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# Gene Section

## Review

# KLK6 (kallikrein-related peptidase 6)

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## Abstract

Review on KLK6, with data on DNA, protein, and where the gene is involved.

**Keywords**

Kallikreins; KlK6; gastric cancer; colorectal cancer; breast cancer; ovarian cancer; laryngeal cancer.

## Identity

**Other names:** Bss, Klk7, PRSS18, PRSS9, SP5, hK6

**HGNC (Hugo):** KLK6

**Location:** 19q13.41

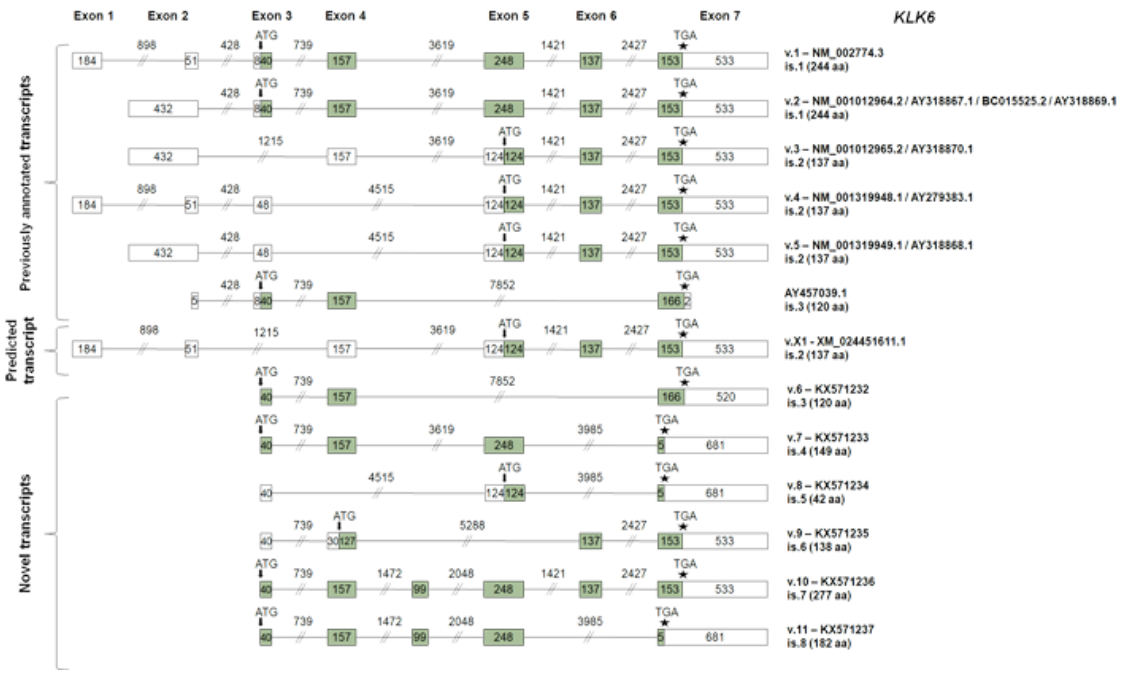


**Figure 1.** Graphic illustration of the KLK6 gene. Boxes denote exons and connecting lines represent introns. The coding sequences are colored in green, while 5' and 3' untranslated regions (UTRs) are shown in white. The numbers inside or outside boxes indicate lengths (nt) of exons and introns, respectively, while the numbers in parentheses indicate lengths (aa) of protein isoforms. Arrows mark the position of the start codons (ATG) and asterisks (*) mark the position of the stop codon (TGA). The figure is drawn in scale, except for the introns containing the (//) symbol. For each transcript, the splice variant number, the GenBank accession number and the protein isoform number are shown next to each transcript (Adamopoulos et al., 2017)


**Figure 2.** Alignment of 4 out of the 8 isoforms of the KLK6 protein. The signal peptide, glycosylation site, catalytic triad, and disulfide bonds are marked on the main isoform (isoform 1). The other four isoforms that are not presented align only partially with the main isoform

# DNA/RNA

## Description

The KLK6 gene is located on 19q chromosome, has a total length of 11.043 nt, and consists of 7 exons and 6 introns.

## Transcription

KLK6 pre-mRNA is subjected to alternative splicing. Six (6) variants had previously been detected, while another 6 transcripts have recently been identified by our research group (Adamopoulos et al., 2017). Furthermore, one more variant is predicted, based on similarity to 50 ESTs. Each of them has a different exon and intron structure. The main variant (variant A) consists of 7 exons and 6 introns. The first 2 introns do not include coding regions and compose the 5UTR. The other 11 variants range from 3 to 7 exons and 2 to 6 introns, while some of them bare similarity to each other. The structures of all variants are clearly illustrated in Figure 1.

## Pseudogene

Not detected so far.

# Protein

## Description

Eight different isoforms of KLK6 protein have been detected, consisting of 244, 137, 120, 149, 42, 138 277, and 182 amino acid (aa) residues, respectively. The KLK6 gene encodes a single-chain pre-proenzyme, which is enzymatically inactive. After the removal of the signal peptide (16 aa) from the pre-proenzyme, an inactive proKLK is formed and secreted to the extracellular space, where it is finally transformed into the active KLK through further cleavage (Bayani Diamandis, 2011).

## Expression

KLK6 is highly expressed in cerebral cortex, tonsil, spleen, esophagus, kidney, fallopian tube and breast.

## Localisation

KLK6 is mainly localized to nucleoplasm, nuclear membrane and cytokinetic bridge.

## Function

KLK6 is a serine protease, involved in proteolytic cascades. KLK6 has been suggested to be autoactivated or activate other proKLKs. When activated, serine proteases are usually regulated by binding to serpins (serine protease inhibitors), which prompts to their inactivation. A preference for Arg over Lys in the substrate P1 position and for Ser or Pro in the P2 position is detected in KLK6 substrate. Three amino acid residues (positions: 62, 106, and 197) constitute the catalytic triad in the main protein isoform (isoform 1, 244 aa) that is responsible for serine protease activity. An Asp residue at position 191 suggests a trypsin-like activity, while chymotrypsin activity is suggested by a loop similar to chymotrypsin 3D-structure. However, chymotrypsin activity is rejected by recent studies. KLK6 is activated against amyloid precursor protein, which is associated with Alzheimer's disease, myelin basic protein, and casein. Furthermore, it participates in the degradation of extracellular matrix (ECM) proteins, namely fibronectin, laminin, vitronectin, laminin and

collagen. It is involved in alpha-synuclein degradation and in the inhibition of its polymerization. This fact demonstrates the potential role of KLK6 in Parkinson's disease. Furthermore, KLK6 plays a role in cancer invasion and metastasis (Bayani Diamandis, 2011).

# Mutations

No mutations have been detected.

# Implicated in

## *Gastric cancer*

**Prognosis**

KLK6 is overexpressed in gastric cancer tissues. Elevated expression of KLK6 is linked to lymphatic invasion and unfavorable patient prognosis and may be associated with pericellular proteolysis. KLK6 gene silencing successfully reduces tumor cell proliferation and invasion (Nagahara et al., 2005).

## *Non-Small Cell Lung Cancer (NSCLC)*

**Prognosis**

KLK6 expression is elevated in NSCLC tumor tissue and is involved in NSCLC development and progression. High KLK6 concentration is related to poor survival rates, and patients with KLK6 overexpression are characterized by unfavorable prognosis (Heuzé-Vourc'h et al., 2009).

## *Ovarian cancer*

**Prognosis**

KLK6 protein expression is elevated in ovarian cancer, in both tumor and surrounding stromal cells. KLK6 is more often overexpressed in serous ovarian carcinoma than in endometrioid and mucinous carcinomas. It has been found to be transcriptionally regulated by hormones; KLK6 represents a downstream molecule by which a hormone-related neoplasm initiates and invades through degradation of the extracellular matrix and interaction with angiogenic factors. Gene amplification is suggested as a possible mechanism of high KLK6 presence in ovarian tumors. KLK6 derived by stromal cells is associated with the aggressive ovarian neoplasm. Unique patterns of N-glycosylation of KLK6 have been found; parts of sialic acid on KLK6 are abundant, almost exclusively, in ovarian cancer cells. KLK6 has been suggested as a prognostic biomarker for ovarian cancer, and is applicable in every stage, including the early one. Furthermore, it can be used in combination with MUC16 (CA-125), KLK10 and KLK13, in a multivariate model with increased prognostic power (Ni et al., 2004; White et al., 2009; Kuzmanov et al., 2009; Seiz et al., 2012).

## *Breast Cancer*

**Prognosis**

In the majority of metastatic breast cancers, KLK6 is deregulated. The mechanism behind this deregulation is genomic DNA methylation. Specifically, KLK6 has a tumor-protective activity against breast cancer, which derives from KLK6 loss-of-function, due to hypermethylation of CpG dinucleotides. On the other hand, overexpression of KLK6 was related to demethylation of the CpG dinucleotides. Modulation of KLK6 expression could serve as a therapeutic target (Pampalakis and Sotiropoulou, 2006).

## *Skin cancer*

**Prognosis**

KLK6 has proved to induce early skin cancer through the development of skin inflammation. Deficiency of KLK6 is linked to the suppression of chemically-induced skin cancer. KLK6 suspends CDH1 (E-cadherin) expression and leads to accumulation of CTNNB1 (beta-catenin). Moreover, it is involved in progression of skin cancer and migration of cancer cells in squamous skin tumors (Klucky et al., 2007). A role of KLK6 in neoplastic transformation and malignant progression in melanoma has been demonstrated, as well (Krenzer et al., 2011).

## *Colorectal cancer (CRC)*

**Prognosis**

KLK6 expression in CRC has been reported to be elevated when a mutation in KRAS oncogene, which is strongly related to CRC, is abundant. Its expression is also increased through caveolin 1 ( CAV1) activity. CAV1 is overexpressed in CRC and acts on the PI3K/AKT pathway, by decreasing the activity of negative regulatory phosphatases, such as PPA1 and PTPA (PP2A). This leads to KLK6 gene overexpression. KLK6 has proved to participate in invasion and KRAS-dependent migration (Henkhaus et al., 2008a). This occurs due to its serine protease-ability to degrade EMC components (collagen, laminin, fibronectin). KLK6 is also involved in proteolytic cascades leading to the activation of certain enzymes which are involved in pericellular proteolysis and subsequently, to tumor invasion. Proteolysis of ECM components leads to disruption of their interaction with cells and is associated with tumor cell growth and malignant transformation. KLK6 serves as a possible indicator in CRC. This is enhanced by the fact that a combined analysis of KLK6 and carcinoembryonic antigen (CEA) in lymph nodes is able to identify CRC patients with high risk of relapse (Henkhaus et al., 2008b; Ohlsson et al., 2012; Petraki et al., 2012).

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