Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

RLN2 (relaxin 2)

Jordan M Willcox, Alastair JS Summerlee

Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph, Guelph, Ontario, N1G 2W1, Canada (JMW, AJSS)

Published in Atlas Database: November 2009

Online updated version : http://AtlasGeneticsOncology.org/Genes/RLN2ID44421ch9p24.html
DOI: 10.4267/2042/44844

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2010 Atlas of Genetics and Cytogenetics in Oncology and Haematology

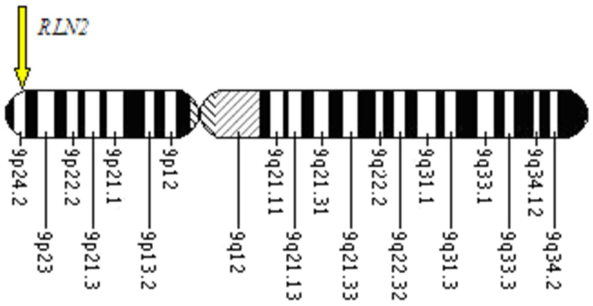
Identity

Other names: H2; RLXH2; bA12D24.1.1; bA12D24.1.2; prorelaxin H2

HGNC (Hugo): RLN2

Location: 9p24.1

Local order: RLN2 is located on chromosome 9 on the reverse strand.



RLN2 is located on chromosome 9 (position shown by yellow arrow).

Note: See also, in the Deep Insight section: RLN2 and its role in cancer.

DNA/RNA

Description

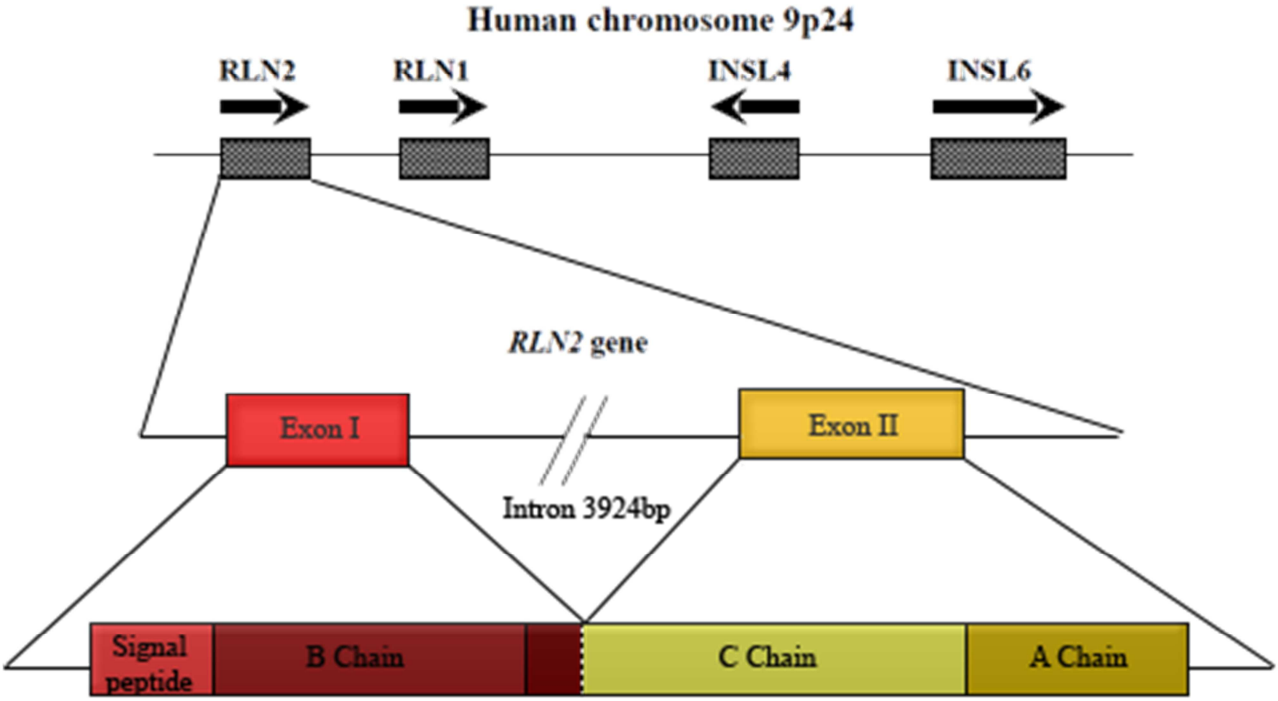
RLN2 is a functioning gene of 4,712 bp comprising 2 exons and 1 intron.

Transcription

The length of the transcript is 588 bp. mRNA is expressed in high levels in ovary and placenta, and in lower levels in fibroblasts, a number of tumours, heart and brain.
Alternate splicing: 2 isoforms: P04090-1, P04090-2.

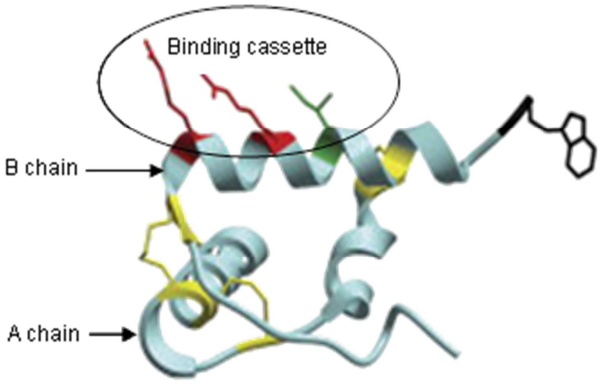
Pseudogene

None but there are a number of similar genes of the same family. These include: RLN1 and RLN2 genes in a tight cluster with INSL4 and INSL6 genes on chromosome 9 at 9p24. The RLN3 gene is located on chromosome 19 at 19p13.3 in close proximity to INSL3 at 19p13.2 and the INSL5 gene is located on chromosome 1 at 1p31.1



Schematic representation of the transcription of the human RLN2 gene. Adapted from Bathgate et al., 2006 (with permission). The gene is located with the RLN1, INSL4 and INSL6 genes on chromosome 9 at 9p24. The RLN2 gene consists of two exons and is transcribed to give preprorelaxin-2 mRNA. Exon I encodes for the signal peptide, the B Chain and part of the C Chain, and Exon II encodes for the remainder of the C Chain and the A chain of H2 relaxin. The arrows on the diagrams indicate the orientation of the genes. Although insulin and H2 relaxin are similar, there is no report that the insulin gene possesses an intron.

Protein



Modified from Westhuizen et al. 2008.
Characteristic two-peptide chain hormone held together by disulphide bonds (shown in yellow) which provide the tertiary form of the molecule. There is a relaxin receptor binding motif (shown in red and green).

Description

Protein length of the precursor peptide is 185 amino acids with a molecular weight 21,043 Daltons.
The functional peptide has 21 amino acids in the A chain and 27 in the B chain and with a molecular weight 5,989 Daltons.
There is a specific binding motif (see diagram above) Arg-X-X-X-Arg-X-X-Ile/Val which are vital for binding and the projection from the tertiary structure is important in binding to the Type C LGR receptor (RXPF1). These receptors have a large and very distinctive ectodomain which includes an LDLa module at the far end of the N-terminus followed by a LRR domain (10 LRR). It is thought that this links with a unique hinge-like region leading into the transmembrane domain. There are seven

transmembrane helices and an intracellular C-terminus.

Expression

mRNA and protein found in brain, heart, skin, lungs, liver, kidney, ovary, uterus, testis, prostate and in prostatic and mammary neoplasia. Expression induced by a variety of factors in different tissues.

Localisation

Cytoplasm.

Function

Brain
- Increased food intake
- Mediates stress behaviour
- Increased fluid intake
- Release of a number of hypothalamic peptides including vasopressin, oxytoxcin, LH, and angiotensin II

Heart
- Increased rate of atrial contraction
- Increased force of atrial contraction
- Reduced fibrosis
- Differentiation and development

- Release of ANP

Vasculature
- Decreased blood pressure
- Decreased total peripheral resistance
- Vasodilation

Skin
- Reduced fibrosis

Lungs
- Increased lung perfusion and gas exchange
- Relaxes bronchi
- Reduced fibrosis
- Reduced degranulation mast cells
- Reduced inflammatory leukocytes

Liver
- Reduced fibosis

Kidney
- Increased GFR
- Increased ERPF
- Increased Na^+ excretion
- Reduced fibrosis

Ovary
- Follicular ripening
- Germ cell maturation

Uterus
- Angiogenesis
- Endometrial thickening

Cervix
- Softening (shift from collagenous to more elastic tissue)

Pelvic ligaments
- Softening (shift from collagenous to more elastic tissue)

Mammary gland
- Differentiation and development

Prostate
- Increased sperm motility
- Possible role in hypertrophy and neoplastic change

Testis
- Possible role in testicular descent in rats

Cancer
- Angiogenesis
- Vasodilation
- Reduced fibrosis
- Reduced apoptosis

Homology

Generally 30-60% sequence homology is observed between relaxin 2 among species.

Mutations

Note

It is assumed that the members of the relaxin-gene family are predominantly functional mutations of an original relaxin gene (RLN3) located on chromosome 19 at 19p13.3 and translocated at some stage predominantly to chromosome 9.

Implicated in

Prostate cancer

Disease

Prostate cancer is the most common form of carcinoma in men (Lippman et al., 2009). If left untreated, this form of cancer becomes highly metastatic, primarily to the bones and lymphatic system. RLN2 is implicated in the progression, development, and spread of prostate cancer. RLN2 increases extra-cellular matrix turnover, promotes tumor invasiveness, and neo-vascularization (Silvertown et al., 2006).

Prognosis

Given that circulating relaxin increases in experimental models of prostate cancer, it is possible RLN2 may be employed as an early marker for prostate cancer and act as a screening mechanism in clinical settings. Furthermore, RLN2 exhibits the potential for genetic therapy to target and neutralize this gene as a novel treatment for prostate cancer.

Oncogenesis

RLN2 has been implicated in the progression of prostate tumors. RLN2 expression is increased in prostate tumors (Silvertown et al., 2006). Antagonism with analogues of RLN2 (Silvertown et al., 2007) demonstrates antagonistic properties and impairs prostate tumor growth and development.

Breast cancer

Disease

Breast cancer is the most common form of carcinoma in women. RLN2 increases the invasiveness of breast cancer cells via the induction of matrix metalloproteinases (MMPs) (Binder et al., 2002). Circulating relaxin also increases in patients with breast cancer (Binder et al., 2004).

Prognosis

Since serum relaxin concentrations are increased in patients with breast cancer, relaxin may be used as a screening tool for breast cancer. Furthermore, RLN2 may be targeted for genetic therapy as a novel treatment for breast cancer.

Oncogenesis

RLN2 increases the oncogenic potential of breast cancer cells by stimulating growth, invasiveness, and metastasis.

Thyroid cancer

Disease

There are four types of thyroid cancer: papillary, follicular, medullary, and anaplastic. While limited research has been conducted with regards to RLN2 and thyroid cancer, it is possible relaxin enhances the course and development of thyroid cancer.

Oncogenesis

RLN2 acts as an autocrine/paracrine factor to enhance growth and invasiveness of thyroid cancer cells (Hombach-Klonisch et al., 2006). RLN2 may also increase motility of thyroid cancer cells thereby contributing to increased metastatic potential.

References

Crawford RJ, Hudson P, Shine J, Niall HD, Eddy RL, Shows TB. Two human relaxin genes are on chromosome 9. EMBO J. 1984 Oct;3(10):2341-5

Hudson P, John M, Crawford R, Haralambidis J, Scanlon D, Gorman J, Tregear G, Shine J, Niall H. Relaxin gene expression in human ovaries and the predicted structure of a

human preprorelaxin by analysis of cDNA clones. EMBO J. 1984 Oct;3(10):2333-9

Stults JT, Bourell JH, Canova-Davis E, Ling VT, Laramee GR, Winslow JW, Griffin PR, Rinderknecht E, Vandlen RL. Structural characterization by mass spectrometry of native and recombinant human relaxin. Biomed Environ Mass Spectrom. 1990 Nov;19(11):655-64

Eigenbrot C, Randal M, Quan C, Burnier J, O'Connell L, Rinderknecht E, Kossiakoff AA. X-ray structure of human relaxin at 1.5 A. Comparison to insulin and implications for receptor binding determinants. J Mol Biol. 1991 Sep 5;221(1):15-21

Hansell DJ, Bryant-Greenwood GD, Greenwood FC. Expression of the human relaxin H1 gene in the decidua, trophoblast, and prostate. J Clin Endocrinol Metab. 1991 Apr;72(4):899-904

Schwabe C, Büllesbach EE. Relaxin: structures, functions, promises, and nonevolution. FASEB J. 1994 Nov;8(14):1152-60

Bogic LV, Mandel M, Bryant-Greenwood GD. Relaxin gene expression in human reproductive tissues by in situ hybridization. J Clin Endocrinol Metab. 1995 Jan;80(1):130-7

Gunnersen JM, Fu P, Roche PJ, Tregear GW. Expression of human relaxin genes: characterization of a novel alternatively-spliced human relaxin mRNA species. Mol Cell Endocrinol. 1996 Apr 19;118(1-2):85-94

Qin X, Garibay-Tupas J, Chua PK, Cachola L, Bryant-Greenwood GD. An autocrine/paracrine role of human decidual relaxin. I. Interstitial collagenase (matrix metalloproteinase-1) and tissue plasminogen activator. Biol Reprod. 1997 Apr;56(4):800-11

Veitia R, Laurent A, Quintana-Murci L, Ottolenghi C, Fellous M, Vidaud M, McElreavey K. The INSL4 gene maps close to WI-5527 at 9p24.1-->p23.3 clustered with two relaxin genes and outside the critical region for the monosomy 9p syndrome. Cytogenet Cell Genet. 1998;81(3-4):275-7

Garibay-Tupas JL, Csiszár K, Fox M, Povey S, Bryant-Greenwood GD. Analysis of the 5'-upstream regions of the human relaxin H1 and H2 genes and their chromosomal localization on chromosome 9p24.1 by radiation hybrid and breakpoint mapping. J Mol Endocrinol. 1999 Dec;23(3):355-65

Garibay-Tupas JL, Bao S, Kim MT, Tashima LS, Bryant-Greenwood GD. Isolation and analysis of the 3'-untranslated regions of the human relaxin H1 and H2 genes. J Mol Endocrinol. 2000 Apr;24(2):241-52

Binder C, Hagemann T, Husen B, Schulz M, Einspanier A. Relaxin enhances in-vitro invasiveness of breast cancer cell lines by up-regulation of matrix metalloproteases. Mol Hum Reprod. 2002 Sep;8(9):789-96

Silvertown JD, Geddes BJ, Summerlee AJ. Adenovirus-mediated expression of human prorelaxin promotes the invasive potential of canine mammary cancer cells. Endocrinology. 2003 Aug;144(8):3683-91

Binder C, Simon A, Binder L, Hagemann T, Schulz M, Emons G, Trümper L, Einspanier A. Elevated concentrations of serum relaxin are associated with metastatic disease in breast cancer patients. Breast Cancer Res Treat. 2004 Sep;87(2):157-66

Humphray SJ, Oliver K, Hunt AR, Plumb RW, Loveland JE, Howe KL, Andrews TD, Searle S, Hunt SE, Scott CE, Jones MC, Ainscough R, Almeida JP, Ambrose KD, Ashwell RI, Babbage AK, Babbage S, Bagguley CL, Bailey J, Banerjee R, Barker DJ, Barlow KF, Bates K, Beasley H, Beasley O, Bird CP, Bray-Allen S, Brown AJ, Brown JY, Burford D, Burrill W, Burton J, Carder C, Carter NP, Chapman JC, Chen Y, Clarke G, Clark SY, Clee CM, Clegg S, Collier RE, Corby N, Crosier M, Cummings AT, Davies J, Dhami P, Dunn M, Dutta I, Dyer LW, Earthrowl ME, Faulkner L, Fleming CJ, Frankish A, Frankland JA, French L, Fricker DG, Garner P, Garnett J, Ghori J, Gilbert JG, Glison C, Grafham DV, Gribble S, Griffiths C, Griffiths-Jones S, Grocock R, Guy J, Hall RE, Hammond S, Harley JL, Harrison ES, Hart EA, Heath PD, Henderson CD, Hopkins BL, Howard PJ, Howden PJ, Huckle E, Johnson C, Johnson D, Joy AA, Kay M, Keenan S, Kershaw JK, Kimberley AM, King A, Knights A, Laird GK, Langford C, Lawlor S, Leongamornlert DA, Leversha M, Lloyd C, Lloyd DM, Lovell J, Martin S, Mashreghi-Mohammadi M, Matthews L, McLaren S, McLay KE, McMurray A, Milne S, Nickerson T, Nisbett J, Nordsiek G, Pearce AV, Peck AI, Porter KM, Pandian R, Pelan S, Phillimore B, Povey S, Ramsey Y, Rand V, Scharfe M, Sehra HK, Shownkeen R, Sims SK, Skuce CD, Smith M, Steward CA, Swarbreck D, Sycamore N, Tester J, Thorpe A, Tracey A, Tromans A, Thomas DW, Wall M, Wallis JM, West AP, Whitehead SL, Willey DL, Williams SA, Wilming L, Wray PW, Young L, Ashurst JL, Coulson A, Blöcker H, Durbin R, Sulston JE, Hubbard T, Jackson MJ, Bentley DR, Beck S, Rogers J, Dunham I. DNA sequence and analysis of human chromosome 9. Nature. 2004 May 27;429(6990):369-74

Figueiredo KA, Palmer JB, Mui AL, Nelson CC, Cox ME. Demonstration of upregulated H2 relaxin mRNA expression during neuroendocrine differentiation of LNCaP prostate cancer cells and production of biologically active mammalian recombinant 6 histidine-tagged H2 relaxin. Ann N Y Acad Sci. 2005 May;1041:320-7

Halls ML, Bathgate RA, Roche PJ, Summers RJ. Signaling pathways of the LGR7 and LGR8 receptors determined by reporter genes. Ann N Y Acad Sci. 2005 May;1041:292-5

Halls ML, Bathgate RA, Summers RJ. Signal switching after stimulation of LGR7 receptors by human relaxin 2. Ann N Y Acad Sci. 2005 May;1041:288-91

Klonisch T, Müller-Huesmann H, Riedel M, Kehlen A, Bialek J, Radestock Y, Holzhausen HJ, Steger K, Ludwig M, Weidner W, Hoang-Vu C, Hombach-Klonisch S. INSL3 in the benign hyperplastic and neoplastic human prostate gland. Int J Oncol. 2005 Aug;27(2):307-15

Radestock Y, Hoang-Vu C, Hombach-Klonisch S. Relaxin downregulates the calcium binding protein S100A4 in MDA-MB-231 human breast cancer cells. Ann N Y Acad Sci. 2005 May;1041:462-9

Bathgate RAD, Hsueh AJW, Sherwood OD.. Physiology and molecular biology of the relaxin peptide family. Knobil and Neilis Physiology of Reproduction. Third Edition. Ed: JD Neill, Elsevier Holland;2006:679-768.

Hombach-Klonisch S, Bialek J, Trojanowicz B, Weber E, Holzhausen HJ, Silvertown JD, Summerlee AJ, Dralle H, Hoang-Vu C, Klonisch T. Relaxin enhances the oncogenic potential of human thyroid carcinoma cells. Am J Pathol. 2006 Aug;169(2):617-32

Silvertown JD, Ng J, Sato T, Summerlee AJ, Medin JA. H2 relaxin overexpression increases in vivo prostate xenograft tumor growth and angiogenesis. Int J Cancer. 2006 Jan 1;118(1):62-73

Bayés M, Rabasseda X, Prous JR. Gateways to clinical trials. Methods Find Exp Clin Pharmacol. 2007 Dec;29(10):697-735

Feng S, Agoulnik IU, Bogatcheva NV, Kamat AA, Kwabi-Addo B, Li R, Ayala G, Ittmann MM, Agoulnik AI. Relaxin promotes prostate cancer progression. Clin Cancer Res. 2007 Mar 15;13(6):1695-702

Maruo N, Nakabayashi K, Wakahashi S, Yata A, Maruo T. Effects of recombinant H2 relaxin on the expression of matrix metalloproteinases and tissue inhibitor metalloproteinase in cultured early placental extravillous trophoblasts. Endocrine. 2007 Dec;32(3):303-10

Silvertown JD, Symes JC, Neschadim A, Nonaka T, Kao JC, Summerlee AJ, Medin JA. Analog of H2 relaxin exhibits antagonistic properties and impairs prostate tumor growth. FASEB J. 2007 Mar;21(3):754-65

Liu S, Vinall RL, Tepper C, Shi XB, Xue LR, Ma AH, Wang LY, Fitzgerald LD, Wu Z, Gandour-Edwards R, deVere White RW, Kung HJ. Inappropriate activation of androgen receptor by relaxin via beta-catenin pathway. Oncogene. 2008 Jan 17;27(4):499-505

Radestock Y, Hoang-Vu C, Hombach-Klonisch S. Relaxin reduces xenograft tumour growth of human MDA-MB-231 breast cancer cells. Breast Cancer Res. 2008;10(4):R71

van der Westhuizen ET, Halls ML, Samuel CS, Bathgate RA, Unemori EN, Sutton SW, Summers RJ. Relaxin family peptide receptors--from orphans to therapeutic targets. Drug Discov Today. 2008 Aug;13(15-16):640-51

Kietz S, Feng S, Agoulnik A, Hombach-Klonisch S. Estrogen and TCDD influence RLN2 gene activity in estrogen receptor-positive human breast cancer cells. Ann N Y Acad Sci. 2009 Apr;1160:367-73

Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, Parsons JK, Bearden JD 3rd, Crawford ED, Goodman GE, Claudio J, Winquist E, Cook ED, Karp DD, Walther P, Lieber MM, Kristal AR, Darke AK, Arnold KB, Ganz PA, Santella RM, Albanes D, Taylor PR, Probstfield JL, Jagpal TJ, Crowley JJ, Meyskens FL Jr, Baker LH, Coltman CA Jr. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2009 Jan 7;301(1):39-51

Mookerjee I, Hewitson TD, Halls ML, Summers RJ, Mathai ML, Bathgate RA, Tregear GW, Samuel CS. Relaxin inhibits renal myofibroblast differentiation via RXFP1, the nitric oxide pathway, and Smad2. FASEB J. 2009 Apr;23(4):1219-29

This article should be referenced as such:

Willcox JM, Summerlee AJS. RLN2 (relaxin 2). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(9):841-845.