Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

# Gene Section
## Review

# KLK7 (kallikrein-related peptidase 7)

**Ying Dong, John Lai, Judith A Clements**

Hormone Dependent Cancer Program, Institute of Health and Biomedical Innovation (IHBI), Queensland University of Technology (QUT), Brisbane, Australia (YD, JL, JAC)

Published in Atlas Database: May 2009

Online updated version: http://AtlasGeneticsOncology.org/Genes/KLK7ID41087ch19q13.html
DOI: 10.4267/2042/44734



## Identity

**Other names:** PRSS6; SCCE; hK7; hSCCE

**HGNC (Hugo):** KLK7

**Location:** 19q13.33

**Local order:** Telomere to centromere.

## DNA/RNA

### Description

The gene encompasses 6.509 kb of gDNA.

### Transcription

Five variant mRNA transcripts have been identi-fied. These include transcripts using different 5' untranslated regions (UTRs) including exon 1 deletions, and transcripts using different 3'UTR regions. Using rapid amplification of cDNA ends (RACE) different KLK7 5'UTR sequences were identified from RNA extracted from pancreas, skin and ovarian cells, suggesting the expression of tissue specific KLK7 transcripts.

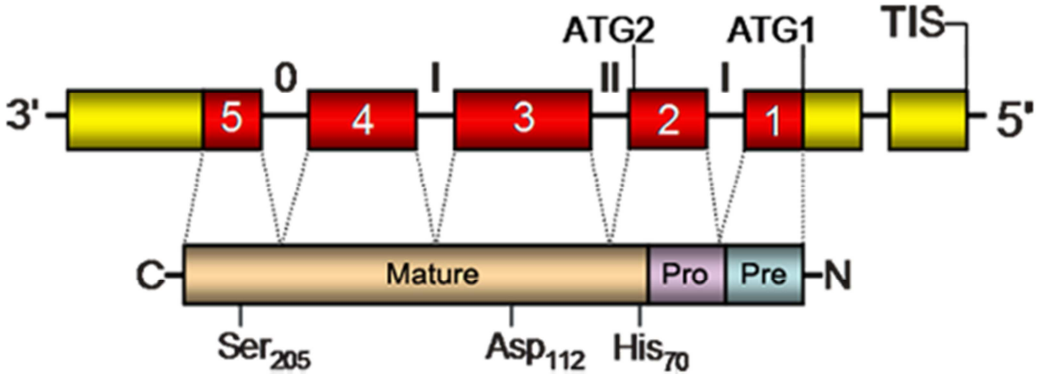
### Pseudogene

Not identified.

## Protein

### Description

Full-length KLK7 (253 amino acids) has a secretion signal (pre-) peptide (22 amino acids), followed by an activation (pro-) peptide (7 amino acids) and the mature chain (224 amino acids) with 1 potential N-linked glycosylation site. The catalytic triad of $His_{70}$, $Asp_{112}$ and $Ser_{205}$ (relative to ATG1) is conserved and is essential for proteolytic activity. After synthesis as a KLK7 full-length protein, the signal peptide is then cleaved and pro-KLK7 (zymogen) is subsequently secreted from the cell. On activation, the propeptide is removed and the zymogen becomes the mature active enzyme.




**Genomic and protein structure of the KLK7 gene.** The KLK7 gene is classically comprised of 5 coding exons (red boxes, classic numerals) and 4 intervening introns with a conserved intron phase pattern (I, II, I, 0). A non-coding exon and untranslated regions are shown in yellow. Also shown is the classical transcription initiation site (TIS) and corresponding translation start site (ATG1). An exon 1 deleted transcript has also been identified which would potentially result in the use of an alternative translation start site (ATG2). The numbering for the amino acid residues of the catalytic triad ($His_{70}$, $Asp_{112}$, $Ser_{205}$) are relative to the full-length protein starting from ATG1.

KLK7 can complex with antileukoprotease (secretory leukocyte protease inhibitor), elafin, Lympho-epithelial Kazal type inhibitor (LEKTI) fragments, and a member of a2-macroglobulin (a2M) protease inhibitor family, a2-macroglobulin-like 1 (a2ML1).

X-ray structures of recombinant full-length KLK7 from E. coli and insect cells have been solved, from which the most distinguishing features of KLK7 are the short 70-80 loop and the unique S1 pocket, which prefers P1 Tyr residues. KLK7 displays a unique chymotrypsin-like specificity for Tyr, which is preferred at P2. In addition, KLK7 exhibits large positively charged surface patches, representing putative exosites for prime side substrate recognition.

Similar to several other KLKs and based on the binding of metal to histidine such as $His_{99}$, the KLK7 activity is inhibited by $Zn^{++}$ and $Cu^{++}$ at low micromolar concentrations. KLK7 induced degradation of corneodesmosin and desmocollin 1 with similar efficiency in acidic (pH 5.6) and neutral (pH 7.2) conditions. KLK7 activity is modulated by water content in stratum corneum as KLK7 activity increased significantly in an environment of high relative humidity. KLK7 also demonstrated a tolerance to water restriction suggesting that it may be adapted to function in the water-restricted stratum corneum. Thus, relative humidity modulates desquamation by its effect upon KLK7 activity, possibly other desquamatory hydrolases and adapted KLK7 function in water-deplete skin.

An N-terminal truncated KLK7 isoform (181 amino acids) initiating from the putative ATG2 would not have the pre-pro-region and 43 amino acids from the N-terminus of full-length KLK7. The histidine which is part of the catalytic triad is also omitted which would result in a proteolytic inactive protein. The presence of this isoform has not yet been confirmed in human tissues or biological fluids.

## Expression

Full-length KLK7 protein was originally purified in human skin and named stratum corneum chymotryptic enzyme (SCCE, hSCCE). KLK7 cDNA was originally isolated from a keratinocyte derived library and designated PRSS6. Although Northern blot analyses have shown that KLK7 mRNA is predominantly localised to skin and pancreas, more sensitive RT-PCR experiments have shown that brain, kidney, ovary, bone, breast, endometrium, spinal cord, lung, prostate tissue and salivary tissue express KLK7 mRNA at low to modest levels. High KLK7 mRNA has been detected in malignancies of ovary, breast, lung and brain.

KLK7 protein has been detected by ELISA in a wide range of tissues at low (adrenal, bladder, cervix, fallopian tube, kidney, lung, lymph node, muscle, ovary, salivary gland, small intestine, spinal cord, spleen, thyroid gland, tonsil, trachea and vagina) to high (oesophagus, heart, liver and skin) levels. Modest levels of KLK7 protein have also been detected in human body fluid, such as, seminal plasma, breast milk, ovarian cancer ascites, salivary and cervicovaginal fluid.

In normal skin, KLK7 is expressed in late epidermal differentiation and found at all sites of epithelial cornification. Consequently, KLK7 is used as a marker for terminal epidermal differentia-tion. In normal epidermis, KLK7 was detected in a population of dendritic cells and in high suprabasal keratinocytes. KLK7 was also found in reconstruct-ted human epidermis and its expression was suppressed by retinoic acid. An increased expres-sion of KLK7 was found in suprabasal cells in orthokeratotic and parakeratotic areas of the lesions of oral lichen planus (an inflammatory disease) and benign oral keratosis (a non-inflammatory disease).

High KLK7 protein levels have been detected in the tissues of lung, breast, ovarian and squamous cervical cancers, oral squamous cell carcinoma and cervical adenocarcinoma tissues from patients. However, KLK7 is down regulated in cancerous prostate tissues compared to normal prostate tissues. KLK7, along with KLK6 and KLK10, is decreased in cerebrospinal fluid of frontotemporal dementia patients.

## Localisation

Full-length KLK7 is localised intracellularly in the cytoplasm prior to secretion. KLK7 protein is co-localised with KLK5 in skin and acinar cells of the pancreas by immunohistochemical staining.

The putative N-terminal truncated KLK7-181 isoform is potentially not secreted as it does not have a signal peptide, and cellular localisation remains to be determined.

## Function

To date, the major biological functions of KLK7 are associated with the skin and related epithelial tissues, such as hair follicles, oral mucosa and glandular lobules. KLK7 is involved in keratiniza-tion, stratum corneum formation, and turnover/ desquamation of the skin through the degradation of cell adhesion glycoproteins, such as corneodes-mosin, desmocollin 1 and plakoglobin. KLK7 has also been shown to cleave insulin B chain, degrade fibronectin, fibrinogen and interleukin 1beta (IL-1b), as well as activate pro-IL-1b. KLK7 and KLK5 can control activation of the human cathelicidin precursor protein, hCAP18, implying their ability to control innate immune defence.

An in vitro study showed that UVB radiation can increase KLK7 and KLK5 expression at both mRNA and protein levels in keratinocyte (HaCat) cells. In the epidermis, the major inhibitor of KLK7, antileukoprotease (secretory leukocyte protease inhibitor) is produced by keratinocytes and can inhibit detachment of corneocytes from human plantar callus in vitro, while a weaker KLK7 inhibitor, elafin (skin-derived antileukoprotease), can reduce the shedding of

corneocytes. Established epidermal mouse models overexpressing KLK7 have been shown to develop chronic itchy dermatitis. Further characterisation of these models also revealed epidermal hyperproliferation, decreased skin barrier function, and decreased expression of MHC II antigen in keratinocytes. These data provide an in vivo pathophysiological foundation that KLK7 plays an important role in skin, such as listed those below.

KLK cascade activation systems have been des-cribed. KLK7 is activated by KLK5 and KLK12. KLK7 activates other members of the kallikrein-related peptidase family including KLK1, KLK2, prostate specific antigen (PSA/KLK3) and KLK9.

The function of the putative N-terminal truncated KLK7 remains to be established.

### Homology

At the protein level, KLK7 shares 28% (KLK12), 33% (KLK9), 36% (KLK10, 11), 37% (KLK1, KLK3/PSA), 38% (KLK2, KLK5, KLK6, KLK13), 40% (KLK8), 41% (KLK14), 43% (KLK4) and 42.6% (KLK15) sequence homology with other members of the kallikrein-related peptidase family.

## Mutations

### Germinal

An AACC insertion in the 3'UTR of the KLK7 gene has been found, which altered the common allele AACC to the rare allele AACCAACC. This insertion was found to be associated with atopic dermatitis.

## Implicated in

### Endocrine related cancers

**Disease**

It has been postulated that KLK7 plays a role in endocrine related cancers given its (a) dysregulated expression in cancerous tissues compared to normal tissues, (b) regulation by hormones, such as, oestradiol, progestins and glucocorticoids and (c) potential roles in degradation of cell-cell adhesion proteins, extracellular matrix (ECM) proteins and activation of other proteases and growth factors.

### Epithelial ovarian carcinoma (EOC)

**Disease**

Kallikrein 7 is highly expressed in serous EOC at both the mRNA and protein levels, and high KLK7 mRNA expression is associated with poorly differentiated, late clinical stage ovarian carcinomas and the volume of residual tumour after surgery. Upregulated KLK7 protein was detected in EOC patient sera and tumour cytosols using ELISA, and in EOC tissue sections using immunohistochemis-try and a quantitative automated in situ immuno-fluorescence-based protein analysis. At the mRNA level, both KLK7 and its exon 1 deleted short KLK7 transcripts were detected in serous EOC cells, while none or only KLK7 short transcript was found in normal ovarian epithelial cells. In addition, a coordinated expression pattern and co-localisation of KLK7 and KLK5 were found in serous EOC cells suggesting a proteolytic cascade between them. Co-overexpression of KLK4, KLK5, KLK6 and KLK7 in ovarian cancer cells (OV-MZ-6) led to increased invasion in vitro and resulted in increased tumour burden in nude mice. A coordinated expression of KLK7 and protease inhibitor antileukoprotease was also found in EOC cells. Of interest, the 110-139 amino acid region of the KLK7 protein incorporates multiple $CD8^+$ CTL and $CD4^+$ helper T cell epitopes, and represents an attractive target antigen for immunotherapy of ovarian cancer.

**Prognosis**

EOC patients with KLK7 mRNA or protein expression in their tumours had a significantly shorter disease-free survival time than those with KLK7 negative tumours. KLK7 is an independent unfavourable predictor of disease-free and overall survival for patients with low grade cancers. KLK7 has been shown to increase specificity for diagnosis and prognosis of EOC in conjunction with other biomarkers, such as CA125, HE4 and B7-H4.

### Breast cancer

**Disease**

KLK7 gene expression was significantly lower in tumour tissues from early stage (I/II) breast cancer patients and tumour cells with progesterone receptors.

**Prognosis**

Two groups have reported conflicting data regarding the prognoses for breast cancer patients and KLK7 expressing tumours. One study found that breast cancer patients with KLK7 positive tumours have relatively shorter disease-free survival and overall survival than patients with KLK7 negative tumours. However, another study reported that breast cancer patients with KLK7 expressing tumours have favourable outcomes compared to those with KLK7 negative tumours.

### Cervical cancer

**Disease**

In a study of 18 cervical cancer cell lines (10 primary and 8 established cell lines) and 8 normal cervical keratinocyte cell lines, KLK7 mRNA expression was detected in the cancer cells (5/10 primary and 4/8 established lines) but not in any of the normal cervical keratinocytes. Interestingly, all five patients, who harbour KLK7 positive tumours that were used to establish the primary cell lines, were found to have metastatic involvement of the pelvic tumour draining lymph nodes. In the same study, tumour restricted expression of KLK7 was confirmed by immunohistochemistry staining in 4 of the 5 primary

squamous cervical tumours, and 1 of the 4 primary adenocarcinomas, but none of the normal cervical epithelial cells. Another immuno-histochemical study showed a significantly higher expression of KLK7 in cervical adenocarcinomas compared to normal endocervical glands.

## Pancreatic cancer

**Disease**

KLK7 is expressed in normal pancreas at mRNA and protein levels, and KLK7 protein is localised in acinar cells of the pancreas by immunohistoche-mical staining. KLK7 is overexpressed in pan-creatic adenocarcinomas at both the mRNA and protein levels. KLK7 expression was also observed in neoplastic cells of all tumours examined using immunohistochemistry with moderate-to-intense staining in 16 of the 23 tumours examined. Only 2 of the 13 nonmalignant tissue specimens displayed moderate KLK7 staining, whereas the remaining specimens showed weak immunoreactivity. In pancreatic cancer cells, KLK7 was shown to i) cleave desmoglein 2, ii) cleave E-cadherin and the ECM protein, fibronectin, iii) enhance urokinase-type plasminogen activator receptor shedding, and iv) reduce cell aggregation and adhesion to vitronectin to promote pancreatic cancer invasion.

## Oral squamous cell carcinoma (OSCC)

**Disease**

cDNA microarray analysis revealed that KLK5, KLK7, KLK8 and KLK10 were upregulated in tumour samples versus normal controls. RT-qPCR analysis confirmed that KLK7 mRNA was most differentially regulated with a 5.3-fold increase, while 2.8-, 4.0- and 3.5-fold increases were observed for KLK5, KLK8, and KLK10, respectively. Immunohistochemical analysis demonstrated strong reactivity for all 4 KLK proteins in both orthotopic murine tumours and human OSCC tissues.

## Lung cancer

**Disease**

KLK7 mRNA levels are decreased in adenocarci-noma compared to matched nonmalignant lung tissue. Similarly, sera of patients with non-small cell lung cancer (NSCLC) have lower protein levels of KLK7, KLK5, KLK8, KLK10 and KLK12 than those from normal subjects. However, a study has reported intense cytoplasmic staining for KLK7, KLK5, KLK6 and KLK8 in 40-90% of squamous cell carcinomas, small cell carcinomas and carci-noid tumours while 20% of tumour cells had intense nuclear staining for KLK7, KLK5 and KLK8.

## Brain tumours

**Disease**

RT-qPCR analysis showed that KLK7 mRNA expression in intracranial tumours was associated with shorter overall survival than those tumours with no KLK7 expression from a survival analysis study of 73 patients with intracranial tumours. Overexpression of KLK7 protein by cultivated brain tumour cells significantly enhanced the invasive potential in a Matrigel invasion assay.

## Colon cancer

**Disease**

One study using a semi-quantitative RT-PCR method showed that the KLK7 gene is up-regulated in colon cancer and its expression predicts poor prognosis for colon cancer patients.

## Skin disorders

**Note**

A majority of studies have concentrated on the concomitant functions of KLK7 and KLK5 in normal human skin and a number of skin disorders given its (a) high expression in pathological conditions compared to normal skin samples, (b) cleavage/degradation of intercellular adhesive glycolproteins and (c) potential of activation and degradation of cytokines, such as interleukin 1beta (IL-1b).

## Netherton syndrome (NS)

**Disease**

NS is a rare but severe inherited disorder that presents the three following characteristics with varying degrees of severity of their symptoms. 1) Ichthyosiform erythroderma - inflamed, red, scaly skin and trichorrhexis invaginata ("bamboo hair"). 2) Short, brittle, lustreless hair and atopic diathesis. 3) Predisposition to allergy problems.

NS patients have mutations in the serine protease inhibitor Kazal-type 5 (SPINK5) gene, encoding the protease inhibitor LEKTI (lympho-epithelial Kazal-type related inhibitor). Early studies using mouse models revealed that SPINK5-deficient mice mimic NS through degradation of desmoglein 1 by epidermal protease. The pathophysiological pro-cesses in the skin and epithelial related tissues of NS patients result from the lack of functional LEKTI protease inhibitor and consequently the over-degradation of corneodesmosomal cadherins by KLK7, KLK5 and KLK14.

The SPINK5 gene is localised chromosome 5. SPINK5 mutations introduce premature termination codons in LEKTI transcripts and lead to the production of truncated LEKTI forms that lack several inhibitory domains. NS is an autosomal recessive condition.

## Atopic dermatitis (AD)

**Disease**

AD is a chronic inflammatory and allergic skin disorder. Multifactorial studies have suggested that both genetic and environmental factors contribute to AD development. A study comprising 103 AD patients

and 261 matched controls revealed a significant association between the rare AACCAACC allele in the 3'UTR of KLK7 with AD. However, another group found that the AACCAACC allele was not associated with AD in a cohort of 99 patients and 189 controls. Neverthe-less, patients with the AACCAACC allele have increased KLK7 protease activity resulting in premature breakdown of corneodesmosomes, and leading to impairment of the epidermal barrier. Furthermore, acute eczematous lesions and clini-cally unaffected skin can further increase produc-tion of KLK7 and epidermal barrier functions are damaged through environmental interactions, such as washing with soap and detergents, or long-term application of corticosteroids. A combination of the above factors leads to a defective skin barrier and increases the risk of allergen penetration and succeeding inflammatory reaction. By ELISA, KLK7 levels were found to be elevated in the stratum corneum of AD patients, and KLK7 in the serum significantly correlated with eosinophil counts in the blood of AD patients, indicative of the body under an allergic condition.

### *Psoriasis*

**Disease**

A number of early studies reported that the chymotrypsin-like activity in stratum corneum was slightly elevated in psoriasis, but KLK7 serum levels did not differ between normal volunteers and patients with psoriasis. It has been confirmed that KLK7 protein levels were similar between non-lesional and lesional skin extracts, but increased amounts of desmoglein 1, plakoglobin and high molecular weight fragments of desmocollin 1 were detected in the lesional skin, suggesting an involve-ment of other proteases.

## References


Egelrud T. Purification and preliminary characterization of stratum corneum chymotryptic enzyme: a proteinase that may be involved in desquamation. J Invest Dermatol. 1993 Aug;101(2):200-4

Egelrud T, Régnier M, Sondell B, Shroot B, Schmidt R. Expression of stratum corneum chymotryptic enzyme in reconstructed human epidermis and its suppression by retinoic acid. Acta Derm Venereol. 1993 Jun;73(3):181-4

Hansson L, Strömqvist M, Bäckman A, Wallbrandt P, Carlstein A, Egelrud T. Cloning, expression, and characterization of stratum corneum chymotryptic enzyme. A skin-specific human serine proteinase. J Biol Chem. 1994 Jul 29;269(30):19420-6

Sondell B, Thornell LE, Stigbrand T, Egelrud T. Immunolocalization of stratum corneum chymotryptic enzyme in human skin and oral epithelium with monoclonal antibodies: evidence of a proteinase specifically expressed in keratinizing squamous epithelia. J Histochem Cytochem. 1994 Apr;42(4):459-65

Egelrud T. [New knowledge of the skin's horny layer may improve understanding of skin diseases]. Nord Med. 1995;110(3):76-8, 87

Skytt A, Strömqvist M, Egelrud T. Primary substrate specificity of recombinant human stratum corneum chymotryptic enzyme. Biochem Biophys Res Commun. 1995 Jun 15;211(2):586-9

Sondell B, Thornell LE, Egelrud T. Evidence that stratum corneum chymotryptic enzyme is transported to the stratum corneum extracellular space via lamellar bodies. J Invest Dermatol. 1995 May;104(5):819-23

Franzke CW, Baici A, Bartels J, Christophers E, Wiedow O. Antileukoprotease inhibits stratum corneum chymotryptic enzyme. Evidence for a regulative function in desquamation. J Biol Chem. 1996 Sep 6;271(36):21886-90

Sondell B, Dyberg P, Anneroth GK, Ostman PO, Egelrud T. Association between expression of stratum corneum chymotryptic enzyme and pathological keratinization in human oral mucosa. Acta Derm Venereol. 1996 May;76(3):177-81

Nylander-Lundqvist E, Egelrud T. Formation of active IL-1 beta from pro-IL-1 beta catalyzed by stratum corneum chymotryptic enzyme in vitro. Acta Derm Venereol. 1997 May;77(3):203-6

Sondell B, Jonsson M, Dyberg P, Egelrud T. In situ evidence that the population of Langerhans cells in normal human epidermis may be heterogeneous. Br J Dermatol. 1997 May;136(5):687-93

Egelrud T.. Stratum Corneum chymotryptic enzyme. In Handbook of proteolytic enzymes. Barrett AJ, Rawlings NP and Woessner JF, Editors., Academic, London. 1998; 87-89.

Ekholm E, Egelrud T. The expression of stratum corneum chymotryptic enzyme in human anagen hair follicles: further evidence for its involvement in desquamation-like processes. Br J Dermatol. 1998 Oct;139(4):585-90

Ekholm E, Sondell B, Strandén P, Brattsand M, Egelrud T. Expression of stratum corneum chymotryptic enzyme in human sebaceous follicles. Acta Derm Venereol. 1998 Sep;78(5):343-7

Ekholm E, Egelrud T. Stratum corneum chymotryptic enzyme in psoriasis. Arch Dermatol Res. 1999 Apr;291(4):195-200

Tanimoto H, Underwood LJ, Shigemasa K, Yan Yan MS, Clarke J, Parmley TH, O'Brien TJ. The stratum corneum chymotryptic enzyme that mediates shedding and desquamation of skin cells is highly overexpressed in ovarian tumor cells. Cancer. 1999 Nov 15;86(10):2074-82

Egelrud T. Desquamation in the stratum corneum. Acta Derm Venereol Suppl (Stockh). 2000;208:44-5

Ekholm E, Egelrud T. Expression of stratum corneum chymotryptic enzyme in relation to other markers of epidermal differentiation in a skin explant model. Exp Dermatol. 2000 Feb;9(1):65-70

Ekholm IE, Brattsand M, Egelrud T. Stratum corneum tryptic enzyme in normal epidermis: a missing link in the desquamation process? J Invest Dermatol. 2000 Jan;114(1):56-63

Yousef GM, Scorilas A, Magklara A, Soosaipillai A, Diamandis EP. The KLK7 (PRSS6) gene, encoding for the stratum corneum chymotryptic enzyme is a new member of the human kallikrein gene family - genomic characterization, mapping, tissue expression and hormonal regulation. Gene. 2000 Aug 22;254(1-2):119-28

Shigemasa K, Tanimoto H, Underwood LJ, Parmley TH, Arihiro K, Ohama K, O'Brien TJ. Expression of the protease inhibitor antileukoprotease and the serine protease stratum corneum chymotryptic enzyme (SCCE) is coordinated in ovarian tumors. Int J Gynecol Cancer. 2001 Nov-Dec;11(6):454-61

Watkinson A, Harding C, Moore A, Coan P. Water modulation of stratum corneum chymotryptic enzyme activity and desquamation. Arch Dermatol Res. 2001 Sep;293(9):470-6

Hansson L, Bäckman A, Ny A, Edlund M, Ekholm E, Ekstrand Hammarström B, Törnell J, Wallbrandt P, Wennbo H, Egelrud T. Epidermal overexpression of stratum corneum chymotryptic enzyme in mice: a model for chronic itchy dermatitis. J Invest Dermatol. 2002 Mar;118(3):444-9

Dong Y, Kaushal A, Brattsand M, Nicklin J, Clements JA. Differential splicing of KLK5 and KLK7 in epithelial ovarian cancer produces novel variants with potential as cancer biomarkers. Clin Cancer Res. 2003 May;9(5):1710-20

Johnson B, Horn T, Sander C, Kohler S, R Smoller B. Expression of stratum corneum chymotryptic enzyme in ichthyoses and squamoproliferative processes. J Cutan Pathol. 2003 Jul;30(6):358-62

Komatsu N, Takata M, Otsuki N, Toyama T, Ohka R, Takehara K, Saijoh K. Expression and localization of tissue kallikrein mRNAs in human epidermis and appendages. J Invest Dermatol. 2003 Sep;121(3):542-9

Kyriakopoulou LG, Yousef GM, Scorilas A, Katsaros D, Massobrio M, Fracchioli S, Diamandis EP. Prognostic value of quantitatively assessed KLK7 expression in ovarian cancer. Clin Biochem. 2003 Mar;36(2):135-43

Ny A, Egelrud T. Transgenic mice over-expressing a serine protease in the skin: evidence of interferon gamma-independent MHC II expression by epidermal keratinocytes. Acta Derm Venereol. 2003;83(5):322-7

Yousef GM, Polymeris ME, Yacoub GM, Scorilas A, Soosaipillai A, Popalis C, Fracchioli S, Katsaros D, Diamandis EP. Parallel overexpression of seven kallikrein genes in ovarian cancer. Cancer Res. 2003 May 1;63(9):2223-7

Borgoño CA, Diamandis EP. The emerging roles of human tissue kallikreins in cancer. Nat Rev Cancer. 2004 Nov;4(11):876-90

Caubet C, Jonca N, Brattsand M, Guerrin M, Bernard D, Schmidt R, Egelrud T, Simon M, Serre G. Degradation of corneodesmosome proteins by two serine proteases of the kallikrein family, SCTE/KLK5/hK5 and SCCE/KLK7/hK7. J Invest Dermatol. 2004 May;122(5):1235-44

Clements JA, Willemsen NM, Myers SA, Dong Y. The tissue kallikrein family of serine proteases: functional roles in human disease and potential as clinical biomarkers. Crit Rev Clin Lab Sci. 2004;41(3):265-312

Diamandis EP, Scorilas A, Kishi T, Blennow K, Luo LY, Soosaipillai A, Rademaker AW, Sjogren M. Altered kallikrein 7 and 10 concentrations in cerebrospinal fluid of patients with Alzheimer's disease and frontotemporal dementia. Clin Biochem. 2004 Mar;37(3):230-7

Ishida-Yamamoto A, Simon M, Kishibe M, Miyauchi Y, Takahashi H, Yoshida S, O'Brien TJ, Serre G, Iizuka H. Epidermal lamellar granules transport different cargoes as distinct aggregates. J Invest Dermatol. 2004 May;122(5):1137-44

Ny A, Egelrud T. Epidermal hyperproliferation and decreased skin barrier function in mice overexpressing stratum corneum chymotryptic enzyme. Acta Derm Venereol. 2004;84(1):18-22

Santin AD, Cane' S, Bellone S, Bignotti E, Palmieri M, De Las Casas LE, Roman JJ, Anfossi S, O'Brien T, Pecorelli S. The serine protease stratum corneum chymotryptic enzyme (kallikrein 7) is highly overexpressed in squamous cervical cancer cells. Gynecol Oncol. 2004 Aug;94(2):283-8

Talieri M, Diamandis EP, Gourgiotis D, Mathioudaki K, Scorilas A. Expression analysis of the human kallikrein 7 (KLK7) in breast tumors: a new potential biomarker for prognosis of breast carcinoma. Thromb Haemost. 2004 Jan;91(1):180-6

Tian X, Shigemasa K, Hirata E, Gu L, Uebaba Y, Nagai N, O'Brien TJ, Ohama K. Expression of human kallikrein 7 (hK7/SCCE) and its inhibitor antileukoprotease (ALP/SLPI) in uterine endocervical glands and in cervical adenocarcinomas. Oncol Rep. 2004 Nov;12(5):1001-6

Vasilopoulos Y, Cork MJ, Murphy R, Williams HC, Robinson DA, Duff GW, Ward SJ, Tazi-Ahnini R. Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. J Invest Dermatol. 2004 Jul;123(1):62-6

Bondurant KL, Crew MD, Santin AD, O'Brien TJ, Cannon MJ. Definition of an immunogenic region within the ovarian tumor antigen stratum corneum chymotryptic enzyme. Clin Cancer Res. 2005 May 1;11(9):3446-54

Brattsand M, Stefansson K, Lundh C, Haasum Y, Egelrud T. A proteolytic cascade of kallikreins in the stratum corneum. J Invest Dermatol. 2005 Jan;124(1):198-203

Descargues P, Deraison C, Bonnart C, Kreft M, Kishibe M, Ishida-Yamamoto A, Elias P, Barrandon Y, Zambruno G, Sonnenberg A, Hovnanian A. Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. Nat Genet. 2005 Jan;37(1):56-65

Egelrud T, Brattsand M, Kreutzmann P, Walden M, Vitzithum K, Marx UC, Forssmann WG, Mägert HJ. hK5 and hK7, two serine proteinases abundant in human skin, are inhibited by LEKTI domain 6. Br J Dermatol. 2005 Dec;153(6):1200-3

Hachem JP, Man MQ, Crumrine D, Uchida Y, Brown BE, Rogiers V, Roseeuw D, Feingold KR, Elias PM. Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. J Invest Dermatol. 2005 Sep;125(3):510-20

Ishida-Yamamoto A, Deraison C, Bonnart C, Bitoun E, Robinson R, O'Brien TJ, Wakamatsu K, Ohtsubo S, Takahashi H, Hashimoto Y, Dopping-Hepenstal PJ, McGrath JA, Iizuka H, Richard G, Hovnanian A. LEKTI is localized in lamellar granules, separated from KLK5 and KLK7, and is secreted in the extracellular spaces of the superficial stratum granulosum. J Invest Dermatol. 2005 Feb;124(2):360-6

Kurlender L, Borgono C, Michael IP, Obiezu C, Elliott MB, Yousef GM, Diamandis EP. A survey of alternative transcripts of human tissue kallikrein genes. Biochim Biophys Acta. 2005 May 25;1755(1):1-14

Planque C, de Monte M, Guyetant S, Rollin J, Desmazes C, Panel V, Lemarié E, Courty Y. KLK5 and KLK7, two members of the human tissue kallikrein family, are differentially expressed in lung cancer. Biochem Biophys Res Commun. 2005 Apr 22;329(4):1260-6

Schechter NM, Choi EJ, Wang ZM, Hanakawa Y, Stanley JR, Kang Y, Clayman GL, Jayakumar A. Inhibition of human kallikreins 5 and 7 by the serine protease inhibitor lympho-epithelial Kazal-type inhibitor (LEKTI). Biol Chem. 2005 Nov;386(11):1173-84

Wang X, Wang E, Kavanagh JJ, Freedman RS. Ovarian cancer, the coagulation pathway, and inflammation. J Transl Med. 2005 Jun 21;3:25

Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, Duff GW, Ward SJ, Tazi-Ahnini R. New

perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J Allergy Clin Immunol. 2006 Jul;118(1):3-21; quiz 22-3

Descargues P, Deraison C, Prost C, Fraitag S, Mazereeuw-Hautier J, D'Alessio M, Ishida-Yamamoto A, Bodemer C, Zambruno G, Hovnanian A. Corneodesmosomal cadherins are preferential targets of stratum corneum trypsin- and chymotrypsin-like hyperactivity in Netherton syndrome. J Invest Dermatol. 2006 Jul;126(7):1622-32

Galliano MF, Toulza E, Gallinaro H, Jonca N, Ishida-Yamamoto A, Serre G, Guerrin M. A novel protease inhibitor of the alpha2-macroglobulin family expressed in the human epidermis. J Biol Chem. 2006 Mar 3;281(9):5780-9

He QC, Tavakkol A, Wietecha K, Begum-Gafur R, Ansari SA, Polefka T. Effects of environmentally realistic levels of ozone on stratum corneum function. Int J Cosmet Sci. 2006 Oct;28(5):349-57

Holzscheiter L, Biermann JC, Kotzsch M, Prezas P, Farthmann J, Baretton G, Luther T, Tjan-Heijnen VC, Talieri M, Schmitt M, Sweep FC, Span PN, Magdolen V. Quantitative reverse transcription-PCR assay for detection of mRNA encoding full-length human tissue kallikrein 7: prognostic relevance of KLK7 mRNA expression in breast cancer. Clin Chem. 2006 Jun;52(6):1070-9

Prezas P, Arlt MJ, Viktorov P, Soosaipillai A, Holzscheiter L, Schmitt M, Talieri M, Diamandis EP, Krüger A, Magdolen V. Overexpression of the human tissue kallikrein genes KLK4, 5, 6, and 7 increases the malignant phenotype of ovarian cancer cells. Biol Chem. 2006 Jun;387(6):807-11

Prezas P, Scorilas A, Yfanti C, Viktorov P, Agnanti N, Diamandis E, Talieri M. The role of human tissue kallikreins 7 and 8 in intracranial malignancies. Biol Chem. 2006 Dec;387(12):1607-12

Shan SJ, Scorilas A, Katsaros D, Rigault de la Longrais I, Massobrio M, Diamandis EP. Unfavorable prognostic value of human kallikrein 7 quantified by ELISA in ovarian cancer cytosols. Clin Chem. 2006 Oct;52(10):1879-86

Tan OL, Whitbread AK, Clements JA, Dong Y. Kallikrein-related peptidase (KLK) family mRNA variants and protein isoforms in hormone-related cancers: do they have a function? Biol Chem. 2006 Jun;387(6):697-705

Yamasaki K, Schauber J, Coda A, Lin H, Dorschner RA, Schechter NM, Bonnart C, Descargues P, Hovnanian A, Gallo RL. Kallikrein-mediated proteolysis regulates the antimicrobial effects of cathelicidins in skin. FASEB J. 2006 Oct;20(12):2068-80

Debela M, Hess P, Magdolen V, Schechter NM, Steiner T, Huber R, Bode W, Goettig P. Chymotryptic specificity determinants in the 1.0 A structure of the zinc-inhibited human tissue kallikrein 7. Proc Natl Acad Sci U S A. 2007 Oct 9;104(41):16086-91

Deraison C, Bonnart C, Lopez F, Besson C, Robinson R, Jayakumar A, Wagberg F, Brattsand M, Hachem JP, Leonardsson G, Hovnanian A. LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. Mol Biol Cell. 2007 Sep;18(9):3607-19

Fernández IS, Ständker L, Forssmann WG, Giménez-Gallego G, Romero A. Crystallization and preliminary crystallographic studies of human kallikrein 7, a serine protease of the multigene kallikrein family. Acta Crystallogr Sect F Struct Biol Cryst Commun. 2007 Aug 1;63(Pt 8):669-72

Hubiche T, Ged C, Benard A, Léauté-Labrèze C, McElreavey K, de Verneuil H, Taïeb A, Boralevi F. Analysis of SPINK 5, KLK 7 and FLG genotypes in a French atopic dermatitis cohort. Acta Derm Venereol. 2007;87(6):499-505

Johnson SK, Ramani VC, Hennings L, Haun RS. Kallikrein 7 enhances pancreatic cancer cell invasion by shedding E-cadherin. Cancer. 2007 May 1;109(9):1811-20

Komatsu N, Saijoh K, Kuk C, Liu AC, Khan S, Shirasaki F, Takehara K, Diamandis EP. Human tissue kallikrein expression in the stratum corneum and serum of atopic dermatitis patients. Exp Dermatol. 2007 Jun;16(6):513-9

Komatsu N, Saijoh K, Kuk C, Shirasaki F, Takehara K, Diamandis EP. Aberrant human tissue kallikrein levels in the stratum corneum and serum of patients with psoriasis: dependence on phenotype, severity and therapy. Br J Dermatol. 2007 May;156(5):875-83

Pampalakis G, Sotiropoulou G. Tissue kallikrein proteolytic cascade pathways in normal physiology and cancer. Biochim Biophys Acta. 2007 Sep;1776(1):22-31

Shaw JL, Diamandis EP. Distribution of 15 human kallikreins in tissues and biological fluids. Clin Chem. 2007 Aug;53(8):1423-32

Yoon H, Laxmikanthan G, Lee J, Blaber SI, Rodriguez A, Kogot JM, Scarisbrick IA, Blaber M. Activation profiles and regulatory cascades of the human kallikrein-related peptidases. J Biol Chem. 2007 Nov 2;282(44):31852-64

Zakabunin AI, Mishukova OV, Khrapov EA, Sergeichev DS, Boiarskikh UA, Sverdlov ED, Filipenko ML. [Cloning and expression of the gene of chymotrypsin-like protease of human kallikrein-7 in Escherichia coli and isolation of recombinant protein]. Mol Gen Mikrobiol Virusol. 2007;(2):21-5

Debela M, Beaufort N, Magdolen V, Schechter NM, Craik CS, Schmitt M, Bode W, Goettig P. Structures and specificity of the human kallikrein-related peptidases KLK 4, 5, 6, and 7. Biol Chem. 2008 Jun;389(6):623-32

Dong Y, Matigian N, Harvey TJ, Samaratunga H, Hooper JD, Clements JA. Tissue-specific promoter utilisation of the kallikrein-related peptidase genes, KLK5 and KLK7, and cellular localisation of the encoded proteins suggest roles in exocrine pancreatic function. Biol Chem. 2008 Feb;389(2):99-109

Eissa A, Diamandis EP. Human tissue kallikreins as promiscuous modulators of homeostatic skin barrier functions. Biol Chem. 2008 Jun;389(6):669-80

Fernández IS, Ständker L, Mägert HJ, Forssmann WG, Giménez-Gallego G, Romero A. Crystal structure of human epidermal kallikrein 7 (hK7) synthesized directly in its native state in E. coli: insights into the atomic basis of its inhibition by LEKTI domain 6 (LD6). J Mol Biol. 2008 Apr 11;377(5):1488-97

Kiyohara C, Tanaka K, Miyake Y. Genetic susceptibility to atopic dermatitis. Allergol Int. 2008 Mar;57(1):39-56

Oikonomopoulou K, Li L, Zheng Y, Simon I, Wolfert RL, Valik D, Nekulova M, Simickova M, Frgala T, Diamandis EP. Prediction of ovarian cancer prognosis and response to chemotherapy by a serum-based multiparametric biomarker panel. Br J Cancer. 2008 Oct 7;99(7):1103-13

Planque C, Li L, Zheng Y, Soosaipillai A, Reckamp K, Chia D, Diamandis EP, Goodglick L. A multiparametric serum kallikrein panel for diagnosis of non-small cell lung carcinoma. Clin Cancer Res. 2008 Mar 1;14(5):1355-62

Psyrri A, Kountourakis P, Scorilas A, Markakis S, Camp R, Kowalski D, Diamandis EP, Dimopoulos MA. Human tissue kallikrein 7, a novel biomarker for advanced ovarian carcinoma using a novel in situ quantitative method of protein expression. Ann Oncol. 2008 Jul;19(7):1271-7

Ramani VC, Haun RS. Expression of kallikrein 7 diminishes pancreatic cancer cell adhesion to vitronectin and enhances urokinase-type plasminogen activator receptor shedding. Pancreas. 2008 Nov;37(4):399-404

Ramani VC, Haun RS. The extracellular matrix protein fibronectin is a substrate for kallikrein 7. Biochem Biophys Res Commun. 2008 May 16;369(4):1169-73

Ramani VC, Hennings L, Haun RS. Desmoglein 2 is a substrate of kallikrein 7 in pancreatic cancer. BMC Cancer. 2008 Dec 17;8:373

Simon M, Tazi-Ahnini R, Jonca N, Caubet C, Cork MJ, Serre G. Alterations in the desquamation-related proteolytic cleavage of corneodesmosin and other corneodesmosomal proteins in psoriatic lesional epidermis. Br J Dermatol. 2008 Jul;159(1):77-85

Singh J, Naran A, Misso NL, Rigby PJ, Thompson PJ, Bhoola KD. Expression of kallikrein-related peptidases (KRP/hK5, 7, 6, 8) in subtypes of human lung carcinoma. Int Immunopharmacol. 2008 Feb;8(2):300-6

Weidinger S, Baurecht H, Wagenpfeil S, Henderson J, Novak N, Sandilands A, Chen H, Rodriguez E, O'Regan GM, Watson R, Liao H, Zhao Y, Barker JN, Allen M,

Reynolds N, Meggitt S, Northstone K, Smith GD, Strobl C, Stahl C, Kneib T, Klopp N, Bieber T, Behrendt H, Palmer CN, Wichmann HE, Ring J, Illig T, McLean WH, Irvine AD. Analysis of the individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (SPINK5), kallikrein-related peptidase 7 (KLK7), and filaggrin (FLG) polymorphisms to eczema risk. J Allergy Clin Immunol. 2008 Sep;122(3):560-8.e4

Xuan Q, Yang X, Mo L, Huang F, Pang Y, Qin M, Chen Z, He M, Wang Q, Mo ZN. Expression of the serine protease kallikrein 7 and its inhibitor antileukoprotease is decreased in prostate cancer. Arch Pathol Lab Med. 2008 Nov;132(11):1796-801

Nin M, Katoh N, Kokura S, Handa O, Yoshikawa T, Kishimoto S. Dichotomous effect of ultraviolet B on the expression of corneodesmosomal enzymes in human epidermal keratinocytes. J Dermatol Sci. 2009 Apr;54(1):17-24

Pettus JR, Johnson JJ, Shi Z, Davis JW, Koblinski J, Ghosh S, Liu Y, Ravosa MJ, Frazier S, Stack MS. Multiple kallikrein (KLK 5, 7, 8, and 10) expression in squamous cell carcinoma of the oral cavity. Histol Histopathol. 2009 Feb;24(2):197-207

Talieri M, Mathioudaki K, Prezas P, Alexopoulou DK, Diamandis EP, Xynopoulos D, Ardavanis A, Arnogiannaki N, Scorilas A. Clinical significance of kallikrein-related peptidase 7 (KLK7) in colorectal cancer. Thromb Haemost. 2009 Apr;101(4):741-7

*This article should be referenced as such:*

Dong Y, Lai J, Clements JA. KLK7 (kallikrein-related peptidase 7). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(4):389-396.