms of thyroid follicular cells:

- 10-80% of hyperfunctioning or 'hot' adenomas (i.e. ademomas with active radioiodide uptake and thyroid hormone synthesis) harbor somatic activating mutations (Parma et al., 1993; Russo et al., 1996; Führer et al., 2007). The highly variable frequency of mutations may reflect geographic differences.
- Activating mutations are largely located in exon 10 encoding the TSHR β-subunit, and are particularly frequent in the sixth transmembrane segment (TM6) important for coupling to G proteins.
- Mutations result in the constitutive activation of adenylate cyclase, stimulating thyrocyte proliferation and thyroid hormone synthesis. As a consequence, hyperfunctioning nodules provoke hyperthyroidism and thyrotoxicosis.

GERMINAL ACTIVATING MUTATIONS					
Familial gestational thyrotoxicosis (excessive response to hCG)					
Arg183Lys	α LRR6				
Hereditary or sporadic congenital hyperthyroidism					
Ser281Asn	α hinge	Leu512Gln	βTM3	Leu629Phe	βTM6
Ala428Val	βTM1	Arg528His	βICL2	Phe631Ser	βTM6
Gly431Ser	βTM1	Ile568Val	βECL2	Thr632Ile	βTM6
Met453Thr	βTM2	Val597Leu/Phe	βTM5	Pro639Ser	βTM6
Met463Val	βTM2	Asp617Tyr	βICL3	Asn650Tyr	βECL3
Ser505Arg/Asn	βTM3	Ala623Val	βICL3	Asn670Ser	βTM7
Val509Ala	βTM3	Met626Iso	βTM6	Cys672Thr	βTM7
GERMINAL INACTIVATING MUTATIONS					
Hereditary TSH resistance leading to congenital hypothyroidism and euthyroid hyperthyrotropinaemia					
Pro27Thr	α N-tail	Gln324Stop	α hinge	Gly498Ser	βTM3
Glu34Lys	α N-tail	Cys390Trp	α hinge	Phe525Leu	βICL2
Cys41Ser	α N-tail	Asp403Asn	α hinge	Met527Thr	βICL2
Arg46Pro	α N-tail	Indel 406-420	α hinge	Trp546Stop	βTM4
Arg109Gln	α LRR3	Asp410Asn	α hinge	Ala553Thr	βTM4
del 156-182	α LRR5-6	Tyr444Stop	βICL1	Ala593Val	βTM5
Pro162Ala	α LRR5	Arg450His	βICL1	Cys600Arg	βTM5
Ile167Asp	α LRR5	Leu467Pro	βTM2	Arg609Stop	βICL3
Gly245Ser	α LRR8	Thr477Ile	βECL1	Leu653Val	βECL3
Leu252Pro	α LRR9	Try488Arg	βECL1	Thr655Stop	βECL3
Arg310Cys	α hinge				
SOMATIC ACTIVATING MUTATIONS					
Hyperfunctioning thyroid adenomas and toxic multinodular goitre					
Ser281Asn/Ile/Thr	α hinge	Asp619Gly	βTM6	Iso635Val	βTM6
del 403	α hinge	Thr620Ile	βTM6	Pro639Ser	βTM6
Ser425Ile	βTM1	Ala623Ile/Phe/Ser/Val	βTM6	Ile640Lys	βTM6
Met453Thr	βTM2	Met626Ile	βTM6	Ala647Val	βTM6
Ile486Met/Phe/Asn	βECL1	Ala627Val	βTM6	Val656Phe	βECL3
Leu512Arg/Gln	βTM3	Leu629Phe	βTM6	Del 658-661	βECL3/TM7
Ile568Thr	βECL2	Ile630Leu/Met	βTM6	Phe666Leu	βTM7
Tyr601Asn	βTM5	Phe631Cys/Ile/Leu/Val	βTM6	Ile691Phe	β C-tail
Ile606Met	βICL3	Thr632Ile/Ala	βTM6	Ala703Gly	β C-tail
del 613-621	βICL3	Asp633Ala/Glu/His/Tyr	βTM6	Gln720Glu	β C-tail
Thyroid carcinoma					
Phe197Ile*	α LRR6	Thr620Iso	βICL3	Asp633His	βTM6
Asp219Glu*	α LRR7	Ala623Ser	βICL3	Asp633Tyr	βTM6
Met453Thr	βTM2	Phe631Ile	βTM6	Leu677Val	βTM7
Ile486Phe	βECL1	Thr632Ala	βTM6	Asn715Asp*	β C-tail
Leu512Arg	βTM3	Thr632Ile	βTM6	Lys723Met*	β C-tail

Table 2: TSHR mutations in thyroid disease. Mutations are listed in terms of the amino acid residues altered and their respective location (α = A subunit, β = B subunit, TM = transmembrane domain, ICL = intracellular loop, ECL = extracellular loop, LRR = leucine-rich repeat, hinge = domain connecting leucine-rich repeats to first transmembrane domain).
Note: * unknown functional status of mutations (Ohno et al., 1995).

- Nonfunctioning or 'cold' adenomas (i.e. not able to accumulate radioiodide or synthesize thyroid hormones) do not harbor TSHR mutations.

Toxic multinodular goiter (Plummer's disease)

Disease

Somatic activating TSHR mutations are a major cause

of Toxic Multinodular Goiter (TMNG), a hyperplastic thyroid enlargement with multiple bilateral nodules:
- 70-80% of hyperfunctioning nodules of TMNG harbor somatic activating mutations, many of which are shared with hyperfunctioning thyroid adenoma suggesting a common pathogenic event (Tonacchera et al., 1998; Tonacchera et al., 2000).
- Different hyperfunctioning nodules within a goiter harbor may distinct TSHR activating mutations, confirming the polyclonal etiology of TMNG. In contrast, nonfunctioning nodules within the same goiter do not harbor mutations.
- TMNG is most common in iodine-deficient areas, and this may reflect the increased mutagenic load associated with chronic TSH stimulation and thyrocyte proliferation.
- A germline polymorphism of codon 727 of TSHR was reported to be associated with TMNG (Gabriel et al., 1999), however a subsequent study failed to substantiate this finding in a European population (Mulhberg et al., 2000).

Thyroid carcinoma

Prognosis

TSHR mRNA in thyroid tumours: Reduced or absent TSHR mRNA in thyroid tumours is a negative prognostic marker, indicative of reduced effectiveness of radioiodine therapy. TSHR expression in thyroid carcinoma correlates with the state of differentiation of tumours, with loss of differentiation resulting in a loss of mRNA expression. Thus, well-differentiated carcinomas (papillary and follicular) show variable TSHR mRNA levels ranging from normal to markedly reduced, whereas undifferentiated anaplastic carcinoma shows absent TSHR mRNA (Brabant et al., 2001; Brönnegård et al., 1994; Shiels et al., 1999). TSHR regulates the thyroid expression of the iodide transporter NIS, and decreased TSHR expression impairs the iodine-concentrating capacity of thyroid tumours.

Circulating TSHR mRNA: TSHR mRNA in peripheral blood has been suggested as a potential molecular marker of circulating thyroid carcinoma cells to aid in the differential diagnosis of malignant and benign thyroid disease preoperatively, and to detect residual, recurrent or metastatic thyroid cancer (Barzon et al., 2004; Chinnappa et al., 2004).

TSHR promoter methylation: TSHR promoter methylation may be a marker for malignancy in thyroid carcinoma (Xing et al., 2003).

Oncogenesis

TSHR mutations: Mutagenic screening of thyroid carcinomas reveals a low incidence of somatic TSHR mutations ranging from 0-22%, suggesting a limited role for TSHR mutations in the pathogenesis of thyroid carcinoma (Matsuo et al., 1993; Russo et al., 1995; Ohno et al., 1995; Spambalg et al., 1996; Esapa et al., 1997; Cetani et al., 1999).

In most cases, somatic activating TSHR mutations occur in hyperfunctioning thyroid carcinomas:
- Met453Thr in papillary carcinoma with hyperfunctioning thyroid nodule (Mirescu et al., 2000).
- Ile486Phe in an autonomously functioning follicular carcinoma presenting a 'hot' nodule causing hyperthyroidism (Camacho et al., 2000).
- Leu512Arg in autonomously functioning papillary carcinoma with 'hot' nodule (Gozu et al., 2004).
- Thr620Ile in follicular carcinoma presenting as autonomous functioning thyroid nodule (Niepomniszcze et al., 2006).
- Ala623Ser in papillary carcinoma with high constitutive adenylate cyclase activity (Russo et al., 1995).
- Phe631Ile and Asp633Tyr in toxic metastasizing follicular thyroid carcinoma; no TSHR mutations in non-functioning lung metastases (Führer et al., 2003).
- Thr632Ile in thyroid hormone-producing follicular carcinoma (Spambalg et al., 1996).
- Asp633His in aggressive insular thyroid carcinoma (poorly-differentiated carcinoma) presenting as an autonomously functioning thyroid nodule and causing severe thyrotoxicosis; TSHR mutation also present in lymph node metastasis (Russo et al., 1997).
- Leu677Val in autonomously functioning Hürthle cell thyroid carcinoma causing thyrotoxicosis (Russo et al., 1999).

Rare cases of TSHR mutations in nonfunctioning thyroid carcinoma have also been reported:
- Thr632Ala in nonfunctioning follicular carcinoma (Spambalg et al., 1996).
- Ala623Ser activating mutation in papillary carcinoma with 'cold' nodule, in patient with past history of Graves' disease (De Cross et al., 2008).

The role of activating TSHR mutations in neoplastic transformation is unclear. Although TSHR activation stimulates thyrocyte proliferation, hyperfunctioning nodules (adenoma or toxic multinodular goiter) are rarely malignant, suggesting that constitutive activation of the cAMP cascade alone is insufficient for the malignant transformation of thyroid follicular cells.

Epigenetics: The TSHR gene promoter is frequently hypermethylated in thyroid carcinoma, with preferential methylation in undifferentiated carcinoma (Xing et al., 2003; Schagdarsurengin et al., 2006). In contrast, TSHR gene promoter is unmethylated in the normal thyroid and in benign tumours (thyroid adenoma). Hypermethylation results in TSHR gene silencing and reduced TSHR expression in some malignant thyroid tumours. In thyroid cancer cell lines, demethylating agents partially restore TSHR expression.

Congenital nongoitrous hypothyroidism-1 (CHNG1)

Disease

Germline inactivation TSHR mutations are a cause of hereditary congenital nongoitrous hypothyroidism.

Inactivating mutations result in variable degrees of TSH resistance, with clinical consequences ranging from euthyroid hyperthyrotropinemia to mild or severe hypothyroidism. CHNG1 is inherited in an autosomal recessive manner, manifesting in homozygotes or compound heterozygotes. However, subclinical hypothyroidism may also manifest in heterozygotes, suggesting autosomal dominant inheritance.

Hereditary nonautoimmune hyperthyroidism

Disease

Germline activating TSHR mutations are a cause of hereditary nonautoimmune congenital hyperthyroidism (autosomal dominant inheritance). Sporadic cases of nonautoimmune congenital hyperthyroidism result from de novo germinal mutations. Activating germline mutations result in constitutive activation of the cAMP pathway in thyrocytes. Mutations are predominantly in exon 10 encoding the transmembrane domains. One activating mutation (Arg183Lys) increases sensitivity towards hCG and manifests in women during pregnancy (familial gestational hyperthyroidism).

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