

Gene Section

Mini Review

PRLR (Prolactin receptor)

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Identity

Other names: PRLR

HGNC (Hugo): PRLR

Location: 5p14-p13

Note:

The PRLR belongs to the class I cytokine receptor family. This receptor binds the pituitary hormone prolactin with high affinity. It contains an extracellular binding domain with 2 fibronectin-like type III domains, a single transmembrane domain, and an intracellular domain required for signal transduction (via JAK-2/ STAT5 and other pathways) that lacks intrinsic kinase activity.

DNA/RNA

Description

The genomic size of human PRLR gene exceeds 200 kB and contains 11 exons, including six non-coding exons 1 alternative spliced to a common non-coding exon 2 and exon 3-10 that encode the full length activating long form of the receptor. Intermediate and various short forms result from alternative splicing. Sequences from exon 11 are present only in the short forms of the receptor S1a and S1b and their respective variants.

Transcription

Transcription of human prolactin receptor gene is regulated by a multiple and tissue-specific promoter (hPIII for exons 1 species hE1 3 and hPN 1-5 for exons 1 species hE1N 1-5). The prolactin receptor promoters belong to the TATA-less/non-initiator class. The hPIII requires Sp1 and C/EBPb elements that bind Sp1/Sp3 and C/EBPb for basal transcriptional activity, while hPN 1 activity is conferred by domains containing an

Ets element and an NR half-site. hPN 2-5 have not been characterized.

Pseudogene

No known pseudogenes.

Protein

Description

Several forms of the human prolactin receptor have been identified including the full length activating receptor (LF) and at least eight other variants (Diagram A and B). These variants differ by the length and composition of their extracellular and/or cytoplasmic domain. In addition to the membrane anchored prolactin receptor there is a soluble isoform (prolactin receptor binding protein - PRLRBP) that is generated by proteolytic cleavage of membrane bound prolactin receptor.

The human prolactin receptor is composed of a single transmembrane domain, a ligand binding extracellular domain and a cytoplasmic domain which is required for signal transduction. Two disulfide-linked cysteines in the D1 subdomain are involved in ligand binding while WSXWS motif in the D2 subdomain is probably required for correct folding and cellular trafficking. Box 1, a proline rich domain highly conserved in the cytokine receptor family, is the JAK2 docking site. The activated JAK2 induced by prolactin (autophosphorylation), phosphorylates the dimerized receptor preferentially Y587 (at a consensus tyrosine phosphorylation site) which is only present in LF and delta S1 (diagram A). This is followed by phosphorylation, dimerization and nuclear translocation of STAT5 which causes transcriptional activation of prolactin responsive genes (i.e. b-casein, b-lactoglobulin, whey acidic protein interferon-regulatory

factor 1 and others). There are other nine tyrosines in the cytoplasmic domain (non-consensus phosphorylation sites) some of which may undergo phosphorylation and may participate in signal transduction. Box2 of unknown function is less conserved in the cytokine receptor family. Prolactin can also activate other tyrosine kinases, including Src family kinases, focal adhesion proteins, Tec kinase, and ErbB kinase. Prolactin induces the GRB2/SOS/Ras/Raf/MAPK signaling cascade. Prolactin through the long form of the receptor stimulates cell proliferation.

The delta-S1 form lacking exon 4 and 5, has reduced affinity for the hormone (due to abbreviated extracellular domain) but displays effective signal transduction. Stimulation of the intermediate form of the receptor (major deletion of exon 10, cytoplasmic domain) only with high concentrations of the ligand exhibits minor cell proliferation. The short forms of the receptor S1a and S1b derived from alternative splicing of exons 10 and 11 are inhibitory of the activation induced by prolactin through the long form of the receptor (see above). Exon 11 is shared by three other species of unknown function which are S1a and S1b

variants (delta 7/11 S1a, delta 4-7/11 S1a and delta 4 S1b).

Expression

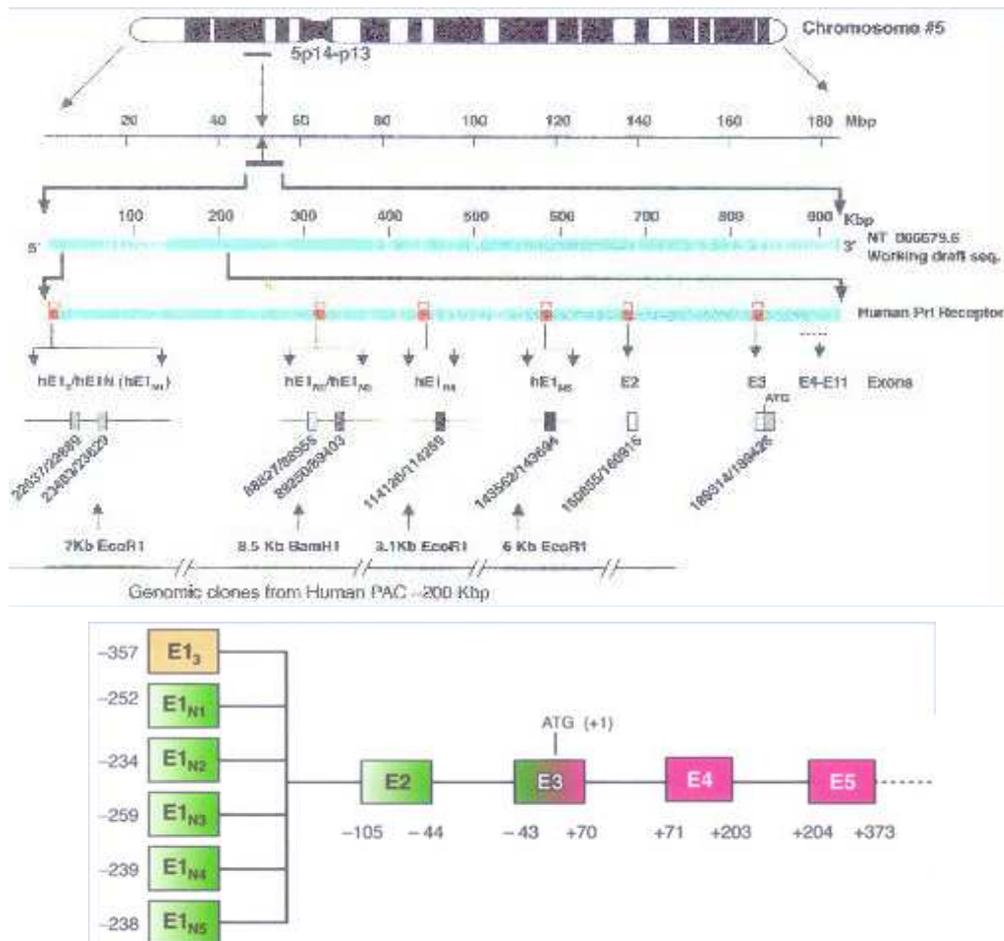
Prolactin receptors have been identified in number of cells and tissues including the mammary gland, organs of the reproductive system, central nervous system, pituitary, adrenal cortex, skin, bone, lung, heart, liver, pancreas, GI tract, kidney, lymphoid tissue. These are also present in breast cancer tissues and cells and in other tumoral tissues/cells.

Localisation

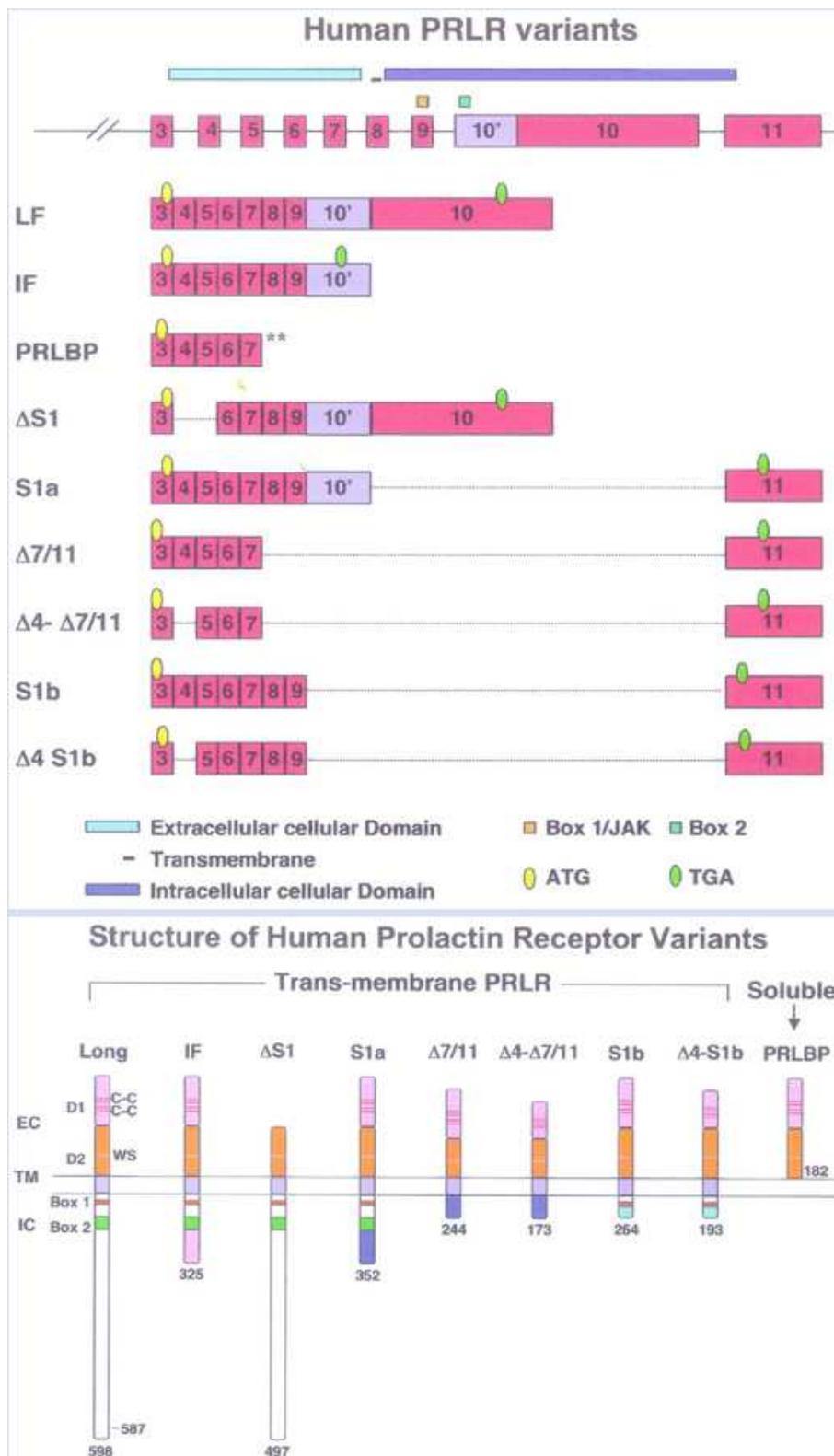
Localized in the cell membrane, but also present intracellularly at various compartments.

Function

The prolactin receptor mediates prolactin signaling and triggers intracellular responses that participate in diverse biological functions including, mammary gland development (proliferation and differentiation), initiation and maintenance of lactation, regulation of water and salt balance, reproduction, gonadal steroidogenesis, embryonic implantation, brain and behavior, and immune-regulation (see description).



Top: Localization of multiple first exons and exons 2-11 of the human prolactin receptor gene in chromosome 5p 14-13. Alternative exons 1: hE1 3 (generic) and hE1N 1-5 (human specific); and Exon2: non-coding exon. Exon3: non-coding/coding ATG translation initiation codon. Exons 4-11: coding exons. Bottom: Schematic representation of multiple exons 1 and alternative splicing to common exon 2.



Schematic representation of human PRLR variants, as deduced from the alternative splicing of the transcripts (Top) and highlight of receptor structure (Bottom). LF: long form. IF: intermediate form. S: short form. 10': partial exon 10.): deletion/splice variant. . D1, D2: N-terminal subdomain. WS: WSXWS motif. C: cysteine. Y: Tyrosine. EC: Extracellular domain. TM: Transmembrane domain. IC: Intracellular domain. Blue boxes (dark and light) in IC represent two unique sequences of short forms derived from exon 11. Aminoacid number excludes the signal peptide. LF deduced sequence from cDNA contains 622aa.

Implicated in

Disease

Changes in the expression of prolactin receptor long forms, were found in breast cancer tissues and cells lines when compared to adjacent normal tissues/cells. Polymorphism of prolactin receptor may be related to breast carcinoma, multiple sclerosis and systemic lupus erythematosus.

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