

## Gene Section

### Review

# ANXA1 (annexin A1)

Flavia Cristina Rodrigues-Lisoni, Tiago Henrique, Eloiza Helena Tajara

Department of Biology and Zootechny, Faculty of Engineering of Ilha Solteira (UNESP), Ilha Solteira, Brazil (FCRL); Department of Molecular Biology, School of Medicine (FAMERP), Sao Jose do Rio Preto, Brazil (TH, EHTDS)

Published in Atlas Database: May 2010

Online updated version: <http://AtlasGeneticsOncology.org/Genes/ANXA1ID653ch9q21.html>  
DOI: 10.4267/2042/44953

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2011 Atlas of Genetics and Cytogenetics in Oncology and Haematology

## Identity

**Other names:** ANX1, LPC1

**HGNC (Hugo):** ANXA1

**Location:** 9q21.13

**Local order:** According to NCBI Map Viewer, genes flanking ANXA1 in centromere to telomere direction on 9q21 are: LOC100289351, RPS20P24, TMC1, RPS27AP15, ALDH1A1, LOC100133307, LOC100132782, ANXA1, LOC138971, LOC100130911, RORB, TRPM6, RNY4P1.

## DNA/RNA

### Description

The exon-intron organization of ANXA1 genes in vertebrates have been described and are highly conserved, each gene consisting of 13 exons of which the first and last are uncoding 5' and 3'

sequences, with the translation initiator codon (AUG) found near the beginning of the second exon (Kovacic et al., 1991).

### Transcription

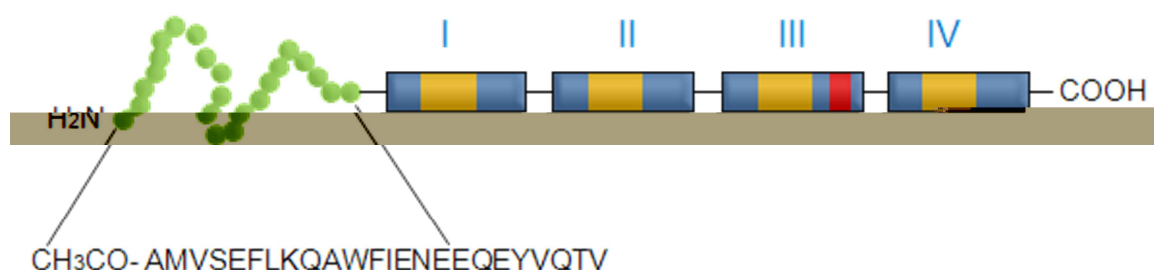
Transcription produces 9 different mRNAs to this gene. The ANXA1 gene is expressed in the tissues: bone, bone marrow, brain, cartilage, cerebellum, cerebrum, cervix, colon, ear, embryonic tissue, endocrine, esophagus, eye, fetus, gastrointestinal tract, heart, kidney, liver, lung, lymph node, lymphoreticular, mammary gland, muscle, nervous, ovary, pancreas, pancreatic islet, parathyroid, peripheral nervous system, pituitary gland, placenta, pooled tissue, prostate, salivary gland, skin, soft tissue, spleen, stem cell, stomach, synovium, t-cell, testis, thymus, thyroid, uncharacterized tissue, uterus, vascular.

### Pseudogene

No known pseudogenes.



**ANXA1 gene.** The ANXA1 gene contains 13 exons, of which the first and last are uncoding 5' and 3' sequences (red regions), with the translation initiator codon (AUG) found near the beginning of the second exon (orange regions).



**Schematic representation of annexin protein.** N-terminal region with amino acids and four repetitions with 70-75 amino acids in C-terminal region.

## Protein

### Note

Belongs to the annexin family. Contains 4 annexin repeats.

### Description

The ANXA1 gene encodes a 38.71 kDa protein. Similarly to other annexins, annexin A1 is characterized by a C-terminal homologous domain with 4 to 8 repeats of 70-75 aminoacids, responsible for calcium and phospholipid binding properties. The variable N-terminal region is unique in length and sequence and includes potential sites of phosphorylation, glycosylation and peptidase action (Gerke and Moss, 2002).

### Expression

The human ANXA1 gene promoter contains consensus sequences for: glucocorticoids, AP-1 and NFIL-6. However the regulation from glucocorticoid (GC) appear to be dependent upon an activation involving NFIL-6 or AP1 (Solito et al., 1998a; Solito et al., 1998b). The GC mediated regulations confirm the original studies which proposed ANXA1 as mediator of the glucocorticoid action (Flower, 1988). In mouse, in contrast, GC regulation is mediated through two consensus sequences present in the upstream region of TATA box (Horlick et al., 1991). However the data of Antonicelli et al. 2001 regarding sequences of the mouse *Anxa1* promoter brought evidence of the involvement of the CREB transcription factor (the cyclic AMP-responding element-binding protein) in the activation of this gene by cyclic AMP and glucocorticoids.

### Localisation

ANXA1 is preferentially localized in the cytoplasm and associated with the plasma membrane or cytoskeleton, but it has also been localized outside the plasma membrane.

### Function

The function of the annexin A1 is far to be clear, it has been involved in signal transduction (Alldridge et al., 1999; de Coupade et al., 2000), vesicle transport

(Diakonova et al., 1997), cell transformation (Violette et al., 1990; Solito et al., 1998a), inflammation (Perretti and Gavins, 2003), cell matrix interaction and apoptosis (Raynal and Pollard, 1994; Solito et al., 2001; Solito et al., 2003).

### Homology

The comparison of conserved and variable residues between human annexin 1 protein and annexin protein from different vertebrates shows amino acid identities of 100% (Pan troglodytes), 91% (Canis familiars), 87% (Mus musculus), 89% (Rattus norvegicus) and 77% (Gallus gallus) (Rodrigues-Lisoni et al., 2006).

## Mutations

### Note

Reduced expression of ANXA1 could be explain by some mechanisms include gene deletions and mutations, hyper-methylation of the promoter with subsequent loss of transcription, and alterations in the post-translation processing (e.g. phosphorylation) of the protein involved in annexins regulation (de Coupade et al., 2000; Rodrigues-Lisoni et al., 2006; Alves et al., 2008).

Lindgren et al. (2001) studied subjects with type 2 diabetes and find a G instead of T at nucleotide position 362 from the transcription start site (exon 5) of ANXA1 gene in all individuals sequenced.

## Implicated in

### Breast cancer

#### Disease

In breast cancer, ANXA1 is believed to function as a tumor suppressor. In study with a tissue microarray using 82 pairs of primary breast cancers and lymph node metastases from archival materials the results revealed that ANXA1 expression was lost in 79% of breast carcinomas, and there was no difference in ANXA1 expression between primary breast carcinoma and lymph node metastasis (Cao et al., 2008).

#### Prognosis

The suppressed ANXA1 expression in breast tissue is correlated with breast cancer development, progression and metastasis (Shen et al., 2006; Wang et al., 2010).

## **Oral squamous cell carcinoma (OSCC)**

### **Disease**

ANXA1 expression could be used as a suitable biomarker for patients with oral cavity cancer and its adoption for complementary non-invasive diagnosis of oral squamous cell carcinoma is suggested. Beyond the anti-inflammatory function, annexin A1 may also play a tumor suppressor role in peripheral blood cells (Faria et al., 2010).

### **Prognosis**

The nuclear localization of ANXA1 protein is a frequent event and could be used as a prognostic factor in OSCC (Lin et al., 2008).

## **Laryngeal squamous cell carcinoma**

### **Disease**

In surgical tissue specimens from 20 patients with laryngeal squamous cell carcinoma, ultrastructural immunocytochemistry analysis showed in vivo down-regulation of ANXA1 expression in the tumor and increased in mast cells and laryngeal squamous carcinoma cell line treated with ANXA1 peptide. Combined in vivo and in vitro analysis demonstrated that ANXA1 plays a regulatory role in laryngeal cancer cell growth (Silistino-Souza et al., 2007).

### **Prognosis**

ANXA1 dysregulation was observed early in laryngeal carcinogenesis, in intra-epithelial neoplasms (Alves et al., 2008).

## **Lung squamous cell carcinoma**

### **Disease**

The ANXA1 expression was identified by shot-gun proteomics strategy in lung squamous cell carcinoma.

### **Prognosis**

The ANXA1 might play an important role in lung squamous cell carcinoma genesis, progression, recurrence, and metastasis and might be used as markers of this carcinoma (Nan et al., 2009).

## **Prostate cancer**

### **Disease**

The reduction of ANXA1 expression, commonly associated with prostate cancer, could be due to elevated activity of histone deacetylases (D'Acunto et al., 2010) and interleukin 6 expression (Inokuchi et al., 2009).

### **Prognosis**

The ANXA1 expression is a contributing factor to the proapoptotic effects in prostate cancer (D'Acunto et al., 2010) and enhancing tumor aggressiveness via the upregulation of interleukin 6 expression and activity (Inokuchi et al., 2009).

## **Leukaemia**

### **Disease**

Immunocytochemical detection of ANXA1 represents a simple, inexpensive, highly sensitive and specific (100%) assay for diagnosis of hairy cell leukaemia. This assay will be especially useful in distinguishing hairy cell leukaemia from splenic lymphoma with villous lymphocytes and variant hairy cell leukaemia, both of which usually respond poorly to treatments that are effective in hairy cell leukaemia (Falini et al., 2004).

### **Prognosis**

The downregulated ANXA1 expression contributes considerably to the drug resistance in leukemia cell line (Zhu et al., 2009).

## **Cervical cancer**

### **Disease**

A close association was observed between ANXA1 expression and tumour cell differentiation in invasive squamous cell carcinoma.

### **Prognosis**

ANXA1 may be an effective candidate for detecting cervical intraepithelial neoplasia lesions and for evaluating tumour cell differentiation in squamous cell carcinoma of the cervix (Wang et al., 2008).

## **Gastric cancer**

### **Disease**

Loss of ANXA1 expression was significantly associated with advanced T stage, lymph node metastasis, advanced disease stage, and poor histological differentiation.

### **Prognosis**

ANXA1 expression decreased significantly as gastric cancer progressed and metastasized, suggesting the importance of ANXA1 as a negative biomarker for gastric cancer development and progression (Yu et al., 2008).

## **Urinary bladder urothelial carcinoma**

### **Disease**

Comparative proteomics and immunohisto-chemistry demonstrated that ANXA1 is up-regulated in high grade urinary bladder urothelial carcinoma as compared to non-high grade carcinomas.

### **Prognosis**

ANXA1 might be related to tumour progression. The ANXA1 overexpression and histological grade predicted disease-specific survival and metastasis-free survival (Li et al., 2010).

## Systemic lupus erythematosus

### Disease

Auto-antibodies against annexin A1 have been detected in patients with auto-immune diseases such as systemic lupus erythematosus (Hirata et al., 1981; Goulding et al., 1989).

## Rheumatoid arthritis

### Disease

ANXA1 has been recently shown to play a key role in T-cell activation and to be highly expressed in T cells from rheumatoid arthritis patients. Treatment of rheumatoid arthritis patients with steroid decreased ANXA1 expression in T cells.

### Prognosis

Steroids regulate the adaptive immune response and suggest that ANXA1 may represent a target for the treatment of autoimmune diseases (D'Acquisto et al., 2008).

## Crohn's disease

### Disease

Corticosteroids are widely used to treat patients with inflammatory bowel disease although the response is variable. Corticosteroids mediate some of their actions through ANXA1, and the induction of autoantibodies to ANXA1 has been proposed as a possible mechanism by which steroid efficacy is suboptimal in vivo (Beattie et al., 1995).

### Prognosis

The high levels of IgM ANXA1 antibodies in patients with Crohn's disease not taking corticosteroids provides further evidence of disturbed immunity in inflammatory bowel disease (Stevens et al., 1993).

## Cystic fibrosis

### Disease

Downregulation and degradation of ANXA1 was found in the bronchoalveolar lavage fluid of patients with cystic fibrosis indicating the susceptibility of these patients to lung inflammation. ANXA1 may be a key protein involved in cystic fibrosis pathogenesis especially in relation to the not well defined field of inflammation in cystic fibrosis (Tsao et al., 1998).

### Prognosis

Decreased expression of annexin A1 contributes to the worsening of the cystic fibrosis phenotype (Bensalem et al., 2005).

## Parkinson's disease

### Disease

ANXA1 expression has been linked to Parkinson's disease. ANXA1 immunoreactivity has been found in amoeboid microglia within the astrocytic envelope of neurons adjacent to or within glial scars in the parkinsonian substantia nigra (Knott et al., 2000).

## Multiple sclerosis

### Disease

ANXA1 expression has been identified in the lesions of multiple sclerosis plaque and correlated with the degree of the disease (Probst-Cousin et al., 2002).

### Prognosis

Strategies aiming at reducing ANXA1 functions or expression in T cells might represent a novel therapeutic approach for multiple sclerosis (Paschalidis et al., 2009).

## References

- Hirata F. The regulation of lipomodulin, a phospholipase inhibitory protein, in rabbit neutrophils by phosphorylation. *J Biol Chem.* 1981 Aug 10;256(15):7730-3
- Flower RJ. Eleventh Gaddum memorial lecture. Lipocortin and the mechanism of action of the glucocorticoids. *Br J Pharmacol.* 1988 Aug;94(4):987-1015
- Goulding NJ, Podgorski MR, Hall ND, Flower RJ, Browning JL, Pepinsky RB, Maddison PJ. Autoantibodies to recombinant lipocortin-1 in rheumatoid arthritis and systemic lupus erythematosus. *Ann Rheum Dis.* 1989 Oct;48(10):843-50
- Violette SM, King I, Browning JL, Pepinsky RB, Wallner BP, Sartorelli AC. Role of lipocortin I in the glucocorticoid induction of the terminal differentiation of a human squamous carcinoma. *J Cell Physiol.* 1990 Jan;142(1):70-7
- Horlick KR, Cheng IC, Wong WT, Wakeland EK, Nick HS. Mouse lipocortin I gene structure and chromosomal assignment: gene duplication and the origins of a gene family. *Genomics.* 1991 Jun;10(2):365-74
- Kovacic RT, Tizard R, Cate RL, Frey AZ, Wallner BP. Correlation of gene and protein structure of rat and human lipocortin I. *Biochemistry.* 1991 Sep 17;30(37):9015-21
- Stevens TR, Smith SF, Rampton DS. Antibodies to human recombinant lipocortin-I in inflammatory bowel disease. *Clin Sci (Lond).* 1993 Apr;84(4):381-6
- Raynal P, Pollard HB. Annexins: the problem of assessing the biological role for a gene family of multifunctional calcium- and phospholipid-binding proteins. *Biochim Biophys Acta.* 1994 Apr 5;1197(1):63-93
- Beattie RM, Goulding NJ, Walker-Smith JA, MacDonald TT. Lipocortin-1 autoantibody concentration in children with inflammatory bowel disease. *Aliment Pharmacol Ther.* 1995 Oct;9(5):541-5
- Diakonova M, Gerke V, Ernst J, Liautard JP, van der Vusse G, Griffiths G. Localization of five annexins in J774 macrophages and on isolated phagosomes. *J Cell Sci.* 1997 May;110 ( Pt 10):1199-213
- Solito E, de Coupade C, Parente L, Flower RJ, Russo-Marie F. Human annexin 1 is highly expressed during the differentiation of the epithelial cell line A 549: involvement of nuclear factor interleukin 6 in phorbol ester induction of annexin 1. *Cell Growth Differ.* 1998 Apr;9(4):327-36
- Solito E, de Coupade C, Parente L, Flower RJ, Russo-Marie F. IL-6 stimulates annexin 1 expression and translocation and suggests a new biological role as class II acute phase protein. *Cytokine.* 1998 Jul;10(7):514-21

- Tsao FH, Meyer KC, Chen X, Rosenthal NS, Hu J. Degradation of annexin I in bronchoalveolar lavage fluid from patients with cystic fibrosis. *Am J Respir Cell Mol Biol*. 1998 Jan;18(1):120-8
- Allridge LC, Harris HJ, Plevin R, Hannon R, Bryant CE. The annexin protein lipocortin 1 regulates the MAPK/ERK pathway. *J Biol Chem*. 1999 Dec 31;274(53):37620-8
- de Coupade C, Gillet R, Bennoun M, Briand P, Russo-Marie F, Solito E. Annexin 1 expression and phosphorylation are upregulated during liver regeneration and transformation in antithrombin III SV40 T large antigen transgenic mice. *Hepatology*. 2000 Feb;31(2):371-80
- Knott C, Stern G, Wilkin GP. Inflammatory regulators in Parkinson's disease: iNOS, lipocortin-1, and cyclooxygenases-1 and -2. *Mol Cell Neurosci*. 2000 Dec;16(6):724-39
- Lindgren CM, Nilsson A, Orho-Melander M, Almgren P, Groop LC. Characterization of the annexin I gene and evaluation of its role in type 2 diabetes. *Diabetes*. 2001 Oct;50(10):2402-5
- Solito E, de Coupade C, Canaider S, Goulding NJ, Perretti M. Transfection of annexin 1 in monocytic cells produces a high degree of spontaneous and stimulated apoptosis associated with caspase-3 activation. *Br J Pharmacol*. 2001 May;133(2):217-28
- Gerke V, Moss SE. Annexins: from structure to function. *Physiol Rev*. 2002 Apr;82(2):331-71
- Probst-Cousin S, Kowolik D, Kuchelmeister K, Kayser C, Neundörfer B, Heuss D. Expression of annexin-1 in multiple sclerosis plaques. *Neuropathol Appl Neurobiol*. 2002 Aug;28(4):292-300
- Perretti M, Gavins FN. Annexin 1: an endogenous anti-inflammatory protein. *News Physiol Sci*. 2003 Apr;18:60-4
- Solito E, Kamal A, Russo-Marie F, Buckingham JC, Marullo S, Perretti M. A novel calcium-dependent proapoptotic effect of annexin 1 on human neutrophils. *FASEB J*. 2003 Aug;17(11):1544-6
- Falini B, Tiacci E, Liso A, Basso K, Sabattini E, Pacini R, Foa R, Pulsoni A, Dalla Favera R, Pileri S. Simple diagnostic assay for hairy cell leukaemia by immunocytochemical detection of annexin A1 (ANXA1). *Lancet*. 2004 Jun 5;363(9424):1869-70
- Bensalem N, Ventura AP, Vallée B, Lipecka J, Tondelier D, Davezac N, Dos Santos A, Perretti M, Fajac A, Sermet-Gaudelus I, Renouil M, Lesure JF, Halgand F, Laprèvote O, Edelman A. Down-regulation of the anti-inflammatory protein annexin A1 in cystic fibrosis knock-out mice and patients. *Mol Cell Proteomics*. 2005 Oct;4(10):1591-601
- Rodrigues-Lisoni FC, Oliani S, Buckingham J, Solito E, Tajara EH. Annexin A1: from gene organization to physiology. *Calcium Binding Proteins*. 2006;1(2):72-6. (REVIEW)
- Shen D, Nooraie F, Elshimali Y, Lonsberry V, He J, Bose S, Chia D, Seligson D, Chang HR, Goodglick L. Decreased expression of annexin A1 is correlated with breast cancer development and progression as determined by a tissue microarray analysis. *Hum Pathol*. 2006 Dec;37(12):1583-91
- Silistino-Souza R, Rodrigues-Lisoni FC, Cury PM, Maniglia JV, Raposo LS, Tajara EH, Christian HC, Oliani SM. Annexin 1: differential expression in tumor and mast cells in human larynx cancer. *Int J Cancer*. 2007 Jun 15;120(12):2582-9
- Alves VA, Nonogaki S, Cury PM, Wünsch-Filho V, de Carvalho MB, Michaluart-Júnior P, Moyses RA, Curioni OA, Figueiredo DL, Scapulatempo-Neto C, Parra ER, Polachini GM, Silistino-Souza R, Oliani SM, Silva-Júnior WA, Nobrega FG, Tajara EH, Zago MA. Annexin A1 subcellular expression in laryngeal squamous cell carcinoma. *Histopathology*. 2008 Dec;53(6):715-27
- Cao Y, Li Y, Edelweiss M, Arun B, Rosen D, Resetkova E, Wu Y, Liu J, Sahin A, Albarracin CT. Loss of annexin A1 expression in breast cancer progression. *Appl Immunohistochem Mol Morphol*. 2008 Dec;16(6):530-4
- D'Acquisto F, Paschalidis N, Raza K, Buckley CD, Flower RJ, Perretti M. Glucocorticoid treatment inhibits annexin-1 expression in rheumatoid arthritis CD4+ T cells. *Rheumatology (Oxford)*. 2008 May;47(5):636-9
- Lin CY, Jeng YM, Chou HY, Hsu HC, Yuan RH, Chiang CP, Kuo MY. Nuclear localization of annexin A1 is a prognostic factor in oral squamous cell carcinoma. *J Surg Oncol*. 2008 May 1;97(6):544-50
- Wang LD, Yang YH, Liu Y, Song HT, Zhang LY, Li PL. Decreased expression of annexin A1 during the progression of cervical neoplasia. *J Int Med Res*. 2008 Jul-Aug;36(4):665-72
- Yu G, Wang J, Chen Y, Wang X, Pan J, Li Q, Xie K. Tissue microarray analysis reveals strong clinical evidence for a close association between loss of annexin A1 expression and nodal metastasis in gastric cancer. *Clin Exp Metastasis*. 2008;25(7):695-702
- Inokuchi J, Lau A, Tyson DR, Ornstein DK. Loss of annexin A1 disrupts normal prostate glandular structure by inducing autocrine IL-6 signaling. *Carcinogenesis*. 2009 Jul;30(7):1082-8
- Nan Y, Yang S, Tian Y, Zhang W, Zhou B, Bu L, Huo S. Analysis of the expression protein profiles of lung squamous carcinoma cell using shot-gun proteomics strategy. *Med Oncol*. 2009;26(2):215-21
- Paschalidis N, Iqbal AJ, Maione F, Wood EG, Perretti M, Flower RJ, D'Acquisto F. Modulation of experimental autoimmune encephalomyelitis by endogenous annexin A1. *J Neuroinflammation*. 2009 Nov 13;6:33
- Zhu F, Wang Y, Zeng S, Fu X, Wang L, Cao J. Involvement of annexin A1 in multidrug resistance of K562/ADR cells identified by the proteomic study. *OMICS*. 2009 Dec;13(6):467-76
- D'Acunto CW, Fontanella B, Rodriguez M, Taddei M, Parente L, Petrella A. Histone deacetylase inhibitor FR235222 sensitizes human prostate adenocarcinoma cells to apoptosis through up-regulation of Annexin A1. *Cancer Lett*. 2010 Sep 1;295(1):85-91
- Faria PC, Sena AA, Nascimento R, Carvalho WJ, Loyola AM, Silva SJ, Durighetto AF, Oliveira AD, Oliani SM, Goulart LR. Expression of annexin A1 mRNA in peripheral blood from oral squamous cell carcinoma patients. *Oral Oncol*. 2010 Jan;46(1):25-30
- Li CF, Shen KH, Huang LC, Huang HY, Wang YH, Wu TF. Annexin-I overexpression is associated with tumour progression and independently predicts inferior disease-specific and metastasis-free survival in urinary bladder urothelial carcinoma. *Pathology*. 2010 Jan;42(1):43-9
- Wang LP, Bi J, Yao C, Xu XD, Li XX, Wang SM, Li ZL, Zhang DY, Wang M, Chang GQ. Annexin A1 expression and its prognostic significance in human breast cancer. *Neoplasma*. 2010;57(3):253-9

---

*This article should be referenced as such:*

Rodrigues-Lisoni FC, Henrique T, Tajara EH. ANXA1 (annexin A1). *Atlas Genet Cytogenet Oncol Haematol*. 2011; 15(2):117-121.

---