

Gene Section Review

ALOX15 (arachidonate 15-lipoxygenase)

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Identity

Hugo: ALOX15

Other names: 15-LOX; EC 1.13.11.33; arachidonate omega 6-lipoxygenase; LOG15

Location: 17p13.3

Local order: Genes flanking ALOX15 in centromere to telomere direction on 17p13 are:

- MYBBP1A 17p13.3 MYB binding protein (P160) 1a,
- GGT6 17p13.2 homolog of gamma-glutamyltransferase 6,
- LOC124974 17p13.2, thioredoxin 1 pseudogene 4,
- SMTNL2 17p13.2 smoothelin-like 2,
- ALOX15 17p13.2 arachidonate 15-lipoxygenase (Homo sapiens),
- PELP1 17p13.2 proline, glutamic acid and leucine rich protein 1,
- ARRB2 17p13 arrestin, beta 2.

Note: Arachidonate 15-Lipoxygenase (15-LOX-1) is one of several LOX isoforms that oxygenates polyunsaturated fatty acids as well as complex substrates such as biomembranes. Its expression is associated with the development of inflammatory diseases such as atherosclerosis, asthma, cancer and osteoporosis.

DNA/RNA

Note: With the exception of ALOX5, all human LOX genes, including ALOX15, are clustered on the short arm of chromosome 17 within a few megabases of each other. ALOX12, which has 86% sequence homology to ALOX15 is in closest proximity (17p13.1). 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

ALOX15 gene spans a region of 10.7 kilo bases and has 14 exons, the sizes being 149, 202, 82, 123, 104, 161, 144, 210, 87, 170, 122, 101, 108 and 859 bps.

Transcription

ALOX15 mRNA has 2702 bps.

TH2 cytokines IL-4 and IL-13 have been shown to transcriptionally upregulate 15-LOX-1 expression via phosphorylation of Signal Transducer and Activator of transcription (STAT) proteins, particularly STAT-1, STAT-3 and STAT-6 and their translocation to the nucleus. Acetylation of histones, which block STAT6 binding at the 15-LOX-1 promoter if they are present as nonacetylated proteins, enables promoter binding of phosphorylated and acetylated STAT6, which in turn may lead to transcriptional activation of the 15-LOX gene.

NSAIDS have been reported to upregulate 15-LOX-1 expression through GATA-6. Ku70/ku80 lupus autoantigen transcription factors have also been reported to be induced by IL-4 and IL-13 in the upregulation of ALOX15. In addition, demethylation of the 5' CpG islands in the promoter region of ALOX15 has been shown to transcriptionally upregulate the gene.

ALOX15 mRNA is expressed in bone marrow, spleen, thymus, spinal cord, heart, skeletal muscle, liver, prostate, kidney and lung.

Pseudogene

The arachidonate 15-lipoxygenase pseudogene (ALOX15P) is located on 17p13.1.

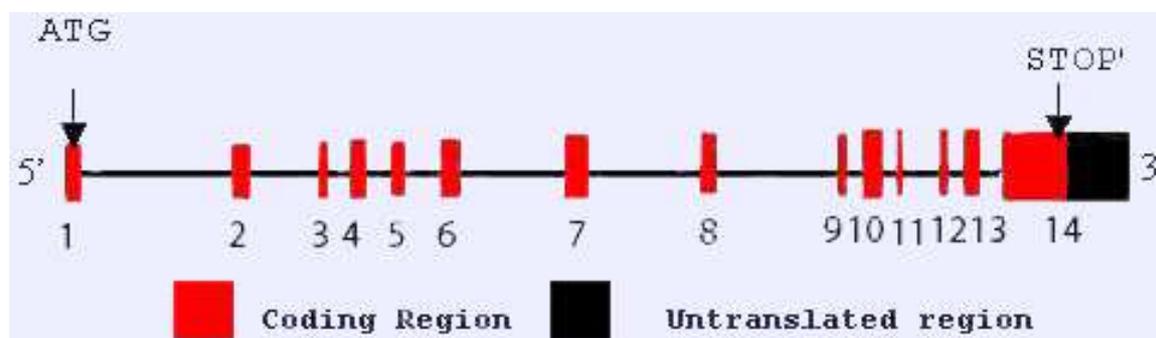


Diagram of the ALOX15 gene. Exons are represented by red boxes (in scale) untranscribed sequences in black, with exon numbers on the bottom. The arrows show the ATG and the stop codons respectively.

Protein

Note: Two different 15-Lipoxygenases exist, 15-LOX-1 (reticulocyte type) and 15-LOX-2 (epidermis type), differentiated by their tissue expression and a 40% homology at the amino acid level. 15-LOX-1 preferentially oxygenates linoleic acid into 13(S)-hydroxyoctadecadienoic acid (13(S)-HPODE) whereas 15-LOX-2 preferentially metabolizes arachidonic acid (AA) to 15S- hydroperoxyeicosatetraenoic acid (15-HETE) with poor activity with linoleic acid (LA).

Description

15-LOX-1 protein consists of 661 amino acids and is 74.7 kDa. It contains 1 gram atom of non-haem non-sulphur bound iron per mole of the enzyme. Conserved domain search, the presence of a polycystin/lipoxygenase/alpha-toxin (PLAT) domain in the 15-LOX-1 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 membrane binding domain of the rabbit reticulocyte 15-LOX are determined by a concerted action of the N-terminal beta-barrel and the C-terminal catalytic domain.

Expression

15-LOX-1 was first purified in rabbit reticulocytes and was subsequently found to be specifically expressed or induced in mast cells, eosinophils, activated monocytes or dendritic cells, and bronchial epithelial cells.

Localisation

Located in the cytoplasm.

Function

15-LOX-1 is a member of the inflammatory leukotriene biosynthesis pathway where, in presence of molecular oxygen, it converts arachidonic acid to (15-HETE). Also acts on C-12 of arachidonate forming products (12-HETE) at a ratio of 12:1 (15-HETE:12-HETE). Preferentially converts linoleic acid to 13(S)-HODE.

Homology

C. familiaris LOC4894581 similar to Arachidonate 15-lipoxygenase;
R. norvegicus: Alox15 arachidonate 12-lipoxygenase;
M. musculus: Alox15 arachidonate 15-lipoxygenase (12/15LOX);
A. thaliana: F12B7.11, F12B7_111 iron ion binding / lipoxygenase.

Mutations

Note: No mutations have been reported for ALOX15 that cause congenital anomalies. Single nucleotide polymorphism (SNP) studies have revealed that a C-to-T base exchange (-292C/T) enhances the transcriptional activity of the ALOX15 promoter in macrophages through the generation of a novel SPI1 transcription factor binding site. In addition, a G to A base exchange (-5229G/A) in the ALOX15 promoter region has been associated with low bone mineral density.

Implicated in

Prostate cancer

Note: Genechip study of the mRNA levels of key enzymes involved in the LA and AA pathways in 18 human donor (normal) prostates compared to 60 prostate tumours showed a lower level of 15-LOX-1 expression (the key enzyme in the LA pathway) in contrast to a higher 15-lipoxygenase-2 expression in donor (normal) prostates. On the other hand, significantly high levels of 15-LOX-1 and low levels of 15-LOX-2/ALOX15B were observed in prostate carcinoma tissues.

Colorectal cancer

Note: The role of 15-LOX-1 in colorectal cancer is controversial with some researchers claiming a mitogenic role through up-regulation of the EGF signaling pathway as well as activation of ERK and down regulation of anti-inflammatory PPAR-gamma transcriptional activity. Its upregulation by mutant

TP53 has been reported. On the other hand, in recent years others have shown that 15-LOX-1 expression is reduced in colorectal cancer and implicated 13(S)-HPODE in the pro-apoptotic functions of 15-LOX-1. 15-LOX-1 expression was shown to be down-regulated in colorectal adenomas (compared with non neoplastic epithelial mucosa) in 87% (13 of 15) of patients with familial adenomatous polyposis resulting in an escape from apoptosis.

Ectopic restoration of 15-LOX-1 expression re-established apoptosis in Caco-2 colon cancer cells. A proapoptotic function ascribed to 15-LOX-1 and 15-LOX-2 in colon cancer is said to be through the activation of the anti-tumorigenic PPAR-gamma and down-regulation of the pro-tumorigenic PPAR-delta/beta. In addition, the apoptotic functions of NSAIDs are reported to be via an upregulation of 15-LOX-1.

Breast cancer

Note: An immunoblot analysis of metastatic human breast carcinoma cells with antibodies to 15-LOX-1 and 15-LOX-2 indicated that it is the 15(S)-LOX-2 isoform that generates 15-HETE and activates specific growth factor receptor-related signalling pathways, thereby initiating signal transduction events resulting in enhanced cell adhesion to the extracellular matrix. However, a second study indicated that both 15-LOX-2 and 15-LOX-1 were expressed at significantly lower levels in metastatic tumours and in patients who died of breast cancer related causes. This reduction is correlated with the disease progression of breast cancer and a poor clinical outcome.

Atherosclerosis

Disease

Atherosclerosis is a chronic proliferative disease of the arterial wall that is associated with aberrant immune reactions. A proatherogenic activity of 12/15LOX via oxidation of low density lipoproteins and formation of foam cells in various rodent atherosclerosis models has been shown. A similar extrapolation to humans has not been convincingly proven, particularly since significantly lower expression of 15-LOX-1 was detected in diseased and normal human arteries when compared to 5-LOX.

Asthma

Disease

Patients with severe asthma with persistent airway eosinophils have been shown to manifest high levels of 15(S)-HETE in bronchoalveolar lavage (BALF), which may be associated with airway fibrosis. In addition, IL-4-induced apoptosis via upregulation of 15-LOX-1 and PPAR-gamma may contribute to severe loss of alveolar structures and infiltration of eosinophils, mononuclear phagocytes, etc., into the lung tissue of chronic asthma patients.

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