

## Gene Section

### Review

# ALOX12 (arachidonate 12-lipoxygenase) Homo sapiens

Sreeparna Banerjee, Asli Erdog

Department of Biology, Middle East Technical University, Ankara 06531, Turkey (SB); Department of Biotechnology, Middle East Technical University, Ankara 06531 Turkey (AE)

Published in Atlas Database: March 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/ALOX12ID620ch17p13.html>  
DOI: 10.4267/2042/38447

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.  
© 2007 Atlas of Genetics and Cytogenetics in Oncology and Haematology

## Identity

**Hugo:** ALOX12

**Other names:** 12-LOX; 12S-type; 12(S)-lipoxygenase; EC 1.13.11.31; LOG12

**Location:** 17p13.1

**Local order:** According to NCBI Map Viewer, genes flanking ALOX15 in centromere to telomere direction on 17p13 are: GABARAP 17p13.1 GABA(A) receptor-associated protein, ASGR2 asialoglycoprotein receptor 2, ALOX12 17p13.1 arachidonate 12-lipoxygenase (Homo sapiens), ALOX12P2 17p13 arachidonate 12-lipoxygenase pseudogene 2, TEKT1 tektin 1, FBXO39 F-box protein 39.

**Note:** Arachidonate 12-Lipoxygenase (12-LOX) is one of several LOX isoforms that has iron as a cofactor and oxygenates polyunsaturated fatty acids. This particular isoform was also the first documented LOX in the animal kingdom.

## DNA/RNA

**Note:** With the exception of ALOX5, all human LOX

genes, including ALOX12, are clustered on the short arm of chromosome 17 within a few megabases of each other. ALOX15, which has 86% sequence homology to ALOX12, is in closest proximity (17p13.2). Since chromosome 17 is known for gene duplications, the multiple LOX genes on the same chromosome may be as a result of such duplications.

### Description

According to Entrez-Gene, ALOX12 gene maps to NC\_000017.9 and spans a region of 16.1 kilo bases. According to Spidey (mRNA to genomic sequence alignment tool), ALOX15 has 14 exons, the sizes being 168, 202, 82, 123, 104, 161, 144, 210, 87, 170, 122, 101, 171 and 490 bp.

### Transcription

ALOX12 mRNA NM\_000697 has 2335bp. Characterization of the 5' flanking region of the human ALOX12 in epidermoid carcinoma A431 cells indicated the presence of two Sp1 recognition motifs residing at -158 to -150 bp and -123 to -114 bp which are essential for gene expression.

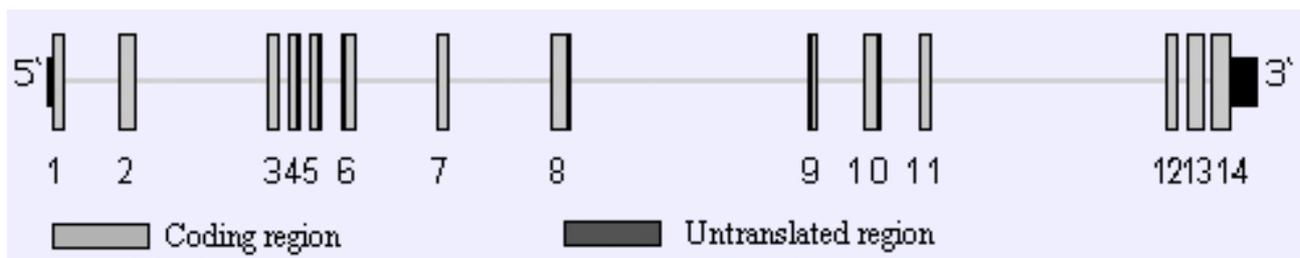


Diagram of the ALOX12 gene. Exons are represented by grey boxes (in scale) untranslated sequences in black, with exon numbers on the bottom.

The proposed mechanism of action is as follows: epidermal growth factor induces MAPK activation in cells, followed by the activation of JUN/AP1. The biosynthesis of c-Jun is thereby increased. Sp1 recruits HDAC1 together with c-Jun to the gene promoter. When Sp1 is deacetylated it interacts with acetylate histone 3, following which p300 is recruited to the gene promoter leading to the enhancement of the expression of 12(S)-lipoxygenase.

### **Pseudogene**

According to Entrez Gene the arachidonate 12-lipoxygenase pseudogene (ALOX12P2) (HGNC: 13742) is located on 17p13.1. This is the 'epidermal type' 12-LOX (e-12LO) that was cloned using a murine e-LO12 probe. Humans express this functional pseudogene in the skin and hair follicles.

## **Protein**

**Note:** 12S-lipoxygenases has three isoforms, named after their site of initial identification: platelet, leukocyte and epidermis. The leukocyte-type enzyme is expressed widely, while the platelet and epidermal enzymes are present in only a relatively limited number of cell types. Owing to the similarities in their genetic location, sequence and biological activities, leukocyte 12-LOX and 15-LOX-1 are often referred to as 12/15 lipoxygenase.

### **Description**

12-LOX protein consists of 662 amino acids, with a molecular weight of 75536 Da and contains non heme iron as a cofactor. According to the NCBI conserved domain search, the presence of a polycystin/lipoxygenase/alpha-toxin (PLAT) domain in the 12-LOX protein allows it access and enables it to catalyze enzymatic lipid peroxidation in complex biological structures via direct dioxygenation of phospholipids and cholesterol esters of biomembranes and plasma lipoproteins. The same conserved domain in 15-LOX-1 also enables it to oxidize complex lipids. Although cytosolic, both types of enzymes need this domain to access their sequestered membrane or micelle bound substrates.

### **Expression**

The platelet type 12-LOX is expressed in the platelets and skin in humans. Based on structural and enzymatic properties, 15-LOX-1 is said to be a homolog of leukocyte type 12-LOX and are both expressed in mast cells, eosinophils, activated monocytes or dendritic cells, and bronchial epithelial cells.

### **Localisation**

All 12-LOX isoforms have been localized to the cytoplasm. In addition, the platelet-type 12S-lipoxygenase was found in both cytosol and microsomal fractions of epidermal cells of human skin.

### **Function**

12-LOX is a member of the inflammatory leukotriene biosynthesis pathway where, in presence of molecular oxygen, it converts arachidonic acid to 12-hydroxyeicosatetraenoic acid (12-HETE). The leukocyte type 12-LOX can, in addition, effectively oxygenate linoleic acid and phospholipids. This isoform can also generate significant amounts of the 15-LOX product in addition to 12-HETE.

### **Homology**

*C. familiaris*: LOC479476 similar to arachidonate 12-lipoxygenase, *P. troglodytes*: ALOX12, *R. norvegicus*: Alox12 (predicted), *M. musculus*: Alox12 arachidonate 12-lipoxygenase (12/15LOX), *D. rerio*: wufb72a11.

## **Implicated in**

### **Inflammation and cancer**

**Note:** End product of arachidonic acid metabolism by the platelet-type 12-LOX 12(S)-Hydroxy eicosatetraenoic acid (12(S)-HETE) is shown to induce invasion, motility, and angiogenesis and protect tumour cells from apoptosis. Great many biological activities of 12(S)-HETE appear to be partly mediated by the activation of NF-kappaB. NF-kappaB is a family of five DNA binding proteins that regulate the expression of a variety of genes involved in host immune responses and inflammation. A direct relationship between platelet-type 12-LOX overexpression and NF-kappaB activation is reported in prostate cancer cells.

### **Polymorphisms associated with diseases**

**Note:** Aberrant arachidonic acid metabolism by 12-lipoxygenase (12-LOX) is implicated in carcinogenesis. Genetic polymorphisms 12-LOX is therefore thought to influence its function and/or expression and may modify the risk for colorectal adenoma. One of the single nucleotide polymorphisms (SNPs) reported in the 12-LOX gene located in exon 6 resulting in an Arg to Gln substitution at amino acid 261 of 12-LOX is in a highly conserved region of the lipoxygenase domain. Data from a community-based, case-control study of incident, sporadic colorectal adenoma that included 162 cases and 211 controls have shown an inverse association between the Arg261Gln polymorphism in 12-LOX and colorectal adenoma (OR, 0.63; 95% CI, 0.40-1.00). A significant interaction also is observed between the 12-LOX polymorphism (Arg261Gln) and the use of nonsteroidal anti-inflammatory drugs. Another study argues that Gln261Arg in ALOX12 does not appear to be associated with colon cancer risk. Studies have shown higher urinary excretion of the arachidonic acid-derived metabolite 12-(S)hydroxyeicosatetraenoic acid (12(S)-HETE) in essential hypertension. For analysis of the association

of polymorphisms in ALOX12 with hypertension and urinary levels of 12(S)-HETE, a study with 200 patients with essential hypertension and 166 matched controls is performed and as a result, the distribution of genotypes of the R261Q (Arg to Gln) polymorphism is found to be significantly different between patients and controls. These results indicate that a nonsynonymous polymorphism in ALOX12 is associated to essential hypertension and to urinary levels of 12(S)-HETE.

Peak BMD is a major determinant of osteoporosis which is a complex disease with both genetic and environmental risk factors. In a population - and family - based association study of ALOX15 and ALOX12, SNPs distributed across the two genes are genotyped. Moderate evidence of association is found between spine BMD and six SNPs in the ALOX12 gene in both men and women. These data conclude that polymorphisms in the ALOX12 gene may contribute to normal variation in spine BMD.

### **Alzheimer's disease**

**Note:** Alzheimer's disease (AD) is a chronic neurodegenerative disorder that impairs cognition and behavior. Although the initiating molecular events are not known, increasing evidence suggests that 12/15-LOX is a major source of oxidative stress which could play a functional role in pathogenesis. Quantitative Western blot analysis confirmed by immunohistochemical studies demonstrate that in affected frontal and temporal regions of AD brains, the amount of 12/15-LOX is higher compared to controls. Also metabolic products of 12/15-LOX are markedly elevated in AD brains compared to controls.

### **Bladder cancer**

**Note:** 12-LOX expression is shown to be induced in bladder cancer tissues by an immunohistochemistry analysis. Also lipoxygenase inhibitors cause marked inhibition of bladder cancer cells in a concentration and time dependent manner. Cells treated with lipoxygenase inhibitors show chromatin condensation, cellular shrinkage, small membrane bound bodies (apoptotic bodies) and cytoplasmic condensation.

### **Testicular cancer**

**Note:** 12-LOX is only slightly expressed in normal testis tissues, however, 12-LOX expression is found to be significant in testicular cancer tissues by immunohistochemistry studies. Specific LOX inhibitors have also been shown to inhibit the growth of testicular cancer in cell lines.

### **Prostate cancer**

**Note:** Research focusing on mechanisms of action of 12-lipoxygenase in prostate cancer cells revealed that overexpression of 12-lipoxygenase in PC-3 cells results in a 3-fold increase in VEGF protein level when compared with vector control cells and there is an

increase in PI3-kinase activity in 12-LOX-transfected PC-3 cells.

The expression of 12-LOX is detected to be low in benign prostatic hyperplasia and normal prostate tissues, whereas marked expression of 12-lipoxygenase is detected in prostatic intraepithelial neoplasia and prostate cancer tissues. The LOX inhibitors cause marked cellular death through apoptosis in prostate cancer cells in a concentration and time-dependent manner.

Another effect of 12-LOX in prostate cancer cells is that increase in 12-LOX expression enhances the metastatic potential of human prostate cancer cells. 12-LOX transfected PC-3 cells show a significant change in cell adhesiveness, spreading, motility, and invasiveness.

### **Breast cancer**

**Note:** Total cellular RNA extraction from 64 frozen tissue samples of breast carcinoma and their corresponding normal adjacent tissues is performed for expression analysis of cyclooxygenase-2 and 12-lipoxygenase using RT-PCR. 62.5% of carcinoma samples showed over-expression of 12-lipoxygenase as compared to normal breast tissues. Results also reveal that and 12-lipoxygenase mRNA expressions are associated with TNM staging in human breast cancer.

A second study indicates that levels of 12-lipoxygenases together with 5-lipoxygenase are also particularly high in tumours from patients who died of breast cancer. Therefore raised level of 12-lipoxygenase might have prognostic value in patients with breast cancer.

## **References**

- Takahashi Y, Glasgow WC, Suzuki H, Taketani Y, Yamamoto S, Anton M, Kühn H, Brash AR. Investigation of the oxygenation of phospholipids by the porcine leukocyte and human platelet arachidonate 12-lipoxygenases. *Eur J Biochem* 1993;218:165-171.
- Yoshimoto T, Yamamoto S. Arachidonate 12-lipoxygenase. *J Lipid Mediat Cell Signal* 1995;12(2-3):195-212.
- Liu YW, Arakawa T, Yamamoto S, Chang WC. Transcriptional activation of human 12-lipoxygenase gene promoter is mediated through Sp1 consensus sites in A431 cells. *Biochem J* 1997;324 (1):133-140.
- Sun D, Elsea SH, Patel PI, Funk CD. Cloning of a human epidermal-type 12-lipoxygenase-related gene and chromosomal localization to 17p13. *Cytogenet Cell Genet* 1998;81(1):79-82.
- McDonnell M, Li H, Funk CD. Characterization of epidermal 12(S) and 12(R) lipoxygenases. *Adv Exp Med Biol* 2002;507:147-153.
- Jiang WG, Douglas-Jones A, Mansel RE. Levels of expression of lipoxygenases and cyclooxygenase-2 in human breast cancer. *Prostaglandins Leukot Essent Fatty Acids* 2003;69:275-281.
- Kandouz M, Nie D, Pidgeon GP, Krishnamoorthy S, Maddipati KR, Honn KV. Platelet-type 12-lipoxygenase activates NF-

- kappaB in prostate cancer cells. Prostaglandins Other Lipid Mediat 2003;71:189-204.
- Nie D, Nemeth J, Qiao Y, Zacharek A, Li L, Hanna K, Tang K, Hillman GG, Cher ML, Grignon DJ, Honn KV. Increased metastatic potential in human prostate carcinoma cells by overexpression of arachidonate 12-lipoxygenase. Clin Exp Metastasis 2003;20:657-663.
- Yoshimura R, Matsuyama M, Tsuchida K, Kawahito Y, Sano H, Nakatani T. Expression of lipoxygenase in human bladder carcinoma and growth inhibition by its inhibitors. J Urol 2003;170:1994-1999.
- Goodman JE, Bowman ED, Chanock SJ, Alberg AJ, Harris CC. Arachidonate lipoxygenase (ALOX) and cyclooxygenase (COX) polymorphisms and colon cancer risk. Carcinogenesis 2004;25:2467-2472.
- Matsuyama M, Yoshimura R, Mitsuhashi M, Hase T, Tsuchida K, Takemoto Y, Kawahito Y, Sano H, Nakatani T. Expression of lipoxygenase in human prostate cancer and growth reduction by its inhibitors. Int J Oncol 2004;24:821-827.
- Praticò D, Zhukareva V, Yao Y, Uryu K, Funk CD, Lawson JA, Trojanowski JQ, Lee VM. 12/15-lipoxygenase is increased in Alzheimer's disease: possible involvement in brain oxidative stress. Am J Pathol 2004;164:1655-1662.
- Yoshimura R, Matsuyama M, Mitsuhashi M, Takemoto Y, Tsuchida K, Kawahito Y, Sano H, Nakatani T. Relationship between lipoxygenase and human testicular cancer. Int J Mol Med 2004;13:389-393.
- Chang WC, Chen BK. Transcription factor Sp1 functions as an anchor protein in gene transcription of human 12(S)-lipoxygenase. Biochem Biophys Res Commun 2005;338(1):117-121.
- Hung JJ, Wang YT, Chang WC. Sp1 deacetylation induced by phorbol ester recruits p300 to activate 12(S)-lipoxygenase gene transcription. Mol Cell Biol 2006;26(5):1770-1785.
- Ichikawa S, Koller DL, Johnson ML, Lai D, Xuei X, Edenberg HJ, Klein RF, Orwoll ES, Hui SL, Foroud TM, Peacock M, Econs MJ. Human ALOX12, but not ALOX15, is associated with BMD in white men and women. J Bone Miner Res 2006;21:556-564.
- Mohammad AM, Abdel HA, Abdel W, Ahmed AM, Wael T, Eiman G. Expression of cyclooxygenase-2 and 12-lipoxygenase in human breast cancer and their relationship with HER-2/neu and hormonal receptors: impact on prognosis and therapy. Indian J Cancer 2006;43:163-168.
- Nie D, Krishnamoorthy S, Jin R, Tang K, Chen Y, Qiao Y, Zacharek A, Guo Y, Milanini J, Pages G, Honn KV. Mechanisms regulating tumor angiogenesis by 12-lipoxygenase in prostate cancer cells. J Biol Chem 2006;281:18601-18609.
- Quintana LF, Guzmán B, Collado S, Clària J, Poch E. A coding polymorphism in the 12-lipoxygenase gene is associated to essential hypertension and urinary 12(S)-HETE. Kidney Int 2006;69:526-530.
- Tan W, Wu J, Zhang X, Guo Y, Liu J, Sun T, Zhang B, Zhao D, Yang M, Yu D, Lin D. Associations of functional polymorphisms in cyclooxygenase-2 and platelet 12-lipoxygenase with risk of occurrence and advanced disease status of colorectal cancer. Carcinogenesis 2006 Dec 6.
- Gong Z, Hebert JR, Bostick RM, Deng Z, Hurley TG, Dixon DA, Nitcheva D, Xie D. Common polymorphisms in 5-lipoxygenase and 12-lipoxygenase genes and the risk of incident, sporadic colorectal adenoma. Cancer 2007;109:849-857.

---

*This article should be referenced as such:*

Banerjee S, Erdog A. ALOX12 (arachidonate 12-lipoxygenase) *Homo sapiens*. Atlas Genet Cytogenet Oncol Haematol.2007; 11(3):222-225.

---