

## Gene Section

### Short Communication

# KLK13 (kallikrein-related peptidase 13)

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## Abstract

Kallikreins (KLKs) constitute a family of 15 homologous secreted serine proteases (KLK1-15), which participate in numerous physiological procedures. All KLKs are encoded by the largest contiguous cluster of protease genes in the human genome (19q13.3-13.4). In specific, the human KLK13 gene spans a region of 8905 nucleotides, comprises 5 exons and 4 intervening introns and produces a single mRNA transcript that encodes KLK13 precursor protein. Like the rest of the KLK genes, KLK13 gene encodes for a trypsin-like serine peptidase, the functions of which are still unclear. KLK13 expression has been detected in a variety of human tissues and is found to be associated with several types of cancer. Evidence has showed that KLK13 can be an independent biomarker of favorable prognosis in breast cancer patients and may potentially be able to identify patients likely to benefit from hormonal treatment. In addition, major prognostic abilities of KLK13 have been confirmed in nonsmall cell lung cancer as well as gastric cancer, as patients with KLK13 overexpression demonstrated significantly longer overall (OS) and disease-free survival (DFS) accordingly. Although the precise localization and structure of the KLK13 gene has now been fully identified, its functional roles and implication mechanisms to human malignancies are still not conveniently understood and merit further investigation.

### Keywords

Kallikreins; KLK13; KLK-L4; KLKL4; biomarker; Proteolytic cascades

## Identity

**Other names:** KLK-L4, KLKL4

**HGNC (Hugo):** KLK13

**Location:** 19q13.33

**Local order:** Telomere to centromere.

**Note:** The name of this gene is "kallikrein-related peptidase 13". The name of its product is "kallikrein-13 precursor".

## DNA/RNA

### Description

The human KLK13 gene is located on the chromosome 19q, spans a region of 8905 nucleotides and comprises 5 exons and 4 intervening introns. In addition, the lengths of the coding regions in each exon are 52, 187, 269, 137, and 189 nucleotides, respectively. (Yousef et al, 2000).

### Transcription

Only one mRNA transcript of the KLK13 gene has been annotated (NM\_015596.1). This mRNA encodes for the kallikrein-13 precursor protein (NP\_056411.1). In addition, evidence derived by automated computational analysis supports the existence of another transcript (XR\_935788.1), which is predicted to be a non-coding transcript and therefore a candidate for nonsense-mediated mRNA decay (NMD). Like most members of the human kallikrein (KLK) gene family, KLK13 is expressed in a wide array of normal human tissues. In detail, KLK13 expression was detected at high levels in the esophagus and tonsil, while lower concentrations of KLK13 mRNA were confirmed in cervix, salivary gland, and vagina. In addition, even lower expression levels have been detected in

various other adult and fetal tissues (Shaw and Diamandis, 2007).

In addition, next-generation sequencing approaches have revealed the existence of one novel alternatively spliced variant of KLK13 that has already been submitted in the GenBank® database (GenBank® accession number: KX595106) and is predicted to be non-coding, since it contains a premature stop codon.

### **Pseudogene**

None.

## **Protein**

### **Description**

The protein encoded by the KLK13 gene is a kallikrein-related serine protease of 277 amino acid residues, with a calculated molecular mass of 30570 Da. Hydrophobicity and structural homology analysis showed that the amino-terminal region of the encoded protein is quite hydrophobic. In addition, evidence suggested that the amino acid segment 1-20 represents the signal peptide, while the segment 21-25 is the activation peptide. As a result, the active form of KLK13 starts from amino acid 26 (Yousef et al, 2000).

### **Expression**

High expression levels of KLK13 protein have been detected in mammary gland, prostate, salivary gland, testis, esophagus and tonsil, but lower expression levels have been found in many other human tissues (breast, kidney, skin, thyroid, trachea, ureter, and lung). In addition, KLK13 secretion in seminal plasma has been confirmed (Kapadia et al, 2003) (Shaw and Diamandis, 2007).

### **Localisation**

Immunohistochemistry studies have demonstrated that KLK13 is generally located in the cytoplasm (Petraiki et al, 2003). However, some nuclear staining of epithelial cells was also observed.

### **Function**

The function of the protein is still unclear. Like all members of the human kallikrein family, KLK13 is predicted to encode a secreted serine protease that is likely present in biological fluids. However, no suitable method for measuring KLK13 protein with high sensitivity and specificity has been established (Kapadia et al, 2003).

### **Homology**

KLK13 protein shares 51% amino acid sequence similarity with the TLSP and zyme genes, 49% with KLK5, 47% with KLK3 as well as 45% with KLK2. In addition, the classical catalytic triad of serine proteases is well conserved in the KLK13 (His<sup>108</sup>, Asp<sup>153</sup>, and Ser<sup>245</sup>) (Yousef et al, 2000).

## **Implicated in**

### **Breast cancer**

#### **Prognosis**

Clinical studies in breast tumour specimens have highlighted KLK13 as an independent favourable prognostic marker in breast cancer. Patients with positive KLK13 expression demonstrate a significantly longer disease-free survival (DFS) and overall survival (OS), as revealed by both univariate and multivariate Cox regression analyses. In addition, KLK13 expression positivity was detected more frequently in estrogen receptor (ER)-positive patients and was also significantly higher in patients over the age of 55 years. As a result, evidence supports that KLK13 can be an independent biomarker of favorable prognosis in breast cancer patients and may potentially be able to identify patients likely to benefit from hormonal treatment (Chang et al, 2002).

### **Non-small cell lung cancer**

#### **Note**

In a recent study, KLK13 mRNA expression levels were assessed using a sensitive quantitative RT-PCR method in patients with non-small cell lung cancer (NSCLC), in order to investigate its prognostic potential in this type of malignancy. KLK13 was found significantly overexpressed in most cancerous tissues compared to the paired normal ones. Additionally, female patients demonstrated higher KLK13 expression levels than male patients.

#### **Prognosis**

Regarding the prognostic abilities of KLK13 in NSCLC, patients characterized with overexpression of KLK13 survived significantly longer and therefore KLK13 expression is a favorable, independent prognostic indicator, in terms of overall survival (OS) (Gueugnon et al, 2015).

### **Gastric cancer**

#### **Note**

The prognostic ability of KLK13 mRNA levels have also been studied in stomach cancer. In detail, after quantitative analysis of KLK13 expression profile was performed in numerous primary gastric carcinoma samples, using an ultra-sensitive (qRT-PCR) methodology, KLK13 expression was found to be downregulated in cancerous tissues, compared to their matching non-cancerous ones.

#### **Prognosis**

Additionally, survival evaluation using Kaplan-Mayer curves revealed that patients overexpressing KLK13 demonstrate not only a significantly increased disease-free survival (DFS), having low risk of disease recurrences, but also a longer overall survival (OS).

Thus, KLK13 can serve as a new favorable tumor biomarker for patients with gastric cancer (Konstantoudakis et al, 2010).

### **Epithelial ovarian carcinoma**

#### **Prognosis**

The clinical value of KLK13 protein (KLK13) as a marker in ovarian cancer has been clarified. KLK13 levels were quantified in numerous ovarian tumor samples using an enzyme-linked immunosorbent assay (ELISA).

After KLK13 concentration in ovarian tumor cytosols was identified, KLK13 levels were associated with various clinicopathological variables, progression-free survival (PFS) and overall survival (OS).

Results indicated that patients with KLK13-positive tumor samples had a significantly longer PFS as well as OS in comparison with KLK13-negative patients. In addition to these findings, survival analysis using Kaplan-Mayer curves revealed a decreased relapse and death hazard in patients with KLK13-positive tumors (Scorilas et al, 2004).

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