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Gene Section
Short Communication

KLK12 (kallikrein-related peptidase 12)

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Abstract

Review on KLK12, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
Kallikreins; KLK12; Prostate cancer; Breast cancer; Gastric cancer; Non-small cell lung cancer;

Identity

Other names: KLK-L5, KLKL5

HGNC (Hugo): KLK12

Location: 19q13.41

Local order: Telomere to centromere

DNA/RNA

Description

The KLK12 gene has a total length of 6.700 nt and consists of 7 exons and 6 intervening introns.
The organization of the KLK12 gene is similar to that of the other KLK family members (Yousef et al., 2000).

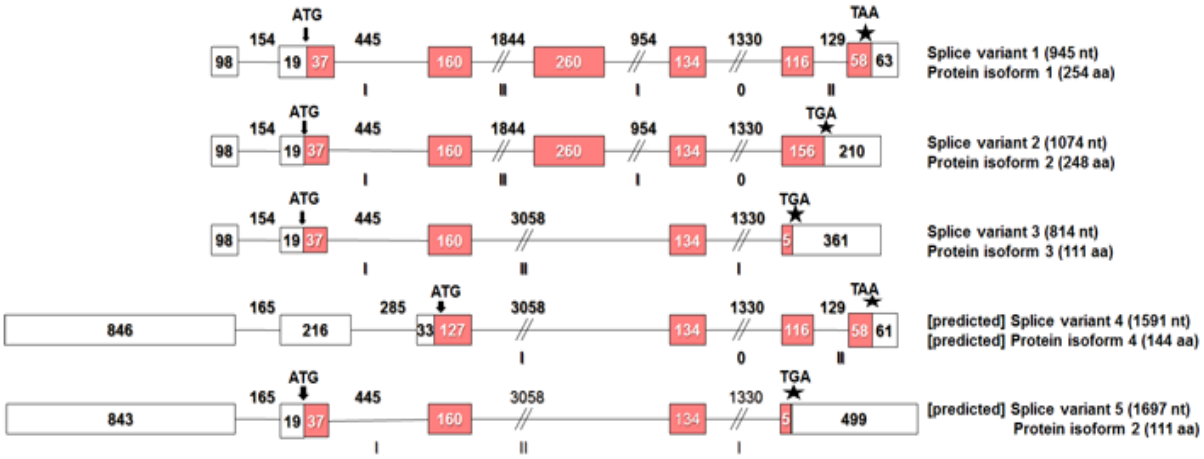

Figure 1. Schematic representation of the KLK12 gene. Exons are shown as boxes and introns as connecting lines. The coding sequences are highlighted as red, while 5' and 3' untranslated regions (UTRs) are shown in white. Numbers inside or outside boxes indicate lengths (nt) of exons and introns, respectively, while numbers in parentheses indicate lengths (aa) of protein isoforms. Arrows show the position of the start codons (ATG) and asterisks (*) denote the position of the stop codons (TAA or TGA). Roman numerals indicate intron phases. The intron phase refers to the location of the intron within the codon; I denotes that the intron occurs after the first nucleotide of the codon, II denotes that the intron occurs after the second nucleotide, and 0 means that the intron occurs between distinct codons. The figure is drawn to scale, except for the introns containing the (//) symbol.

Four different types of genetic polymorphisms have been identified so far: one at a splice-donor site of intron 4 (c.457+2T>C), two in exon 6 (c.618_619delTG:p.Cys206fsX72 and c.735G>A:p.Met245Ile), and one in intron 3. The c.457+2T>C polymorphism was found at a high frequency (allele frequency:0.63), compared to the frequencies of the two polymorphisms in exon 6 (allele frequency:0.01) (Shinmura et al., 2004).

Transcription

The KLK12 gene is subjected to alternative splicing, generating three splice variants, which are considered to encode distinct protein isoforms (Kurlender et al., 2005). Each coding splice variant consists of a distinctive exon combination. The predominant transcript, consisting of 945 nt, includes all 7 exons and encodes isoform 1 precursor. The second transcript uses alternate splice sites in the 3' coding region, in comparison with the aforementioned variant, generating a protein with a distinct C-terminus compared to the isoform 1 precursor. The third transcript lacks an exon in the coding region and uses alternate splice sites in the 3' coding region, compared to the first variant, generating a protein with a shorter and distinct C-terminus compared to isoform 1.

Two more splice variants are predicted to be encoded by the KLK12 gene, based on automatic sequence analysis of expressed sequence tags (ESTs). One of them is similar to the third variant; it differs only by having longer 5'- and 3'-untranslated regions (5'-UTR and 3'-UTR). The second one contains a 3'-extended exon 2, which abolishes the original translation start codon (ATG); an alternative start codon located in exon 3 is predicted to be used.

Pseudogene

Not identified so far.

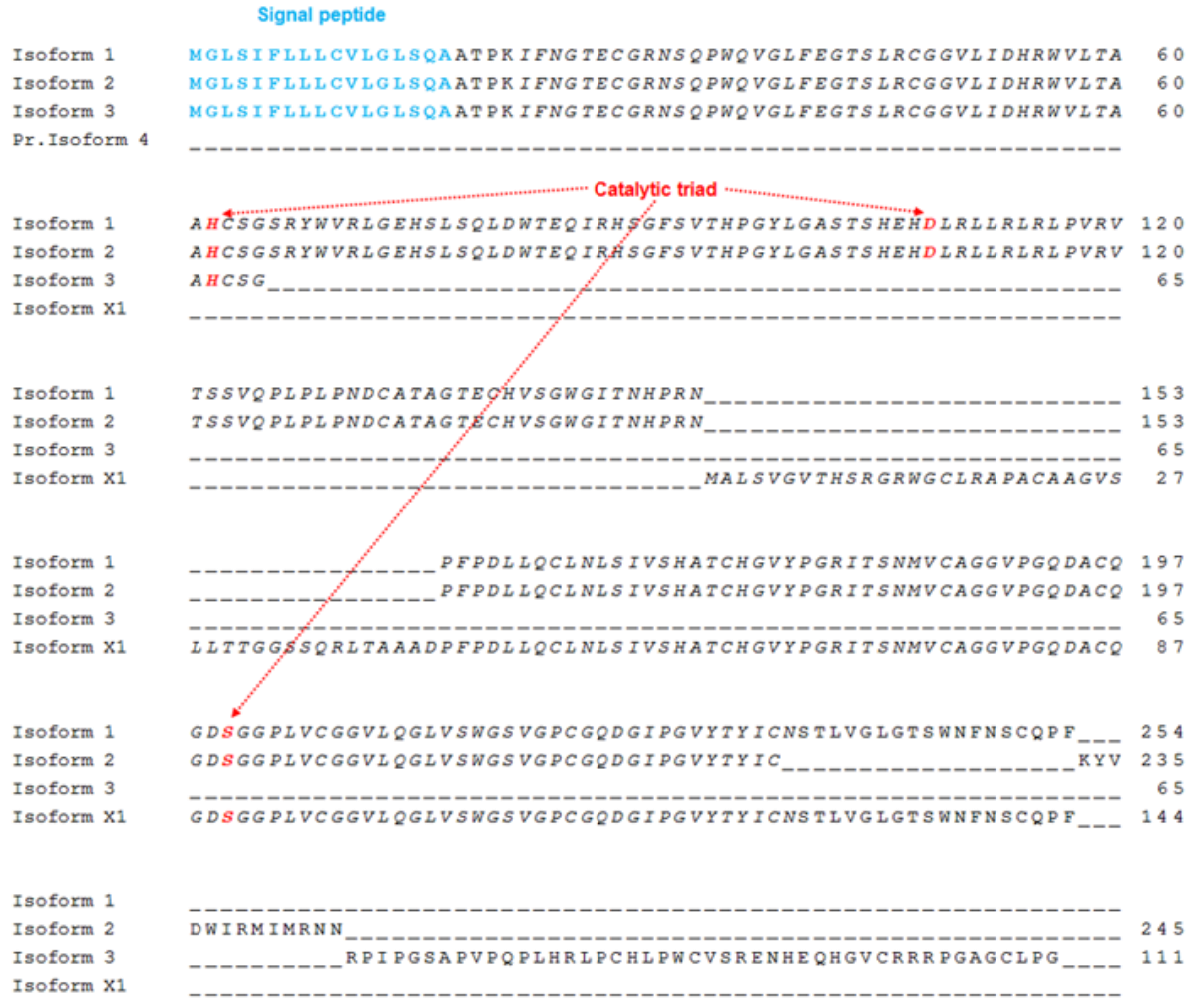

Figure 2. Alignment of amino acid sequences of the precursors of the KLK12 protein isoforms. The three amino acid residues (positions: 62, 108, and 200) constituting the catalytic triad that is required for protease activity are shown in red. The N-terminal signal peptide (positions 1-17) is shown in light blue.

Protein

Description

The main KLK12 isoform (isoform 1) precursor, designated as the classical one, consists of 254 amino acid residues and has a molecular mass of 25.3 kDa. The N-terminal signal peptide comprises 17 amino acid residues. KLK12 is a secreted trypsin-like serine protease, cleaving peptide bonds after both arginine and lysine (Memari et al., 2007; Yousef et al., 2000). KLK12 protein isoforms are synthesised as inactive precursor zymogens that are cleaved at the position 21 during limited proteolysis to generate their active forms. Three amino acid residues (positions: 62, 108, and 200) constitute the catalytic triad that is required for protease activity. KLK12 isoform 2 has a distinct C-terminus compared to isoform 1, and its precursor form consists of 248 amino acid residues. KLK12 isoform 3 has a shorter and distinct C-terminus compared to isoform 1, and its precursor form consists of 111 amino acid residues.

KLK12 is secreted as an inactive pro-enzyme, which can be self-activated to gain enzymatic activity. Active KLK12 shows trypsin-like activity, but quickly loses its activity due to autodegradation. KLK12 activity can also be rapidly inhibited by zinc ions and by α2-antiplasmin through covalent complex formation. It has been suggested that KLK12 participates in enzymatic cascades involving other KLKs (Memari et al., 2007). KLK12 is able to cleave all six members of the CCN family (CYR61, CTGF, NOV, WISP1, WIPS2, and WISP3) at different proteolytic sites, thus indirectly regulating the bioavailability and activity of several growth factors through processing of their CCN-binding partners (Guillon-Munos et al., 2011). In vivo substrates include also the thrombolytic zymogens plasminogen, urokinase, and plasma kallikrein. Another substrate of KLK12 secreted by the respiratory tract is influenza HA protein (Hamilton and Whittaker, 2013). Furthermore, KLK12 participates in the control of angiogenesis via a PDGFB-dependent paracrine pathway (Kryza et al., 2013; Kryza et al., 2014). On the other hand, the proteolytic activity of KLK12 is inhibited by the action of serine peptidase inhibitor, Kazal type 6 (SPINK6) in the skin (Kantyka et al., 2011).

Expression

KLK12 mRNA is primarily expressed in the salivary gland, stomach, uterus trachea, prostate, thymus, lung, colon, brain, breast, and thyroid gland. However, lower levels of KLK12 mRNA expression are found in other tissues too, including testis, pancreas, small intestine, and spinal cord (Yousef et al., 2000).

Implicated in

Prostate cancer

KLK12 single nucleotide polymorphism (SNP) rs3865443 is significantly associated with increased risk of prostate cancer; still, this association has been described as marginal (Lose et al., 2013).

Breast cancer

Note

KLK12 mRNA expression is downregulated in breast cancer tissues and is upregulated by steroid hormones in breast and prostate cancer cell lines (Talieri et al., 2012; Yousef et al., 2000).

Prognosis

KLK12 variant 3 expression is downregulated in breast tumors of small size, high grade, and advanced TNM stage. Moreover, KLK12 variant 3 overexpression is associated with superior disease-free survival (DFS) rates for breast cancer patients, as well as with elevated progesterone receptor (PR) concentration (Talieri et al., 2012).

Gastric cancer

Note

Expression of the KLK12 gene is significantly upregulated in gastric cancer tissues, as compared with normal gastric tissues, both at the mRNA and protein level.

Prognosis

KLK12 overexpression is significantly associated with lymph node metastasis, histological type, and TNM. Furthermore, patients with gastric tumors showing high KLK12 expression have a significantly worse five-year survival rate than those with tumors with low KLK12 expression (Zhao et al., 2012).

Non-small cell lung cancer

KLK12 levels are lower in sera from non-small cell lung cancer patients than in sera from normal controls. Serum KLK12 concentration is likely to be associated with disease stage (Planque et al., 2008).

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