

## Gene Section

### Short Communication

# KLK9 (kallikrein-related peptidase 9)

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## Abstract

Kallikreins (KLKs) represent the largest cluster of serine peptidases, which is composed of 15 members (KLK1-15). The human kallikrein-related peptidase 9 gene (KLK9), like the rest of the KLK genes, encodes for a trypsin-like serine peptidase. Serine peptidases are a group of protein-cleaving enzymes that contain a serine residue in their active site.

Kallikreins constitute a subfamily of serine peptidases that cleave kininogen and release vasoactive peptides (kinins). The human KLK9 gene is located at 19q13.41 and consists of 5 exons and 4 intervening introns. Although KLK9 expression has been detected in various normal human tissues, differences in mRNA and protein expression levels have been observed. Like other KLKs, KLK9 is found differentially expressed in multiple human malignancies. Clinical studies regarding the KLK9 expression analysis in breast cancer tissues have demonstrated that KLK9 mRNA expression possesses significant prognostic ability and therefore could be a strong, independent marker of favorable prognosis in patients with breast cancer. In addition, the prognostic potential of the KLK9 mRNA expression levels in ovarian cancer has been clarified, since patients with KLK9-positive tumors demonstrate significantly longer progression-free and overall survival in comparison with KLK9-negative patients.

Finally, KLK9 could serve as a prognostic biomarker for patients diagnosed with high-grade astrocytoma,

as its expression level is associated with decreased survival of patients.

Although the precise localization and structure of the KLK9 gene has now been fully characterized, its functional roles and connections to human diseases are still incompletely understood and merit further investigation.

### Keywords

Kallikreins; KLK9; KLK-L3; KLKL3; biomarker; proteolytic cascades; breast cancer; ovarian cancer; astrocytoma

## Identity

**Other names:** KLK-L3, KLKL3

**HGNC (Hugo):** KLK9

**Location:** 19q13.41

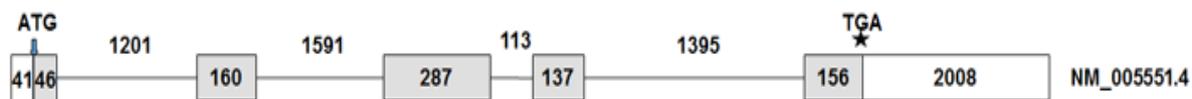
**Local order:** Telomere to centromere.

**Note:** The name of this gene is "kallikrein-related peptidase 9", while the name of its product is "kallikrein-9 precursor".

## DNA/RNA

### Description

The KLK9 gene consists of 5 exons and 4 intervening introns, spanning a region of 7081 bp genomic DNA.



Detailed structure of the annotated full-length mRNA transcript (NM\_005551.4) of the KLK9 gene. The full-length KLK9 mRNA transcript is composed of 5 exons. Exons are depicted as boxes and introns as lines; gray and white boxes represent coding and non-coding exons, respectively. Numbers inside boxes and above lines indicate the length of each exon or intron in nucleotides. Finally, the translation start and stop codons are also shown.

## Transcription

A single mRNA transcript (NM\_005551.4) of the KLK9 gene, with a total length of 1438 nucleotides, has been annotated. Expression of the KLK9 gene has been detected in various normal human tissues; still, differences in mRNA and protein expression levels have been observed. In particular, the highest mRNA levels of the KLK9 gene have been detected in stomach and vagina. In addition, KLK9 is expressed in high levels in the brain, cervix, esophagus, and fallopian tube, while normal expression levels are observed in breast, prostate, testis, thymus, thyroid, liver, lung, small intestine, spinal cord, and trachea (Shaw and Diamandis, 2007).

However, recent evidence derived from next-generation sequencing approaches has confirmed the existence of 10 novel alternative KLK9 transcripts (KLK9 v.2 -> v.11) that have already been submitted in GenBank® database (GenBank® accession numbers: KX571238 - KX571247 accordingly).

## Pseudogene

Not yet identified.

## Protein

### Description

The protein encoded by the KLK9 gene is a kallikrein-related serine protease of 250 amino acid residues, with a calculated molecular mass of 25.6 kDa. Similar to other tissue kallikreins, the KLK9 protein is produced as a pre-proenzyme consisting of 250 amino acids, which is processed into a mature form with enzymatic activity (229 amino acids). In addition, KLK9 protein harbors a signal peptide of 19 amino acid residues and a 3-aa pro-segment (Yousef and Diamandis, 2000).

### Localisation

KLK9 is mainly localized in the cytoplasm.

### Function

Like the rest of the KLK genes, the KLK9 gene encodes for a trypsin-like serine peptidase. Serine peptidases are a group of protein-cleaving enzymes that contain a serine residue in their active site. Kallikreins constitute a subfamily of serine

peptidases that cleave kininogen and release vasoactive peptides (kinins) (Schachter, 1980).

## Homology

Homology tests have demonstrated that human KLK9 protein shares the highest homology with human KLK11 (40%). In addition, KLK9 protein sequence is 38% homologous with the sequence of KLK5 and 33% homologous with the one of tissue kallikrein (KLK1) (Yousef and Diamandis, 2000).

## Mutations

No germinal or somatic mutations have been associated with cancer.

## Implicated in

### Breast cancer

#### Prognosis

Clinical studies regarding the expression analysis of the KLK9 gene in breast cancer tissues have demonstrated that KLK9 mRNA expression possesses strong prognostic ability. In particular, breast cancer patients with KLK9-positive tumors exhibit significantly longer disease-free survival (DFS) as well as overall survival (OS) compared to those who are KLK9-negative. As a result, mRNA overexpression of the KLK9 gene in breast tumors is found to be associated with increased DFS and OS leading to the conclusion that KLK9 mRNA levels could be a strong, independent marker of favorable prognosis in breast cancer (Yousef et al., 2003).

### Ovarian cancer

#### Prognosis

Similar studies regarding the KLK9 mRNA expression analysis in ovarian tumor samples have clarified the prognostic potential of the KLK9 gene in ovarian cancer. KLK9 mRNA overexpression can serve as an independent favorable prognostic marker for ovarian cancer patients, since patients with KLK9-positive tumors demonstrated significantly longer progression-free and overall survival in comparison with KLK9-negative patients (Yousef et al., 2001).

### Astrocytoma

#### Prognosis

KLK9 protein expression analysis in two distinct tissue microarrays containing grade III and IV astrocytoma samples revealed that increased KLK9 expression is associated with decreased survival of patients, thus suggesting its utility as a prognostic biomarker for patients diagnosed with high-grade astrocytoma (Drucker et al., 2015).

## References

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