

## Gene Section

### Review

# KLK4 (kallikrein-related peptidase 4)

John Lai, Ying Dong, Judith A Clements

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

Published in Atlas Database: January 2009

Online updated version : <http://AtlasGeneticsOncology.org/Genes/KLK4ID41084ch19q13.html>

DOI: 10.4267/2042/44638

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2009 Atlas of Genetics and Cytogenetics in Oncology and Haematology

### Identity

**Other names:** ARM1; EMSP; EMSP1; KLK-L1; MGC116827; MGC116828; Prostase; PRSS17; PSTS

**HGNC (Hugo):** KLK4

**Location:** 19q13.33

**Local order:** Telomere to centromere.

### DNA/RNA

#### Description

The gene encompasses 4.38 kb of gDNA.

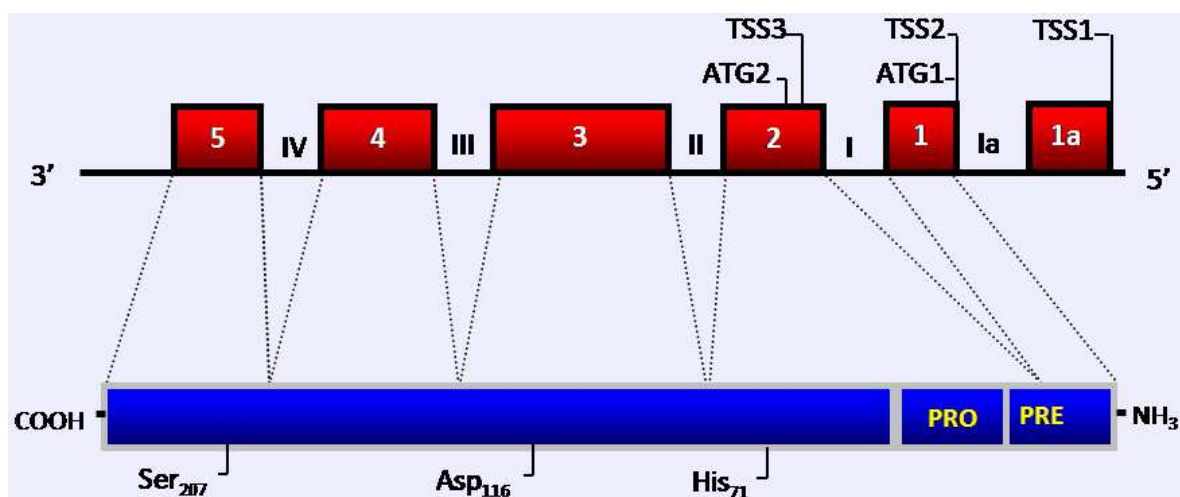
#### Transcription

Three alternative transcription start sites (TSSs)

have been predicted or identified experimentally for the KLK4 gene. TSS1 was identified using 5' RACE and is located 639 bp upstream of TSS2, which was predicted using in silico analysis. TSS3 was also identified using 5' RACE and is located 1396 bp downstream of TSS1. Nine KLK4 variant transcripts have been identified. These variants include the TSS variants, variants with 5' UTR deletion for TSS1 and TSS2 transcripts, exon 4 deletion and partial intron II (12bp) insertion variants, intron 3 insertion variants, and variants with combinations thereof.

#### Pseudogene

Not identified.



Genomic and protein structure of the KLK4 gene. The KLK4 gene is classically comprised of 5 exons (grey boxes, classic numerals) and 4 introns (roman numerals), although extra 5' UTR sequences in exon 1a have also been described. Shown here are the three putative alternative transcription start sites (TSS1, TSS2 and TSS3). Also shown are the positions of ATG1 and ATG2 that would be utilised from these variant transcripts. The amino acid numbering for the residues of the catalytic triad (His71, Asp116, Ser207) are relative to the full-length protein starting from ATG1.

## Protein

### Description

Two KLK4 protein isoforms, full-length KLK4 (254 amino acids) and an N-terminal truncated KLK4 (205 amino acids) have been described. Full-length KLK4 has a secretion signal (pre-) peptide (26 amino acids), followed by an activation (pro-) peptide (4 amino acids) and the mature chain (224 amino acids) with 1 potential N-linked glycosylation site. The catalytic triad of His71, Asp116, Ser207 (relative to Met = 1 and encoded by ATG1 in exon 1) is conserved and is essential for proteolytic activity. After synthesis as a KLK4 full-length protein, the signal peptide is then cleaved and pro-KLK4 (zymogen) is subsequently secreted from the cell. Upon activation, the propeptide is removed to generate the mature active enzyme. KLK4 complexes with alpha(1)-antitrypsin and alpha(2)-antiplasmin and alpha(2)-macroglobulin. The N-terminal truncated KLK4 isoform initiated from the ATG2 in exon 2, has the pre-pro-region and 9 amino acids from the mature KLK4 omitted, although the catalytic triad remains. Further, the truncated KLK4 isoform is not glycosylated despite retaining the potential N-linked glycosylation site.

### Expression

The KLK4 gene was originally designated the PRSS17 gene and was cloned from the cells of the enamel organ epithelia of developing teeth in pig using degenerate primers encoding the EMPS1 protein. Subsequent studies in human tissues using Northern blot analysis have shown that KLK4 mRNA expression is predominantly localised to the prostate, although more sensitive RT-PCR experiments have shown that the breast, ovary, endometrium, salivary gland, lung, adrenal gland, colon, trachea, brain, testis, spinal cord, thyroid, skin and kidney also express KLK4 mRNA at low to modest levels. KLK4 mRNA has also been detected in sebaceous glands, sweat glands, hair follicles, stratum basale, stratum spinosum and stratum granulosum by *in situ* hybridisation experiments. In pig, KLK4 mRNA is expressed in the endometrium in the early stages of the oestrous cycle.

KLK4 protein has been detected in a wide range of tissues at low (adrenal, aorta, brain, breast, cervix, heart, kidney, liver, muscle, pancreas, pituitary, salivary gland, small intestine, spinal cord, spleen, testis, skin, thyroid, and uterus) to high (prostate) levels. Modest levels of KLK4 protein have also been detected in body fluid, such as seminal plasma and urine. High KLK4 levels have also been detected in the prostate, breast and ovarian cancer tissues from patients.

### Localisation

Full-length KLK4 encodes a secreted protein and is

localised intracellularly to the cytoplasm, although GFP labelled N-terminal truncated isoforms have been found to be predominantly localised to the nucleus.

### Function

To date, the major biological function of KLK4 has been derived from porcine studies which have shown that KLK4 is important in dental enamel mineralisation by degrading amelogenin, the major protein in the enamel matrix of developing teeth. More recently, KLK4 was also reported to degrade porcine enamelin which is another protein found in developing teeth. Further, in mice, KLK4 was only expressed by transition and maturation stage ameloblasts, which is consistent with KLK4 functioning primarily to degrade the enamel matrix in developing teeth.

The role of KLK4 in the prostate, a tissue that highly expresses KLK4, is less clearly defined although it is thought to be important in prostate cancer progression given its role in degrading extracellular matrix (ECM) proteins in teeth, and potentially increasing IGF levels by degrading IGFBP3, IGFBP4, IGFBP5, IGFBP6. KLK4 is also reported to activate pro-HGFA and thereby potentially leading to tumour progression through activation of the MET receptor. A substrate specificity screening study has shown that full-length KLK4 has trypsin-like specificity and potentially activates proteins, such as, prostate specific antigen (PSA)/KLK3, bone morphogenetic protein (BMP) family and parathyroid hormone-related protein (PTHrP) that are involved in normal and neoplastic prostate (patho)-physiology. Recombinant KLK4 was also reported to be a better activator of PSA and single chain urokinase-type plasminogen activator than KLK2. More recently, KLK4 was shown to activate other members of the kallikrein-related peptidase family including KLK1, KLK2, KLK3, KLK5, KLK6, KLK9, KLK11, KLK12, KLK13, KLK14, KLK15. However, the precise physiological role for KLK4 in the prostate and other tissues remains to be identified. The function of the N-terminal truncated KLK4 remains to be established.

### Homology

At the protein level, KLK4 shares 25% (KLK12), 29% (KLK10), 31% (KLK9), 34% (KLK1, 2, 3), 35% (KLK8, 13), 36% (KLK6), 37% (KLK15), 40% (KLK14), 43% (KLK7), 45% (KLK5) sequence homology with other members of the kallikrein-related peptidase family. Unlike KLK1, KLK2 and KLK3, KLK4 lacks the "kallikrein loop", a region of 11 amino acids encoded in exon 3 and thought to be important in the substrate specificity of these enzymes. KLK4 shares 72% sequence homology to the porcine EMPS1 protein. Bayesian phylogenetic analyses suggests that KLK4, KLK5 and KLK14 may form a sub-family within the kallikrein-related peptidase gene family.

## Mutations

### Germinal

A mutation in the KLK4 gene (G.2142>A) that encodes for a truncated KLK4 protein that lacks S207, which is necessary for catalytic activity, has been shown to associate with autosomal recessive hypomaturation amelogenesis imperfecta, which is a disorder affecting tooth enamel formation. Comparison of tooth enamel in patients with the G- and A-alleles suggest that wild-type KLK4 (G allele) is important for the final removal of the extracellular enamel matrix proteins for normal enamel maturation.

## Implicated in

### Hormone dependent cancers

#### Note

It has been proposed that like PSA, encoded by the KLK3 gene, the KLK4 gene may play a role in hormone dependent cancers given its (a) higher expression in endocrine cells (b) regulation by hormones such as androgens, oestradiol and progestins (c) dysregulated expression in cancer cells and (d) potential role in extra-cellular matrix degradation and growth factor activation.

### Prostate cancer

#### Note

Hormone dependent cancer.

#### Disease

Kallikrein 4 has been reported to be more highly expressed in cancerous than benign prostate tissues at both the mRNA and protein levels. For example, a tissue microarray study carried out on 42 benign and 207 malignant prostate tissues found that KLK4 was more highly expressed in prostate cancer cells when compared to benign cells, although one study using sandwich-type immunoassay on 16 malignant and 18 benign prostate tissues found no difference in KLK4 expression. It has also been shown that KLK4 specific antibodies can be detected in sera from prostate cancer patients. In prostate cancer cells, KLK4 has been shown to be up-regulated by androgens at both the mRNA and protein level. In two expression studies using Northern blot analysis, KLK4 mRNA expression was found to be up-regulated by 18- and 1.7 -fold after treatment of LNCaP cells with R1881 for 24 and 48 hr, respectively. Further, prostate cancer cells (PC-3 and DU145) transfected with KLK4 have also been shown to have increased cellular migration, proliferation and colony formation. Over-expression of KLK4 in prostate cancer cells has also been associated with increased migration of these cells to SaOs2 conditioned media and greater attachment to bone matrix proteins collagens I and IV. The role of KLK4 in prostate biology is thought to be mediated in part through activation of the PAR-1/F2R and PAR-2/F2RL1

signalling pathways, although the precise mechanisms and importance in prostate cancer remain to be identified.

### Cytogenetics

Comparison of two human prostate cell lines, P69SV40Tag (P69) and its tumorigenic subline, M12, and 11 prostate cancer cases showed LOH in M12 at 19q13.42, which is proximal to the KLK4 locus.

### Hybrid/Mutated gene

No KLK4 fusion transcript or protein has been reported thus far.

### Epithelial ovarian carcinoma

#### Note

Hormone dependent cancer.

#### Disease

Kallikrein 4 is more highly expressed in serous ovarian carcinomas at both the mRNA and protein levels, and high KLK4 mRNA expression is associated with poorly differentiated and late clinical stage ovarian carcinomas. KLK4 mRNA was also found to be expressed in tumour cells isolated from ascites fluid in 60% (6/10) of ovarian cancer patients. KLK4 protein expression was also found to be more highly expressed in paclitaxel-resistant (79/93; 85%) than paclitaxel-sensitive tumours (20/33; 61%), suggesting that KLK4 may have utility as a predictive marker for chemoresistant ovarian cancers. Co-overexpression of KLK4, 5, 6 and 7 in ovarian cancer cells (OV-MZ-6) led to increased invasion in vitro and simultaneous expression of these KLKs in nude mice resulted in increased tumour burden.

### Prognosis

KLK4 mRNA expression in tumour tissues indicates shorter overall and progression free survival time for epithelial ovarian carcinoma patients. It is also an independent indicator of poor prognosis in patients with grade 1 and 2 tumours.

### Breast cancer

#### Note

Hormone dependent cancer.

#### Disease

Comparison of RNA levels from normal and malignant breast tissue using real time RT-PCR showed that KLK4 expression was up-regulated in cancer cells. Further analysis using laser dissection of these tumours and immuno-histochemistry showed that the observed increase of KLK4 expression was due to increased expression in the surrounding stromal cells.

### Endometrial cancer

#### Note

Hormone dependent cancer.

#### Disease

KLK4 protein levels were shown by Western blot analysis to be up-regulated in endometrial KLE cells in

response to both oestradiol and progesterin. This response was increased when cells were simultaneously treated with oestrogen and progesterone.

### **Non-small cell lung cancer (NSCLC)**

#### **Disease**

Using a KLK4 ELISA on 51 patients with NSCLC and 50 normal controls, it was shown that KLK4 may have utility as a lung cancer biomarker when used in conjunction with KLK8, KLK10, KLK11, KLK12, KLK13, and KLK14.

## **References**

- Scully JL, Bartlett JD, Chaparian MG, Fukae M, Uchida T, Xue J, Hu CC, Simmer JP. Enamel matrix serine proteinase 1: stage-specific expression and molecular modeling. *Connect Tissue Res.* 1998;39(1-3):111-22; discussion 141-9
- Simmer JP, Fukae M, Tanabe T, Yamakoshi Y, Uchida T, Xue J, Margolis HC, Shimizu M, DeHart BC, Hu CC, Bartlett JD. Purification, characterization, and cloning of enamel matrix serine proteinase 1. *J Dent Res.* 1998 Feb;77(2):377-86
- Nelson PS, Gan L, Ferguson C, Moss P, Gelinis R, Hood L, Wang K. Molecular cloning and characterization of prostase, an androgen-regulated serine protease with prostate-restricted expression. *Proc Natl Acad Sci U S A.* 1999 Mar 16;96(6):3114-9
- Stephenson SA, Verity K, Ashworth LK, Clements JA. Localization of a new prostate-specific antigen-related serine protease gene, KLK4, is evidence for an expanded human kallikrein gene family cluster on chromosome 19q13.3-13.4. *J Biol Chem.* 1999 Aug 13;274(33):23210-4
- Yousef GM, Obiezu CV, Luo LY, Black MH, Diamandis EP. Prostase/KLK-L1 is a new member of the human kallikrein gene family, is expressed in prostate and breast tissues, and is hormonally regulated. *Cancer Res.* 1999 Sep 1;59(17):4252-6
- Gan L, Lee I, Smith R, Argonza-Barrett R, Lei H, McCuaig J, Moss P, Paepers B, Wang K. Sequencing and expression analysis of the serine protease gene cluster located in chromosome 19q13 region. *Gene.* 2000 Oct 17;257(1):119-30
- Hu JC, Ryu OH, Chen JJ, Uchida T, Wakida K, Murakami C, Jiang H, Qian Q, Zhang C, Ottmers V, Bartlett JD, Simmer JP. Localization of EMSP1 expression during tooth formation and cloning of mouse cDNA. *J Dent Res.* 2000 Jan;79(1):70-6
- Hu JC, Zhang C, Sun X, Yang Y, Cao X, Ryu O, Simmer JP. Characterization of the mouse and human PRSS17 genes, their relationship to other serine proteases, and the expression of PRSS17 in developing mouse incisors. *Gene.* 2000 Jun 13;251(1):1-8
- Obiezu CV, Diamandis EP. An alternatively spliced variant of KLK4 expressed in prostatic tissue. *Clin Biochem.* 2000 Oct;33(7):599-600
- Clements J, Hooper J, Dong Y, Harvey T. The expanded human kallikrein (KLK) gene family: genomic organisation, tissue-specific expression and potential functions. *Biol Chem.* 2001 Jan;382(1):5-14
- Dong Y, Kaushal A, Bui L, Chu S, Fuller PJ, Nicklin J, Samarantunga H, Clements JA. Human kallikrein 4 (KLK4) is highly expressed in serous ovarian carcinomas. *Clin Cancer Res.* 2001 Aug;7(8):2363-71
- Korkmaz KS, Korkmaz CG, Pretlow TG, Saatcioglu F. Distinctly different gene structure of KLK4/KLK-L1/prostase/ARM1 compared with other members of the kallikrein family: intracellular localization, alternative cDNA forms, and Regulation by multiple hormones. *DNA Cell Biol.* 2001 Jul;20(7):435-45
- Myers SA, Clements JA. Kallikrein 4 (KLK4), a new member of the human kallikrein gene family is up-regulated by estrogen and progesterone in the human endometrial cancer cell line, KLE. *J Clin Endocrinol Metab.* 2001 May;86(5):2323-6
- Obiezu CV, Scorilas A, Katsaros D, Massobrio M, Yousef GM, Fracchioli S, Rigault de la Longrais IA, Arisio R, Diamandis EP. Higher human kallikrein gene 4 (KLK4) expression indicates poor prognosis of ovarian cancer patients. *Clin Cancer Res.* 2001 Aug;7(8):2380-6
- Takayama TK, McMullen BA, Nelson PS, Matsumura M, Fujikawa K. Characterization of hK4 (prostase), a prostate-specific serine protease: activation of the precursor of prostate specific antigen (pro-PSA) and single-chain urokinase-type plasminogen activator and degradation of prostatic acid phosphatase. *Biochemistry.* 2001 Dec 18;40(50):15341-8
- Day CH, Fanger GR, Retter MW, Hylander BL, Penetrante RB, Houghton RL, Zhang X, McNeill PD, Filho AM, Nolasco M, Badaro R, Cheever MA, Reed SG, Dillon DC, Watanabe Y. Characterization of KLK4 expression and detection of KLK4-specific antibody in prostate cancer patient sera. *Oncogene.* 2002 Oct 10;21(46):7114-20
- Hu JC, Sun X, Zhang C, Liu S, Bartlett JD, Simmer JP. Enamelysin and kallikrein-4 mRNA expression in developing mouse molars. *Eur J Oral Sci.* 2002 Aug;110(4):307-15
- Hural JA, Friedman RS, McNabb A, Steen SS, Henderson RA, Kalos M. Identification of naturally processed CD4 T cell epitopes from the prostate-specific antigen kallikrein 4 using peptide-based in vitro stimulation. *J Immunol.* 2002 Jul 1;169(1):557-65
- Obiezu CV, Soosaipillai A, Jung K, Stephan C, Scorilas A, Howarth DH, Diamandis EP. Detection of human kallikrein 4 in healthy and cancerous prostatic tissues by immunofluorometry and immunohistochemistry. *Clin Chem.* 2002 Aug;48(8):1232-40
- Olsson AY, Lundwall A. Organization and evolution of the glandular kallikrein locus in *Mus musculus*. *Biochem Biophys Res Commun.* 2002 Nov 29;299(2):305-11
- Ryu O, Hu JC, Yamakoshi Y, Villemain JL, Cao X, Zhang C, Bartlett JD, Simmer JP. Porcine kallikrein-4 activation, glycosylation, activity, and expression in prokaryotic and eukaryotic hosts. *Eur J Oral Sci.* 2002 Oct;110(5):358-65
- Simmer JP, Hu JC. Expression, structure, and function of enamel proteinases. *Connect Tissue Res.* 2002;43(2-3):441-9
- Hart TC, Hart PS, Gorry MC, Michalec MD, Ryu OH, Uygur C, Ozdemir D, Firatli S, Aren G, Firatli E. Novel ENAM mutation responsible for autosomal recessive amelogenesis imperfecta and localised enamel defects. *J Med Genet.* 2003 Dec;40(12):900-6
- 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
- Nagano T, Oida S, Ando H, Gomi K, Arai T, Fukae M. Relative levels of mRNA encoding enamel proteins in enamel organ epithelia and odontoblasts. *J Dent Res.* 2003 Dec;82(12):982-6

- Xi Z, Kaern J, Davidson B, Klock TI, Risberg B, Tropé C, Saatcioglu F. Kallikrein 4 is associated with paclitaxel resistance in ovarian cancer. *Gynecol Oncol*. 2004 Jul;94(1):80-5
- Xi Z, Klock TI, Korkmaz K, Kurys P, Elbi C, Risberg B, Danielsen H, Loda M, Saatcioglu F. Kallikrein 4 is a predominantly nuclear protein and is overexpressed in prostate cancer. *Cancer Res*. 2004 Apr 1;64(7):2365-70
- Dong Y, Bui LT, Odorico DM, Tan OL, Myers SA, Samaratunga H, Gardiner RA, Clements JA. Compartmentalized expression of kallikrein 4 (KLK4/hK4) isoforms in prostate cancer: nuclear, cytoplasmic and secreted forms. *Endocr Relat Cancer*. 2005 Dec;12(4):875-89
- Hu JC, Yamakoshi Y, Yamakoshi F, Krebsbach PH, Simmer JP. Proteomics and genetics of dental enamel. *Cells Tissues Organs*. 2005;181(3-4):219-31
- Matsumura M, Bhatt AS, Andress D, Clegg N, Takayama TK, Craik CS, Nelson PS. Substrates of the prostate-specific serine protease kallikrein/KLK4 defined by positional-scanning peptide libraries. *Prostate*. 2005 Jan 1;62(1):1-13
- Michael IP, Kurlender L, Memari N, Yousef GM, Du D, Grass L, Stephan C, Jung K, Diamandis EP. Intron retention: a common splicing event within the human kallikrein gene family. *Clin Chem*. 2005 Mar;51(3):506-15
- Obiezu CV, Diamandis EP. Human tissue kallikrein gene family: applications in cancer. *Cancer Lett*. 2005 Jun 16;224(1):1-22
- Obiezu CV, Shan SJ, Soosaipillai A, Luo LY, Grass L, Sotiropoulou G, Petraki CD, Papanastasiou PA, Levesque MA, Diamandis EP. Human kallikrein 4: quantitative study in tissues and evidence for its secretion into biological fluids. *Clin Chem*. 2005 Aug;51(8):1432-42
- Stephanopoulos G, Garefalaki ME, Lyroutdia K. Genes and related proteins involved in amelogenesis imperfecta. *J Dent Res*. 2005 Dec;84(12):1117-26
- Veveris-Lowe TL, Lawrence MG, Collard RL, Bui L, Herington AC, Nicol DL, Clements JA. Kallikrein 4 (hK4) and prostate-specific antigen (PSA) are associated with the loss of E-cadherin and an epithelial-mesenchymal transition (EMT)-like effect in prostate cancer cells. *Endocr Relat Cancer*. 2005 Sep;12(3):631-43
- Elliott MB, Irwin DM, Diamandis EP. In silico identification and Bayesian phylogenetic analysis of multiple new mammalian kallikrein gene families. *Genomics*. 2006 Nov;88(5):591-9
- Fernando SC, Buck JS, Ashworth MD, Ross JW, Geisert RD, DeSilva U. Porcine endometrial and conceptus tissue kallikrein 1, 4, 11, and 14 gene expression. *Reproduction*. 2006 Dec;132(6):939-47
- Oikonomopoulou K, Scorilas A, Michael IP, Grass L, Soosaipillai A, Rosen B, Murphy J, Diamandis EP. Kallikreins as markers of disseminated tumour cells in ovarian cancer-- a pilot study. *Tumour Biol*. 2006;27(2):104-14
- 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
- Whitbread AK, Veveris-Lowe TL, Lawrence MG, Nicol DL, Clements JA. The role of kallikrein-related peptidases in prostate cancer: potential involvement in an epithelial to mesenchymal transition. *Biol Chem*. 2006 Jun;387(6):707-14
- Wright JT. The molecular etiologies and associated phenotypes of amelogenesis imperfecta. *Am J Med Genet A*. 2006 Dec 1;140(23):2547-55
- Yamakoshi Y, Hu JC, Fukae M, Yamakoshi F, Simmer JP. How do enamelysin and kallikrein 4 process the 32-kDa enamel? *Eur J Oral Sci*. 2006 May;114 Suppl 1:45-51; discussion 93-5, 379-80
- Borgoño CA, Gavigan JA, Alves J, Bowles B, Harris JL, Sotiropoulou G, Diamandis EP. Defining the extended substrate specificity of kallikrein 1-related peptidases. *Biol Chem*. 2007 Nov;388(11):1215-25
- Gao J, Collard RL, Bui L, Herington AC, Nicol DL, Clements JA. Kallikrein 4 is a potential mediator of cellular interactions between cancer cells and osteoblasts in metastatic prostate cancer. *Prostate*. 2007 Mar 1;67(4):348-60
- Hu JC, Simmer JP. Developmental biology and genetics of dental malformations. *Orthod Craniofac Res*. 2007 May;10(2):45-52
- Klock TI, Kilander A, Xi Z, Waehre H, Risberg B, Danielsen HE, Saatcioglu F. Kallikrein 4 is a proliferative factor that is overexpressed in prostate cancer. *Cancer Res*. 2007 Jun 1;67(11):5221-30
- Lawrence MG, Veveris-Lowe TL, Whitbread AK, Nicol DL, Clements JA. Epithelial-mesenchymal transition in prostate cancer and the potential role of kallikrein serine proteases. *Cells Tissues Organs*. 2007;185(1-3):111-5
- Pavlic A, Petelin M, Battelino T. Phenotype and enamel ultrastructure characteristics in patients with ENAM gene mutations g.13185-13186insAG and 8344delG. *Arch Oral Biol*. 2007 Mar;52(3):209-17
- Santos MC, Hart PS, Ramaswami M, Kanno CM, Hart TC, Line SR. Exclusion of known gene for enamel development in two Brazilian families with amelogenesis imperfecta. *Head Face Med*. 2007 Jan 31;3:8
- Wang XJ, Ji P, Guo HM, Yi XZ. [Exclusion of candidate genes in a family with amelogenesis imperfecta]. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2007 Jun;25(3):249-52
- 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
- Bailleul-Forestier I, Molla M, Verloes A, Berdal A. The genetic basis of inherited anomalies of the teeth. Part 1: clinical and molecular aspects of non-syndromic dental disorders. *Eur J Med Genet*. 2008 Jul-Aug;51(4):273-91
- Chow TF, Crow M, Earle T, El-Said H, Diamandis EP, Yousef GM. Kallikreins as microRNA targets: an in silico and experimental-based analysis. *Biol Chem*. 2008 Jun;389(6):731-8
- 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
- Lee SK, Hu JC, Bartlett JD, Lee KE, Lin BP, Simmer JP, Kim JW. Mutational spectrum of FAM83H: the C-terminal portion is required for tooth enamel calcification. *Hum Mutat*. 2008 Aug;29(8):E95-9
- Lu Y, Papagerakis P, Yamakoshi Y, Hu JC, Bartlett JD, Simmer JP. Functions of KLK4 and MMP-20 in dental enamel formation. *Biol Chem*. 2008 Jun;389(6):695-700
- Mangé A, Desmetz C, Berthes ML, Maudelonde T, Solassol J. Specific increase of human kallikrein 4 mRNA and protein levels in breast cancer stromal cells. *Biochem Biophys Res Commun*. 2008 Oct 10;375(1):107-12
- Mukai S, Fukushima T, Naka D, Tanaka H, Osada Y, Kataoka H. Activation of hepatocyte growth factor activator zymogen

(pro-HGFA) by human kallikrein 1-related peptidases. FEBS J. 2008 Mar;275(5):1003-17

Papagerakis P, Lin HK, Lee KY, Hu Y, Simmer JP, Bartlett JD, Hu JC. Premature stop codon in MMP20 causing amelogenesis imperfecta. J Dent Res. 2008 Jan;87(1):56-9

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

Ramsay AJ, Dong Y, Hunt ML, Linn M, Samaratinga H, Clements JA, Hooper JD. Kallikrein-related peptidase 4 (KLK4) initiates intracellular signaling via protease-activated receptors (PARs). KLK4 and PAR-2 are co-expressed during prostate cancer progression. J Biol Chem. 2008 May 2;283(18):12293-304

Sun Z, Fan D, Fan Y, Du C, Moradian-Oldak J. Enamel proteases reduce amelogenin-apatite binding. J Dent Res. 2008 Dec;87(12):1133-7

Wright JT, Hart TC, Hart PS, Simmons D, Suggs C, Daley B, Simmer J, Hu J, Bartlett JD, Li Y, Yuan ZA, Seow WK, Gibson CW. Human and mouse enamel phenotypes resulting from mutation or altered expression of AMEL, ENAM, MMP20 and KLK4. Cells Tissues Organs. 2009;189(1-4):224-9

---

*This article should be referenced as such:*

Lai J, Dong Y, Clements JA. KLK4 (kallikrein-related peptidase 4). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(12):944-949.

---