

## Gene Section

### Short Communication

# KLK14 (kallikrein-related peptidase 14)

Christos K. Kontos, Andreas Scorilas

Department of Biochemistry and Molecular Biology, National and Kapodistrian University of Athens, Athens, Greece / [ascorilas@biol.uoa.gr](mailto:ascorilas@biol.uoa.gr)

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## Abstract

Review on KLK14, with data on DNA, on the protein encoded, and where the gene is implicated.

### Keywords

Kallikreins; KLK14; Prostate cancer; Breast cancer; Gastric cancer; Non-small cell lung cancer;

## Identity

**Other names:** KLK-L6

**HGNC (Hugo):** KLK14

**Location:** 19q13.41

**Local order:** Telomere to centromere.

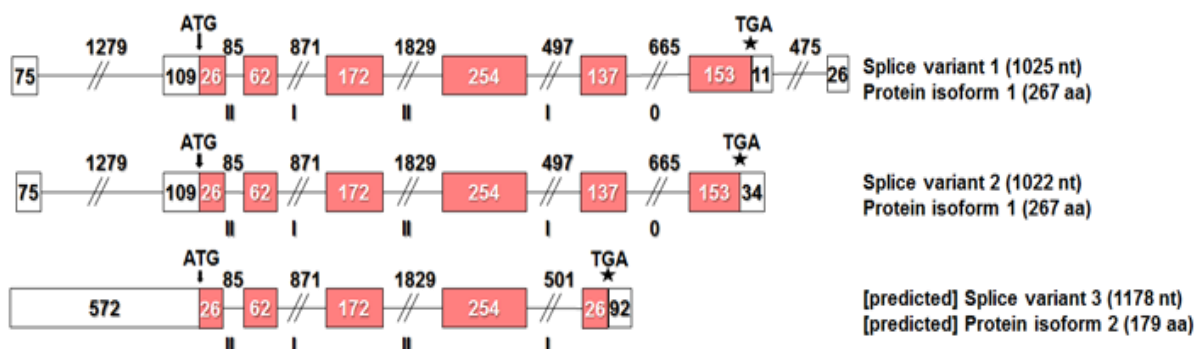
## DNA/RNA

### Description

The KLK14 gene has a total length of 6.700 nt and consists of 8 exons and 7 intervening introns. The organization of the KLK14 gene is similar to that of the other KLK family members (Hooper et al., 2001; Yousef et al., 2001).

### Transcription

The KLK14 gene is subjected to alternative splicing, generating two splice variants, which encode the same protein (Kurlender et al., 2005). These two splice variants differ only in their 3'-untranslated region (3'-UTR).



**Figure 1.** Schematic representation of the KLK14 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.

|               |  |     |
|---------------|--|-----|
| Isoform 1     | MSLRVLGSGTWPSPAPKMFLLLTALQVLAIAMTQSQEEDENKIIIGGHTCTRSSQPWQAALLA  | 60  |
| Pr. Isoform 1 | MSLRVLGSGTWPSPAPKMFLLLTALQVLAIAMTQSQEEDENKIIIGGHTCTRSSQPWQAALLA  | 60  |
| Isoform 1     | GPRRRFLCGGALLSGQWVITAAHCGRPI LQVALGKHNLRWEATQQVLRVVRQVTHPNYN     | 120 |
| Pr. Isoform 1 | GPRRRFLCGGALLSGQWVITAAHCGRPI LQVALGKHNLRWEATQQVLRVVRQVTHPNYN     | 120 |
| Isoform 1     | SRTHDNDLMLLQLQQPARIGRAVRPIEVTQACASPGTSCRVS GWGTISSPIARYPASLQC    | 180 |
| Pr. Isoform 1 | SRTHDNDLMLLQLQQPARIGRAVRPIEVTQACASPGTSCRVS GWGTISSPI_____        | 171 |
| Isoform 1     | VNINIS PDEV CQKAYPRTITPGMVCAGVPQGGK DSCQGD SGGPLVCRGQLQGLVSWGMER | 240 |
| Pr. Isoform 1 | -----  | 171 |
| Isoform 1     | CALPGYPGVYTNLCKYRSWIEETMRDK                                      | 267 |
| Pr. Isoform 1 | -----GTPPLCNA  | 179 |

**Figure 2.** Alignment of amino acid sequences of the precursors of the KLK14 protein isoforms. The three amino acid residues (positions: 83, 127, and 220) constituting the catalytic triad that is required for protease activity are shown in red. The N-terminal signal peptide (positions 1-34) is shown in light blue.

One more splice variant is predicted to be encoded by the KLK14 gene, based on automatic sequence analysis of expressed sequence tags (ESTs). This splice variant uses the same start codon, but uses an alternate splice sites in the 3' coding region, in comparison with the aforementioned variants, generating a protein with a distinct C-terminus compared to the classical isoform precursor.

### Pseudogene

Not identified so far.

## Protein

### Description

The classical KLK14 isoform (isoform 1) precursor consists of 267 amino acid residues and has a molecular mass of 29.1 kDa. The N-terminal signal peptide comprises 34 amino acid residues. KLK14 is a secreted serine protease having dual activity, trypsin- and chymotrypsin-like, with a preference for cleavage after arginine residues (Felber et al., 2005; Rajapaksei and Takahashi, 2007). KLK14 protein is synthesized as inactive precursor zymogen that is cleaved at the position 41 during limited proteolysis to generate its active form (Borgono et al., 2007). Three amino acid residues (positions: 83, 127, and 220) constitute the catalytic triad that is required for protease activity.

### Expression

KLK14 mRNA is primarily expressed in the prostate, salivary gland, stomach, lung, spleen, uterus, thymus, liver, small intestine, and cerebellum while lower levels of expression are found in many other tissues. KLK14 mRNA expression is downregulated in malignant breast, testicular, prostatic, and ovarian tumors (Yousef et al., 2001).

### Function

Several human protein substrates for KLK14 have already been identified, including major components of the extracellular matrix such as collagens I-IV, fibronectin, laminin, kininogen, fibrinogen, plasminogen (PLG), vitronectin (VTN), and insulin-like growth factor-binding proteins 2 and 3 (IGFBP2 and IGFBP3) (Borgono et al., 2007; Felber et al., 2005). Thus, this secreted cancer-related peptidase may be involved in several facets of tumor progression, including growth, invasion, and angiogenesis, as well as in arthritic disease via deterioration of cartilage (Borgono et al., 2007). Additionally, KLK14 is implicated in other physiological functions too, such as desquamation and activation of signaling molecules associated with inflammation and cancer (de Veer et al., 2012). In fact, this enzyme may be responsible for as much as 50% of the total trypsin-like activity in stratum corneum, thus suggesting an important role for this very efficient protease under normal and disease conditions in the skin (Stefansson et al., 2006). KLK14 can also directly cleave semenogelins I and II (SEMG1 and SEMG2), thus playing a major role in seminal clot liquefaction (Emami et al., 2008). In addition, active KLK14 is efficiently able to cleave C3, the point of convergence of the complement cascade, indicating a potential modulation of C3-mediated functions. Thus, it participates in the activation of the innate immune response (Oikonomopoulou et al., 2013). Members of the proteinase-activated receptor (PAR) family constitute also targets of KLK14; their activation upon cleavage by KLK14 leads to differential signaling and affects tissue function (Ramachandran et al., 2012). For instance, KLK14 acts on proteinase-activated receptor 2 (F2RL1 or

PAR2) to induce MAPK3/ MAPK1 (ERK1/ERK2) signaling pathway in colon cancer ID: 5006> cells (Gratio et al., 2011). Besides its other actions, human KLK14 activates the KLK proteolytic cascade (Emami and Diamandis, 2008). Very recently, it has also been suggested that elevated KLK14 activity contributes at multiple levels the activation of the oncogenic hepatocyte growth factor (HGF)/MET signaling in prostate cancer and other human malignancies (Reid et al., 2016).

Regarding the regulation of the enzymatic activity of KLK14, the serpins SERPINA1 (alpha-1 antitrypsin), SERPINF2 (alpha-2 antiplasmin), SERPINC1 (antithrombin III), and SERPINA3 (alpha-1 antichymotrypsin), as well as SERPINE1 (plasminogen activator inhibitor-1) constitute inhibitors of this serine protease. Moreover, citrate enhance KLK14 activity, whereas zinc ions exert inhibitory action on KLK14 (Borgono et al., 2007; Felber et al., 2006). SPINK5 (LEKTI) fragments specifically inhibit KLK14 as well as other KLKs, thus controlling desquamation through a pH-dependent interaction (Deraison et al., 2007)

## Implicated in

### Prostate cancer

#### Note

KLK14 is expressed by both benign and malignant glandular epithelial cells of the prostate (Hooper et al., 2001). However, KLK14 is significantly overexpressed in the majority of cancerous prostatic tissue specimens, as compared with their non-malignant counterparts.

#### Prognosis

Moreover, KLK14 protein overexpression was associated with advanced stage, high tumor grade, and high Gleason score ( $\geq 7$ ) (Rabien et al., 2008; Yousef et al., 2003). Moreover, high KLK14 levels predict biochemical relapse of prostate cancer patients, independently of other established prognostic factors (Rabien et al., 2008). Therefore, KLK14 has been suggested as a candidate novel marker for prostate cancer diagnosis and prognosis (Yousef et al., 2003), as well as for the detection of cases at risk of disease progression after radical prostatectomy (Rabien et al., 2008).

Three common genetic variants in the KLK14 locus were shown to be associated with higher Gleason score ( $\geq 7$ ). Two of them, namely rs17728459 and rs4802765, are both located upstream of the transcribed KLK14 region, whereas the third one (rs35287116) is located inside KLK14 coding region and accounts for a p.Gln33Arg substitution in the KLK14 signal peptide (Lose et al., 2012).

### Breast cancer

#### Note

KLK14 mRNA overexpression was observed in malignant breast tumors in comparison with normal breast tissues and benign breast tumors (Fritzsche et al., 2006; Papachristopoulou et al., 2011).

#### Prognosis

KLK14 mRNA overexpression was associated with high tumor grade and tumor volume, as well as with negative estrogen receptor (ER) status (Papachristopoulou et al., 2011). Accordingly, cytoplasmic KLK14 protein expression was significantly higher in invasive breast carcinomas than in normal breast tissue specimens.

Moreover, KLK14 protein overexpression was associated with high histological grade and positive nodal status. However, it failed to predict patient outcome (Fritzsche et al., 2006). Additionally, serum KLK14 levels were elevated in 40% of patients with breast cancer (Borgono et al., 2003). Thus, KLK14 constitutes a potential diagnostic biomarker in breast cancer, while its prognostic utility is questionable. Moreover, KLK14 mRNA expression has been suggested as a biomarker for prediction of breast cancer patients' response to chemotherapy (Papachristopoulou et al., 2013).

### Ovarian cancer

KLK14 is considered to be involved in the malignant behavior of ovarian cancer cells (Zhang et al., 2012). KLK14 protein levels were higher in 40% of ovarian cancer tissues, as compared to normal ovarian tissues.

Moreover, serum KLK14 levels were elevated in 65% of patients with ovarian cancer (Borgono et al., 2003). Thus, KLK14 constitutes a potential biomarker in ovarian cancer and a therapeutic target, as well (Borgono et al., 2003; Zhang et al., 2012).

### Salivary gland cancer

Both pleomorphic adenoma and adenoid cystic carcinoma of the salivary glands showed elevated KLK14 expression than normal glands and mucoepidermoid carcinoma tissues.

These observed differences in KLK14 protein levels imply that KLKs may aid in the differential diagnosis of salivary gland tumors.

KLK14 is considered as a promising novel biomarker for salivary gland tumors (Hashem et al., 2010).

### Chronic lymphocytic leukemia

#### Note

KLK14 mRNA overexpression is able to successfully distinguish patients with chronic lymphocytic leukemia (CLL) from non-leukemic population.

#### Prognosis

Furthermore, although not clearly associated to clinical staging or other prognostic factors including

IGHV mutational status and CD38 expression, high KLK14 mRNA expression predicts poor overall survival of B-CLL patients. The unfavorable prognostic value of KLK14 mRNA positivity in peripheral blood mononuclear cells of B-CLL patients was shown to be independent of established prognostic factors of this hematological malignancy. As a result, KLK14 mRNA expression has been suggested as a prognostic biomarker of overall survival of B-CLL patients (Kontos et al., 2016)

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