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Gene Section
Review

LHCGR (luteinizing hormone/choriogonadotropin receptor)

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Identity

Other names: HHG, LCGR, LGR2, LH/CGR, LHR, LHRHR, LSH-R, ULG5

HGNC (Hugo): LHCGR

Location: 2p16.3

Note: The LHR belongs to the glycoprotein hormone receptor subfamily of the G protein-coupled receptor family (GPCR), with leucine rich repeat motifs, (Minegishi et al., 1990; Jia et al., 1991).

DNA/RNA

Description

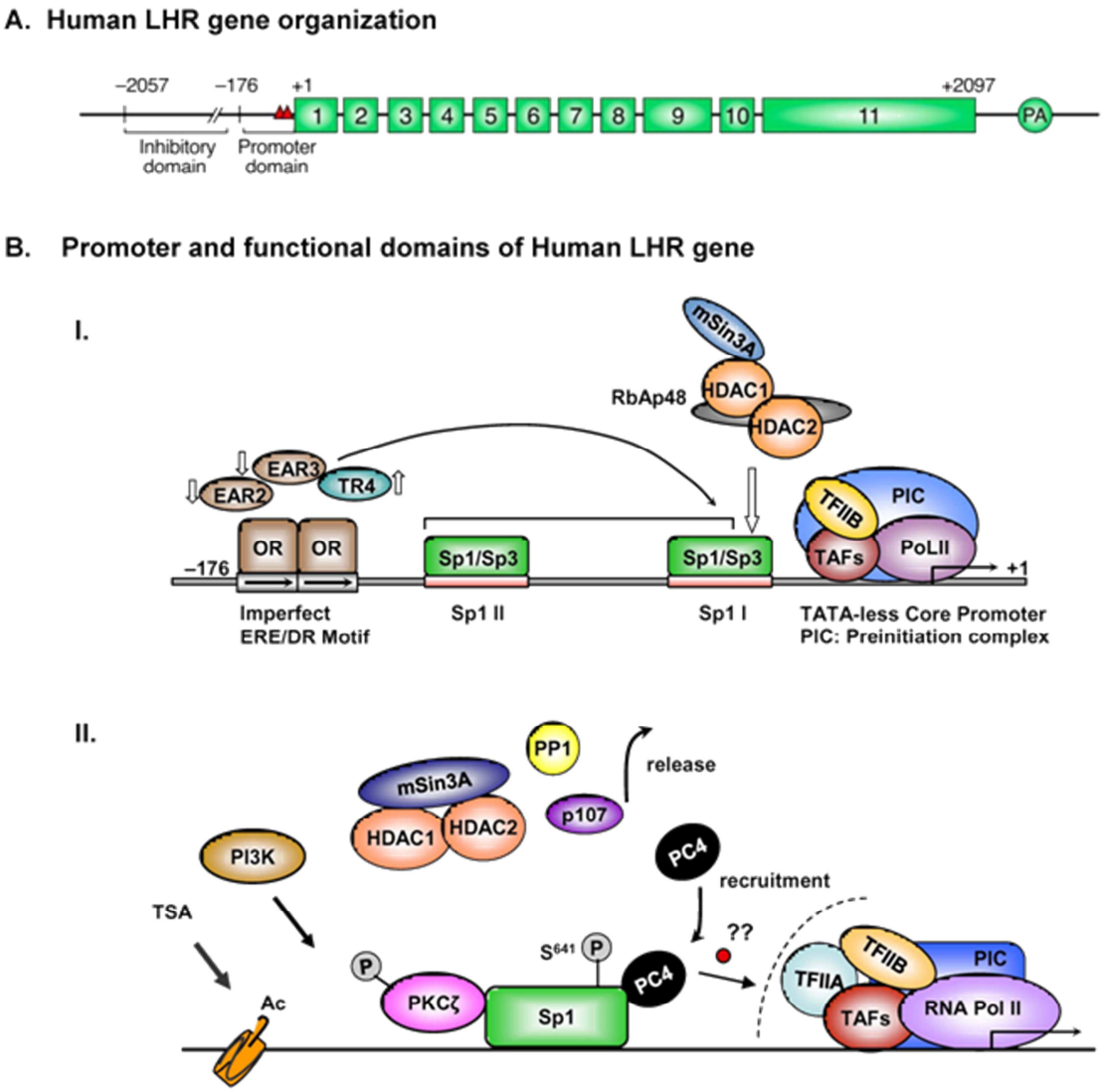
Human LHR gene is encoded by a single copy gene. The human LHR gene (> 80 Kb) consists of 11 coding exons separated by 10 introns (Atger et al., 1995). At least seven alternatively spliced variants of the hLHR were reported (deletion of exon 8 or 9 or 10, or partial deletion of exon 11 combined with or without deletion of exon 9, and insertion of exon 6A) (Laue et al., 1996; Gromoll et al., 2000; Madhra et al., 2004; Kossack et al., 2008).

Transcription

Multiple LHR mRNA transcriptional start sites are located within the -176 bp TATA-less 5' flanking promoter domain (Geng et al., 1999; Dufau and Tsai-Morris, 2007).
Additional upstream transcriptional start sites (> -176 bp) were identified in human testicular mRNA and human choriocarcinoma JAR cell. EREhs (-161 to -171 bp) and upstream sequences (-177 to -2056 bp) are inhibitory.
Activation of the human LHR promoter through Sp1 and Sp3 factors at Sp1 sites is negatively regulated by cross-talk among the transcription factors EAR3/COUP-TFI, Sp1, TFIIB, and independently by histone deacetylase-mSin3A co-repressor complex, p107 repressor at the Sp1 I site (review: Zhang and Dufau, 2004; Dufau and Tsai-Morris, 2007; Dufau et al., 2010).

Pseudogene

No known pseudogenes.



A: Human LHR gene organization. B: 5' flanking regulatory domains and the 176 bp promoter with its functional domains (Geng et al., 1999; Dufau and Tsai-Morris, 2007). B-I Promoter associated transcription factor Sp1 bound to cognate DNA sites, Sp1-I and Sp1-II, constitutively (Geng et al., 1999). Co-repressor complex (HDAC/mSin3A) associates with Sp1-I (Zhang et al., 2000; Zhang et al., 2001; Zhang et al., 2002; Zhang et al., 2003; Zhang et al., 2004). Upstream inhibitory domain (ERE-DR Motif) that bind orphan receptors EAR2 and EAR3, inhibitory and TR4, stimulatory (arrows). B-II, Histone deacetylase inhibitor (TSA)-induced LHR transcriptional activation through chromatin changes cause release of cell specific phosphatases (PP1, PP2A) (Zhang et al 2008). This permits phosphorylation of Sp1 at S641 via PI3K/PKCzeta (Zhang, 2006), and the release of repressor p107 and corepressor HDAC/mSin3A (Zhang et al., 2008; Dufau et al., 2010). Recruitment of Positive Coactivator4 PC4 induced by changes in chromatin structure is required for transcriptional activation that follows recruitment of TFIIB and Pol II (Liao et al., 2008; Liao et al., 2011). PC4 might function as a linker to bridge Sp1 to PIC through a not-yet identified protein(s) (red circle). Triangle: multiple transcriptional start sites. PA: polyadenylation sites. Open arrow, up: activation, down: inhibition. ERE: estrogen response element. DR: direct repeat. OR: orphan receptor. Sp1 I, Sp1 II: Sp1 sites. PIC: preinitiation complex.

Protein

Description

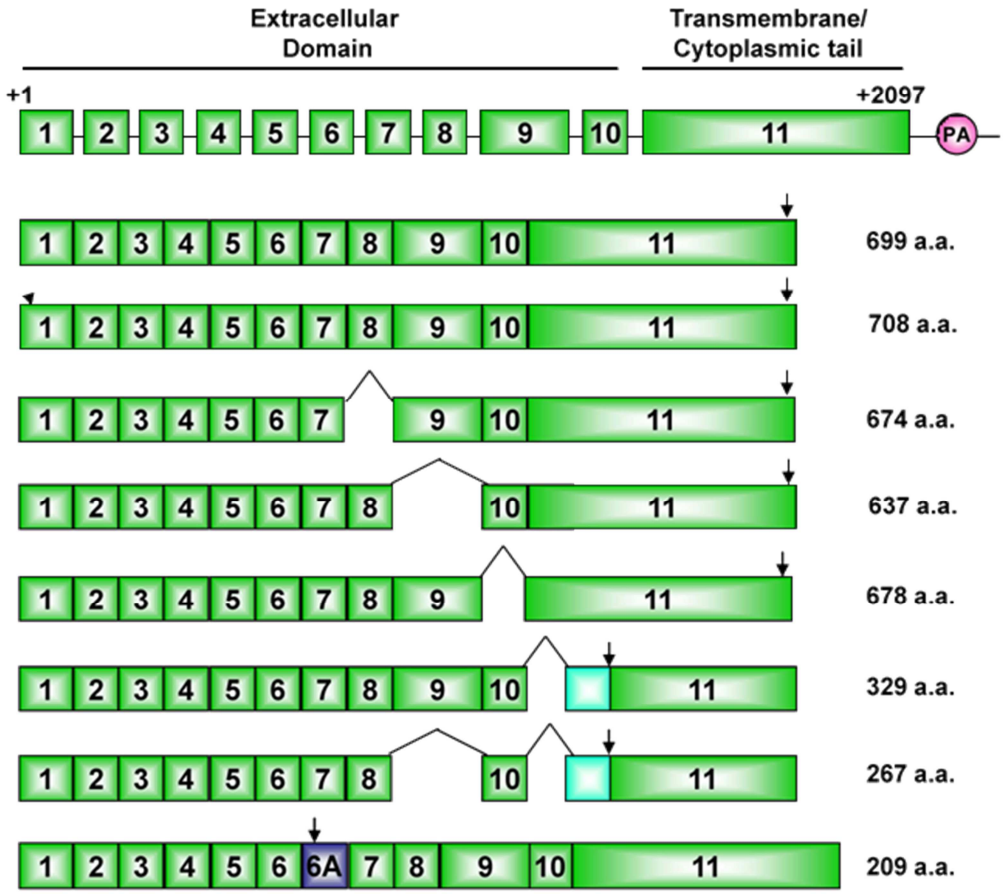
The cDNA for the human LHR encodes 699 amino acids (Minegishi et al., 1990; Jia et al., 1991).

The receptor is composed of two functional units: the extracellular hormone-binding domain and the seven-membrane transmembrane/cytoplasmic module, which is the anchoring unit that transduces the signal initiated in the extracellular domain and couples to G proteins. The large extracellular domain binds LH and hCG with high affinity.

Expression

LHR is predominantly expressed in gonads.

The LHR has also been identified in several non-gonadal tissues (review, Rao, 2001), including human nonpregnant uterus, placenta (Reshef et al., 1990), fallopian tubes (Lei et al., 1993), uterine vessels, (Toth et al., 1994), umbilical cord (Rao et al., 1993), brain (Lei et al., 1993), breast (Meduri et al., 1997; Carlson et al., 2004), and adrenal gland (Lehmann et al., 1975).



Schematic representation of human LHR variants, as deduced from the alternative splicing of the transcripts. Arrow-head: LQ insertion. Exon 6A resides in intron 6, transcripts are terminated by a poly A tail (terminal) or via internal splice sites to produce a 150 bp (short) or 207 bp (long) internal exon and continue to exon 7-11 (Kossack et al., 2008). In all cases a truncated LHR protein of 209 aa is generated. Arrow: Stop codon.

Localisation

Predominantly localized in the cell membrane.

Function

The LHR mediates gonadotropin signaling and triggers intracellular responses that participate in gonadal maturation and function, as well as in the regulation of steroidogenesis and gametogenesis (review, Richards et al., 1988; Dufau, 1998; Dufau and Tsai-Morris, 2007). Luteinizing hormone through its surface receptors on the Leydig cell maintains general metabolic processes and steroidogenic enzymes to regulate the production of androgens. In the ovary, LH promotes follicular development, at stages beyond early antral follicles including the formation of preovulatory follicles and corpora lutea. Target disruption of LH receptor in the mouse revealed a normal prenatal development and lack of postnatal sexual development (Lei et al., 2001; Zhang et al., 2001). This indicated that LH/LHR action in male rodents is not required or can be compensated by other hormone(s) or factors during fetal life which is in sharp contrast with the situation in the human. The major changes in sexual development observed after birth in the mouse included significant inhibition of testis growth and descent and of sex accessory organs. Testosterone could partially restore spermatogenesis and fertility (Pakarainen et al., 2005; Yuan et al., 2006).

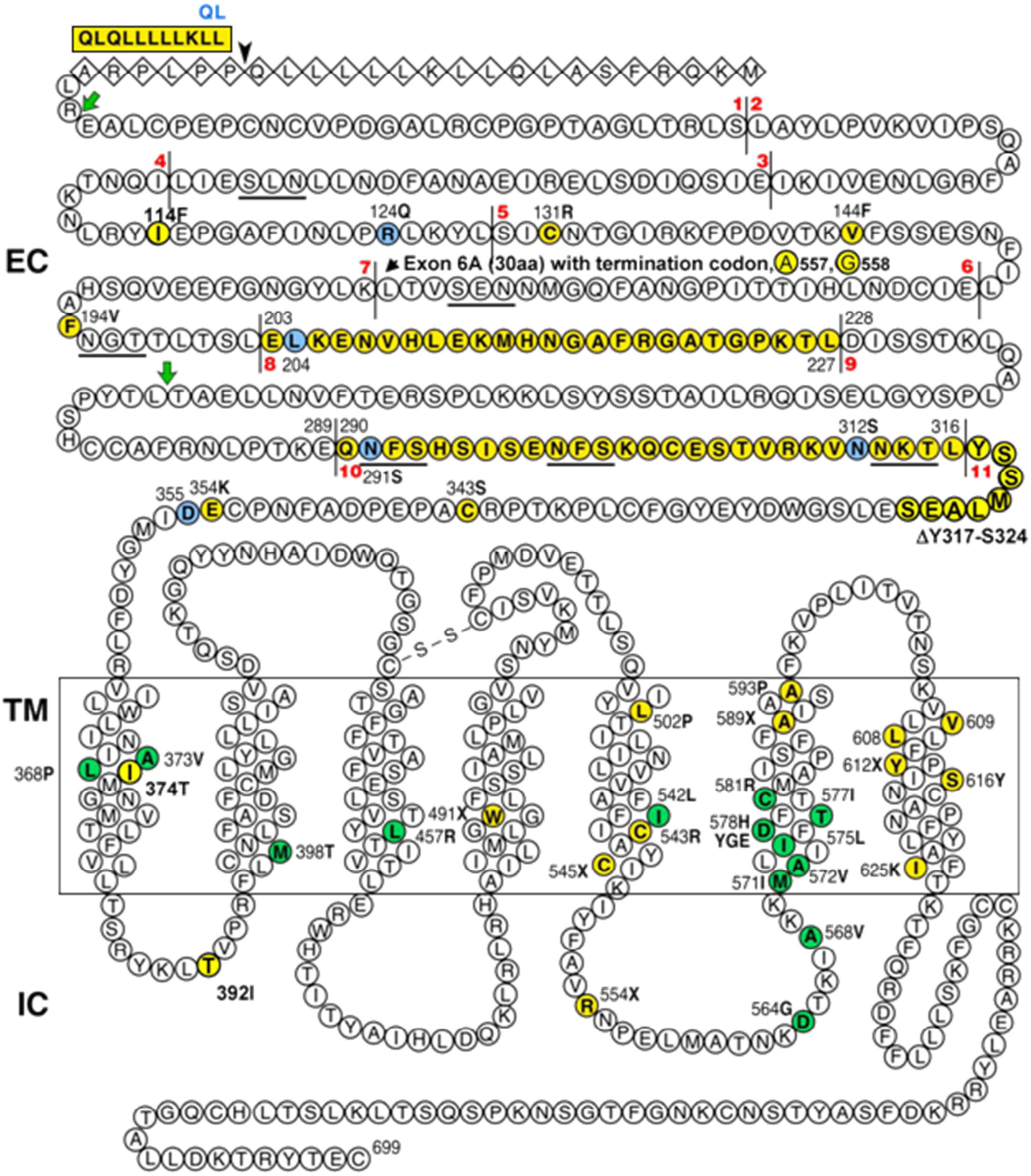
Homology

The percent identity below represents identity using Global pairwise alignment function (GAP).
M. musculus: 83,2
R. Norvegicus: 85,2
D. Melanogaster: 40,1
A. gambiae: 39,7
C. elegans: 30,7

Mutations

Note

Polymorphisms were detected in exon 1, 4, 8, 10 and 11. Nucleotides insertion / deletion, single nucleotide mutation were detected in exons 1, 5, 7, 8, 10 and 11.
Deletions of exon 8 or 9 or 10 (splice variants) were also detected (See reviews Themmen and Huhtaniemi, 2000; Dufau and Tsai-Morris, 2007 and Segaloff, 2009).
Mutations were also found in the unique cryptic exon 6A (Kossack et al., 2008).



EC: Extracellular domain. TM: Transmembrane domain. IC: Intracellular domain. Triangle box: the putative signal peptide. Vertical lines indicate exons. Normal amino acid residue (white circle). X: Stop. Activating mutations noted as green in familial male precocious puberty (FMPP)-autosomal dominant and/or sporadic male-limited precocious puberty (SMPP) or other; inactivating mutations in Leydig cells hypoplasia (LCH) noted in yellow. Polymorphism noted in blue. Underlined: N-glycosylation sites.

Polymorphism: Without a known effect- missense mutation: R124Q, N291S, N312S. Silent mutation: L204, D355.

Activating mutations: Most of these mutations are located in the sixth TM domain (TM6) and C terminal region of the third intracellular loop. Mutations also occur in other transmembrane helices except TM4 and TM7 (see figure). TM1: L368P, A373V; TM2: M398T; TM3: L457R; TM5: I542L; ICL3: D564G, A568V; TM6: M571I, A572V, I575L, T577I, D578G/Y/H/E, C581R. TM: transmembrane., ICL: intracellular loop.

Inactivating mutations: I114F, C131R, V144F, F194V, C343S, E354K, I374T, T392I, W491X, L502P, C543R, C545X, R554X, A589X, A593P, Y612X, S616Y and I625K. Deletion - ΔL608/V609, aa 203-227 (exon 8), aa 228-289 (exon 9), aa 290-316 (exon 10), ΔY317-S324 (exon 11). Insertion: aa18 - LLKLLLLLQLQ. A cryptic exon 6A (resides in intron 6) with mutations

(A557C or G558C).

Implicated in

Disease

Review: Themmen and Huhtaniemi, 2000; Dufau and Tsai-Morris, 2007; Segaloff, 2009. Refer to these reviews for individual mutations.

Breast cancer

Note

The ^{18}LQ insertion associated with adverse outcome in breast cancer patients could result from estrogen exposure in female carriers via increased LHR activity (Powell et al., 2003; Piersma et al., 2006).

Prognosis

Mutations may be linked to breast cancer prognosis.

Familial male precocious puberty (FMPP) and sporadic male-limited precocious puberty (SMPP)

Note

FMPP is a gonadotropin independent precocious puberty, also known as testotoxicosis characterized by premature Leydig cell differentiation, hyperplasia and early spermatogenesis. It presents a clinical phenotype in the heterozygous form of LHR activating mutations. Signs of puberty are found at 1 to 4 yr old of age with elevated androgen production due to LHR mutations in transmembranes 1, 2, 3, 5 and 6 (see mutation section-activating mutation). Those mutants are constitutively active. Mutations cause elevated basal levels of cAMP compared to WT in cells transfected with mutated LHR construct. A similar phenotype is observed in sporadic cases of this disorder. Association of FMPP and SMPP with development of testicular tumors are due to a missense mutation (D578G) which is the most common form of the condition in USA. Somatic mutation of the LHR (D578H) was found in the patients with Leydig cell adenoma and no history of FMPP.

Male pseudohermaphroditism or Leydig cell hypoplasia (LCH) with various degree of hypogonadism severity

Note

There are two types of LCH associated with inactivating mutation of LHR. Clinical phenotype expressed in homozygous (most cases) or compound heterozygous (few cases) is caused by deletion, insertion, truncation or missense mutation (see mutation section) in extracellular or transmembrane regions of the LHR. Also, a genomic defect with mutation in the cryptic exon 6A (residing in the intron 6) could lead to LCH. Type I LCH with 46XY disorder of sex development reveals a complete disruption of LH/hCG signaling in male patients characterized by a female external phenotype with a blind-ending vagina and cryptochidism. Type II LCH is characterized by reduced response to LH/hCG signaling, micropenis and/or hypospadias. 46XX siblings (carrying similar inactivating mutation of LHR) of affected 46XY individuals are infertile with normal female external genitalia but enlarged cystic ovaries and primary or secondary amenorrhea. Elevated serum LH is shown in both genders of patients. The underlining mechanism of the LCH caused by inactivating mutation of LHR might be associated with misfolding, reduced LH/hCG binding affinity and/or intracellular retention of the mutant LHR.

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