Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

LHCGR (luteinizing hormone / choriogonadotropin receptor)

Chon-Hwa Tsai-Morris, Maria L Dufau

Section on Molecular Endocrinology, Endocrinology and Reproduction Research Branch, NICHD, National Institutes of Health, Bethesda, MD 20892-4510, USA (CHTM, MLD)

Published in Atlas Database: August 2004

Online updated version : http://AtlasGeneticsOncology.org/Genes/LHRID288.html
DOI: 10.4267/2042/38122

Identity

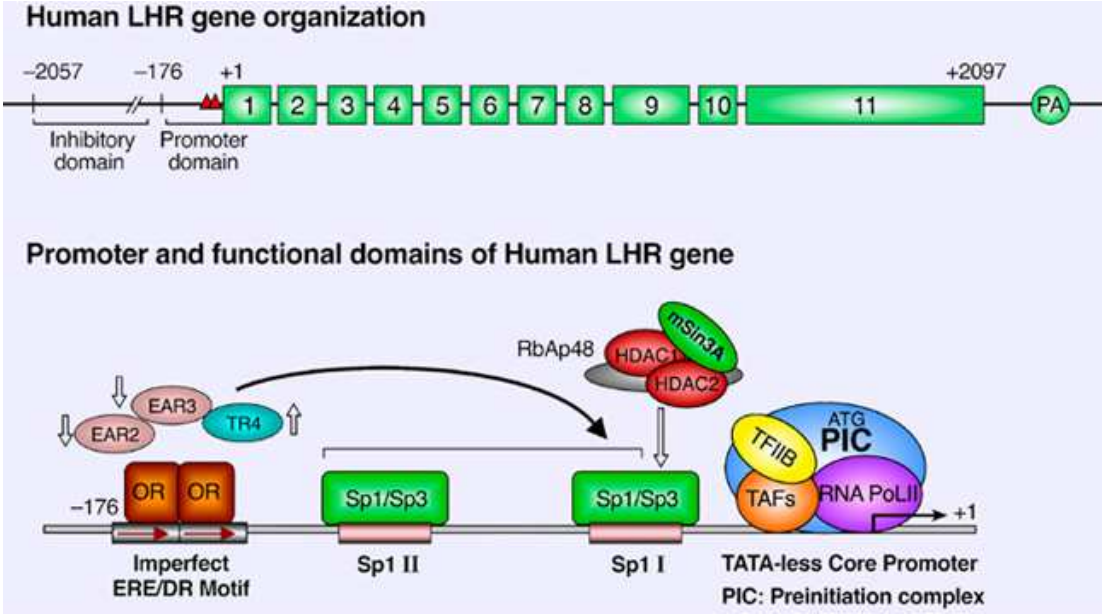
Other names: LHR (Luteinizing hormone receptor); LCGR; LGR2; LHCGR (luteinizing hormone/choriogonadotropin receptor); LH/CG-R, LSH-R (lutropin-choriogonadotropic hormone receptor)

HGNC (Hugo): LHCGR

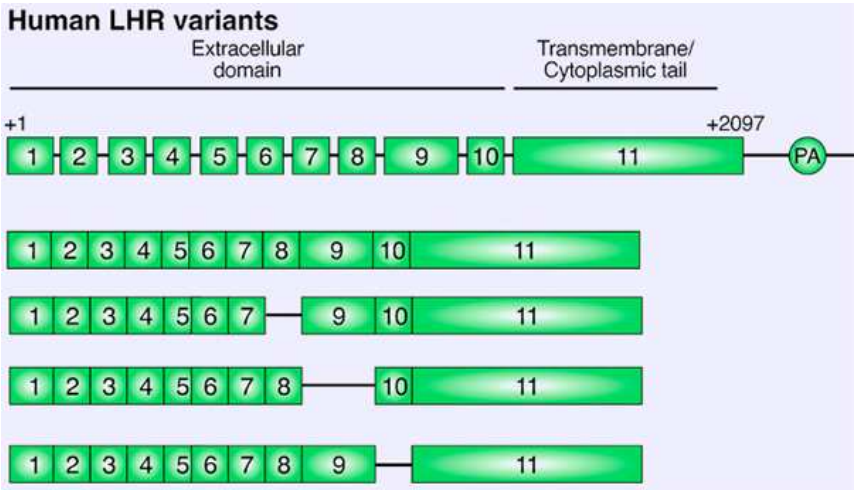
Location: 2p21

Note

The LHR belongs to the glycoprotein hormone receptor subfamily, with leucine rich repeat motifs, of the G protein-coupled receptor family (GPCR).



Human LHR gene organization (Upper panel), 5' flanking regulatory domains and 176 bp promoter with its functional domains, associated transcription factors and silencing regulatory complex (HDAC/mSin3A) (lower panel). Triangle: multiple transcriptional start sites. PA: poly adenylation sites. Open arrow, up: activation, down: inhibition. ERE: estrogen responsive element. DR: direct repeat. OR: orphan receptor. Sp1 I, Sp1 II: Sp1 sites. PIC: preinitiation complex.



Schematic representation of human LHR variants, as deduced from the alternative splicing of the transcripts.

DNA/RNA

Description

The genomic size of human LHR gene is about 80 Kb and consists of 11 coding exons separated by 10 introns. At least three alternatively spliced variants of the hLHR (deletion of exon 8 or 9 or 10) were reported.

Transcription

Multiple LHR mRNA transcriptional start sites are located within the -176 bp TATA-less 5' flanking promoter domain. 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 Sp1/3 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 complex at the Sp1 I site.

Pseudogene

No known pseudogenes.

Protein

Description

The cDNA for the human LHR encodes 699 amino acids. 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, including human nonpregnant uterus, placenta, fallopian tubes, uterine vessels, umbilical cord, brain, and lymphocyte.

Localisation

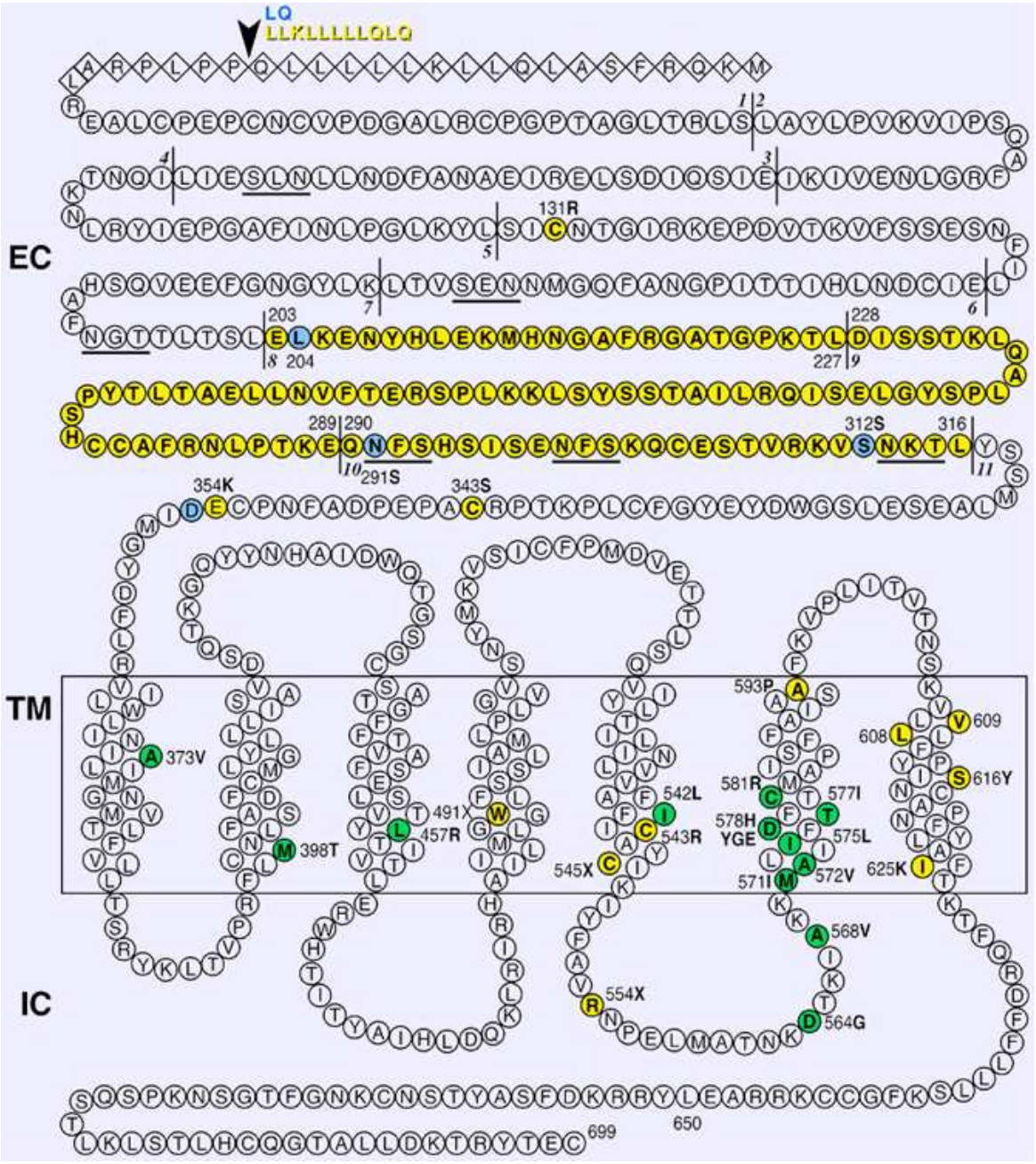
Predominantly localized in the cell membrane.

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. 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.

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.



Legend diagram: 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.

Mutations

Note

Polymorphism detected in exon 1, 8, 10 and 11. Nucleotides insertion/deletion, single nucleotide mutation detected in exon 1, 5, 7, 8, 10 and 11. Deletions of exon 8 or 9 or 10 (splice variants).

Polymorphism: N291S, N312S. Deletion - L204, D355. Insertion at aa 18 – IQ.

Activating mutation: A373V, M398T, L457R, I542L, D564G, A568V, M571I, A572V, I575L, T577I, D578G/Y/H/E, C581R

Inhibiting mutation: C131R, F194V, C343S, E354K, W491X, C543R, C545X, R554X, A593P, S616Y and I625K. Deletion - L608, V609, aa 203-227 (exon 8), aa 228-289 (exon 9), and aa 290-316 (exon 10). Insertion: aa18 - LLKLLLLLQLQ.

Implicated in

Note

Activating mutations: Human familial male precocious puberty (FMPP) and sporadic male-limited precocious puberty (SMPP) - gonadotropin independent precocious puberty with Leydig cell hyperplasia.
Inactivating mutations: Male: Leydig cell hypoplasia (LCH) with various degree of hypogonadism severity, pseudohermaphroditism. Female: Infertility hypergonadotropic hypogonadism and primary amenorrhea.
Association of FMPP and testicular seminoma (D578G) - 1 patient or nodular Leydig cell hyperplasia (D578G) - 1 patient.
Somatic mutation of the LHR (D578H) with Leydig cell adenoma and no history of FMPP (3 patients).
Mutations may be linked to breast cancer prognosis (18LQ insert).

References

Loosfelt H, Misrahi M, Atger M, Salesse R, Vu Hai-Luu Thi MT, Jolivet A, Guiochon-Mantel A, Sar S, Jallal B, Garnier J. Cloning and sequencing of porcine LH-hCG receptor cDNA: variants lacking transmembrane domain. Science. 1989 Aug 4;245(4917):525-8

McFarland KC, Sprengel R, Phillips HS, Köhler M, Rosemblit N, Nikolics K, Segaloff DL, Seeburg PH. Lutropin-choriogonadotropin receptor: an unusual member of the G protein-coupled receptor family. Science. 1989 Aug 4;245(4917):494-9

Minegishi T, Nakamura K, Takakura Y, Miyamoto K, Hasegawa Y, Ibuki Y, Igarashi M, Minegish T [corrected to Minegishi T. Cloning and sequencing of human LH/hCG receptor cDNA. Biochem Biophys Res Commun. 1990 Nov 15;172(3):1049-54

Tsai-Morris CH, Buczko E, Wang W, Dufau ML. Intronic nature of the rat luteinizing hormone receptor gene defines a soluble receptor subspecies with hormone binding activity. J Biol Chem. 1990 Nov 15;265(32):19385-8

Jia XC, Oikawa M, Bo M, Tanaka T, Ny T, Boime I, Hsueh AJ. Expression of human luteinizing hormone (LH) receptor: interaction with LH and chorionic gonadotropin from human but not equine, rat, and ovine species. Mol Endocrinol. 1991 Jun;5(6):759-68

Koo YB, Ji I, Slaughter RG, Ji TH. Structure of the luteinizing hormone receptor gene and multiple exons of the coding sequence. Endocrinology. 1991 May;128(5):2297-308

Tsai-Morris CH, Buczko E, Wang W, Xie XZ, Dufau ML. Structural organization of the rat luteinizing hormone (LH) receptor gene. J Biol Chem. 1991 Jun 15;266(17):11355-9

Zhang R, Tsai-Morris CH, Kitamura M, Buczko E, Dufau ML. Changes in binding activity of luteinizing hormone receptors by site directed mutagenesis of potential glycosylation sites. Biochem Biophys Res Commun. 1991 Dec 16;181(2):804-8

Tsai-Morris CH, Xie X, Wang W, Buczko E, Dufau ML. Promoter and regulatory regions of the rat luteinizing hormone receptor gene. J Biol Chem. 1993 Feb 25;268(6):4447-52

Tsai-Morris CH, Geng Y, Xie XZ, Buczko E, Dufau ML. Transcriptional protein binding domains governing basal expression of the rat luteinizing hormone receptor gene. J Biol Chem. 1994 Jun 3;269(22):15868-75

Atger M, Misrahi M, Sar S, Le Flem L, Dessen P, Milgrom E. Structure of the human luteinizing hormone-choriogonadotropin receptor gene: unusual promoter and 5' non-coding regions. Mol Cell Endocrinol. 1995 Jun;111(2):113-23

Kawate N, Kletter GB, Wilson BE, Netzloff ML, Menon KM. Identification of constitutively activating mutation of the luteinising hormone receptor in a family with male limited gonadotrophin independent precocious puberty (testotoxicosis). J Med Genet. 1995 Jul;32(7):553-4

Kremer H, Kraaij R, Toledo SP, Post M, Fridman JB, Hayashida CY, van Reen M, Milgrom E, Ropers HH, Mariman E. Male pseudohermaphroditism due to a homozygous missense mutation of the luteinizing hormone receptor gene. Nat Genet. 1995 Feb;9(2):160-4

Tsai-Morris CH, Geng Y, Buczko E, Dufau ML. Characterization of diverse functional elements in the upstream Sp1 domain of the rat luteinizing hormone receptor gene promoter. J Biol Chem. 1995 Mar 31;270(13):7487-94

Zhang R, Cai H, Fatima N, Buczko E, Dufau ML. Functional glycosylation sites of the rat luteinizing hormone receptor required for ligand binding. J Biol Chem. 1995 Sep 15;270(37):21722-8

Laue LL, Wu SM, Kudo M, Bourdony CJ, Cutler GB Jr, Hsueh AJ, Chan WY. Compound heterozygous mutations of the luteinizing hormone receptor gene in Leydig cell hypoplasia. Mol Endocrinol. 1996 Aug;10(8):987-97

Zhang R, Buczko E, Dufau ML. Requirement of cysteine residues in exons 1-6 of the extracellular domain of the luteinizing hormone receptor for gonadotropin binding. J Biol Chem. 1996 Mar 8;271(10):5755-60

Dufau ML. The luteinizing hormone receptor. Annu Rev Physiol. 1998;60:461-96

Geng Y, Tsai-Morris CH, Zhang Y, Dufau ML. The human luteinizing hormone receptor gene promoter: activation by Sp1 and Sp3 and inhibitory regulation. Biochem Biophys Res Commun. 1999 Sep 24;263(2):366-71

Tsai-Morris CH, Geng Y, Buczko E, Dehejia A, Dufau ML. Genomic distribution and gonadal mRNA expression of two human luteinizing hormone receptor exon 1 sequences in random populations. Hum Hered. 1999 Jan;49(1):48-51

Gromoll J, Eiholzer U, Nieschlag E, Simoni M. Male hypogonadism caused by homozygous deletion of exon 10 of the luteinizing hormone (LH) receptor: differential action of human chorionic gonadotropin and LH. J Clin Endocrinol Metab. 2000 Jun;85(6):2281-6

Latronico AC. Naturally occurring mutations of the luteinizing hormone receptor gene affecting reproduction. Semin Reprod Med. 2000;18(1):17-20

Themmen APN, Huhtaniemi IT. Mutations of gonadotropins and gonadotropin receptors: elucidating the physiology and pathophysiology of pituitary-gonadal function. Endocr Rev. 2000 Oct;21(5):551-83

Wu SM, Leschek EW, Rennert OM, Chan WY. Luteinizing hormone receptor mutations in disorders of sexual development and cancer. Front Biosci. 2000 Mar 1;5:D343-52

Zhang Y, Dufau ML. Nuclear orphan receptors regulate transcription of the gene for the human luteinizing hormone receptor. J Biol Chem. 2000 Jan 28;275(4):2763-70

Rao CV. An overview of the past, present, and future of nongonadal LH/hCG actions in reproductive biology and medicine. Semin Reprod Med. 2001;19(1):7-17

Zhang Y, Dufau ML. EAR2 and EAR3/COUP-TFI regulate transcription of the rat LH receptor. Mol Endocrinol. 2001 Nov;15(11):1891-905

Ascoli M, Fanelli F, Segaloff DL. The lutropin/choriogonadotropin receptor, a 2002 perspective. Endocr Rev. 2002 Apr;23(2):141-74

Fanelli F, Puett D. Structural aspects of luteinizing hormone receptor: information from molecular modeling and mutagenesis. Endocrine. 2002 Aug;18(3):285-93

Shenker A. Activating mutations of the lutropin choriogonadotropin receptor in precocious puberty. Receptors Channels. 2002;8(1):3-18

Zhang Y, Dufau ML. Silencing of transcription of the human luteinizing hormone receptor gene by histone deacetylase-mSin3A complex. J Biol Chem. 2002 Sep 6;277(36):33431-8

Powell BL, Piersma D, Kevenaar ME, van Staveren IL, Themmen AP, Iacopetta BJ, Berns EM. Luteinizing hormone signaling and breast cancer: polymorphisms and age of onset. J Clin Endocrinol Metab. 2003 Apr;88(4):1653-7

Zhang Y, Dufau ML. Dual mechanisms of regulation of transcription of luteinizing hormone receptor gene by nuclear orphan receptors and histone deacetylase complexes. J Steroid Biochem Mol Biol. 2003 Jun;85(2-5):401-14

Nakamura K, Yamashita S, Omori Y, Minegishi T. A splice variant of the human luteinizing hormone (LH) receptor modulates the expression of wild-type human LH receptor. Mol Endocrinol. 2004 Jun;18(6):1461-70

This article should be referenced as such:

Tsai-Morris CH, Dufau ML. LHCGR (luteinizing hormone/choriogonadotropin receptor). Atlas Genet Cytogenet Oncol Haematol. 2004; 8(4):289-293.