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Gene Section
Review

KLK8 (kallikrein-related peptidase 8)

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Identity

Other names: HNP, NP, NRPN, PRSS19, TADG14

HGNC (Hugo): KLK8

Location: 19q13.41

Local order: Telomere to centromere.

Note

This gene is one of the fifteen kallikrein subfamily members located in a cluster on chromosome 19. Kallikreins are a subgroup of serine proteases having diverse physiological functions.

DNA/RNA

Description

The KLK8 gene is approximately 7.8 kb in length, consisting of 8 exons (5 of them are coding exons) and 7 introns.

Transcription

Human KLK8 was originally cloned (Yoshida et al., 1998) as the human ortholog of the mouse brain protease neuropsin (Chen et al., 1995). Using Northern blot and RT-PCR analyses, it has been shown that KLK8 is expressed mainly in breast, cervix, esophagus, skin, ovary, testis, salivary glands and vagina. Adrenal, brain, colon, heart, kidney, lung, muscle and prostate also express KLK8 mRNA at medium to low levels. The transcription start site of KLK8 appears tissue-specific (Lu et al., 2009). Eight alternatively spliced variants have been identified for the KLK8 gene. These variants differ in the number and length of the 5' untranslated exons and/or coding exons. The splice variants are predicted to encode 6 protein isoforms.

Type 1 and Type 2 transcripts differ in their coding exon 2 sequence. Type 2 includes extra 45 amino acids at the N-terminus of the coding exon 2.

Thus, Type 1 and Type 2 KLK8 mRNA variants produce 2 zymogens that differ only in their propeptide sequences. Type 2 variant is absent in nonhuman primates, and is thus a human-specific splice form (Li et al., 2004; Lu et al., 2007). Type 1 mRNA is predominantly expressed in the pancreas and Type 2 mRNA in adult brain and hippocampus. Type 2 KLK8 is also abundantly expressed in fetal brain, placenta and in human embryonic stem cells, suggesting a potential role in embryogenesis (Mitsui et al., 1999; Lu et al., 2009).

The Type 3 mRNA variant includes coding exons 1, 4, and 5 and encodes a truncated form of the KLK8 protein (Magklara et al., 2001). Type 4 variant lacks coding exons 2, 3, 4.

It encodes a putative protein of 32 amino acid residues that contains the KLK8 signal peptide and another peptide that is not related to KLK8 (Magklara et al., 2001).

Type 3 and Type 4 mRNAs are abundant in many normal tissues (brain, pancreas, skin) and are overproduced in ovarian and lung cancers (Magklara et al., 2001; Planque et al., 2010). Coding exon 2 is missing in Type 5 mRNA whereas Type 6 mRNA lacks coding exon 3. For these both variants, the alternative splicing creates a stop codon that prematurely terminates translation. Type 5 and Type 6 mRNAs were detected in lung cancer cell lines and tissues (Sher et al., 2006; Planque et al., 2010).

Pseudogene

None identified.

The KLK8 gene comprises 8 exons (dark color, classic numerals) and 7 introns. Shown here are the 6 alternative transcripts predicted to encode protein variants (only the coding exons are depicted). Yellow boxes: non coding sequences; blue and green boxes: coding sequences. Sequences coding for identical amino acids are indicated in green whereas blue designates sequences generating distinct amino acids.

Protein

Description

The canonical KLK8 protein encoded by Type 1 mRNA has a secretion signal (pre-) peptide (28 amino acids), followed by an activation (pro-) peptide (4 amino acids) and the mature chain (228 amino acids) with 1 potential N-linked glycosylation site. The catalytic triad of His73, Asp120, Ser212 (relative to Met = 1) is conserved and is essential for proteolytic activity. After synthesis as a KLK8 precursor, the signal peptide is then cleaved and pro-KLK8 (zymogen) is subsequently secreted from the cell. Upon activation, the propeptide is removed to generate the mature active enzyme. Type 2 KLK8 has an insert of 45 amino acids between Ala23 and Gly24 at the C-terminus of the leader sequence of canonical KLK8. Therefore, this isoform has larger signal peptide and propeptide and has been produced intact as recombinant protein (Lu et al., 2009). Beside the canonical KLK8 protein, only the predicted peptide encoded by KLK8 Type 4 mRNA has been yet detected in vivo. This form was identified by mass spectrometry in bronchoalveolar lavage fluid (Oumeraci et al., 2011).

Expression

KLK8 protein has been detected in a wide range of tissues at low (10 to 100 ng/g, adrenal, cervix, heart, kidney, liver, ovary, salivary gland, vagina) to high (1 µg to 10 µg/g, breast, esophagus, skin, tensil) levels (Shaw and Diamandis, 2007).

KLK8 has also been detected in body fluid, such as milk, amniotic fluid, cerebrospinal fluid, seminal plasma, serum, saliva and sweat (Kishi et al., 2003; Shaw and Diamandis, 2007; Eissa et al., 2011).

Age at the first full term pregnancy (FFTP) influences secretion of KLK8 protein in breast milk. Indeed in a recent study, a significant increase in KLK8 expression was observed from the onset of lactation to breast weaning depending on FFTP age (26) (Qin et al., 2012).

Localisation

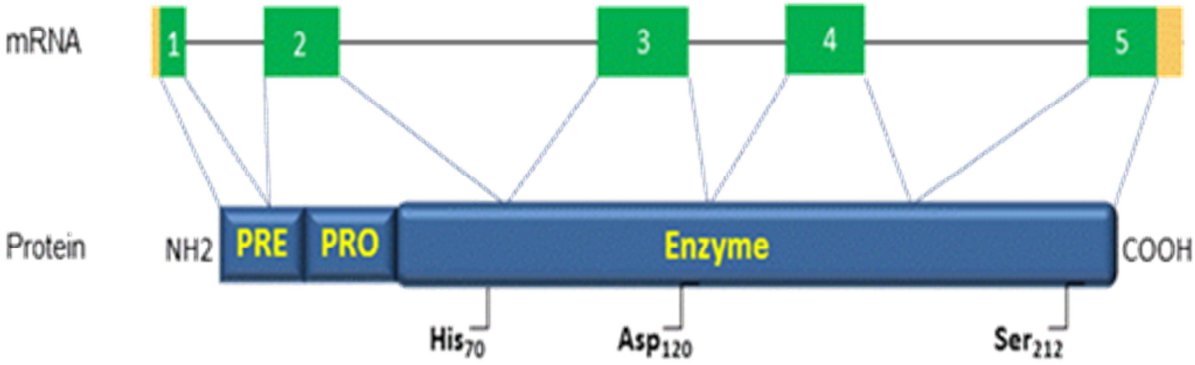
KLK8 is a secreted protein and is localized intracellularly to the cytoplasm.

In epidermis, KLK8 is localized within the trans-Golgi network, lamellar granules and intercellular spaces between the stratum granulosum and stratum corneum (Ishida-Yamamoto et al., 2004).

Diffuse cytoplasmic staining was observed for KLK8 in the secretory segment in eccrine sweat glands and in the intradermal sensory nerve (Komatsu et al., 2005).

KLK8 is present in relatively high levels in ductal cells, as well as in non-ductal cells, of normal salivary gland tissues and benign and malignant salivary gland tumors (Darling et al., 2008).

In brain, KLK8 is expressed in the cell body of oligodendrocytes (He et al., 2001).



Schematic structure of the KLK8 Type1 protein. The amino acid numbering for the residues of the catalytic triad (His70, Asp120, Ser212) are relative to the full-length protein starting from Met1.

Function

KLK8 is a serine protease which exhibits trypsin-like activity with strong preference for Arg over Lys in the P1 position (Kishi et al., 2006; Eissa et al., 2011). KLK8 activity is inhibited by general serine protease inhibitors such as a2-antiplasmin, protein C inhibitor and PI-6 (Proteinase inhibitor 6) (Scott et al., 2007). Several potential substrates have been identified for KLK8 in human or mouse including extracellular matrix components (Single-chain tPA, fibronectin, gelatin, collagen type IV, fibrinogen) (Rajapakse et al., 2005), cell adhesion molecules (L1cam) and membranous receptors (EphB2, PAR2) (Matsumoto-Miyai et al., 2003; Nakamura et al., 2006; Attwood et al., 2011; Ramachandran et al., 2012), antimicrobial peptides (LL-37) and zymogens of kallikrein-related peptidases (proKLK1 and proKLK11) (Eissa et al., 2011). The physiological functions of KLK8 are not fully understood. Accumulating evidence has suggested pivotal roles for KLK8 in development, maturation and cognitive functions. KLK8 induces neurite outgrowth and fasciculation of cultured hippocampal neurons. Plays a role in the formation and maturation of orphan and small synaptic boutons in the Schaffer-collateral pathway, regulates Schaffer-collateral long-term potentiation in the hippocampus and is required for memory acquisition and synaptic plasticity (Komai et al., 2000; Oka et al., 2002; Nakamura et al., 2006; Terayama et al., 2007; Horii et al., 2008; Yoshida, 2010; Ishikawa et al., 2011; Shiosaka and Ishikawa, 2011). KLK8 has also been involved in skin desquamation and wound healing and in keratinocyte proliferation (Inoue et al., 1998; Kirihara et al., 2003; Kishibe et al., 2007; Yoshida, 2010; Eissa et al., 2011; Kishibe et al., 2012). It has been shown that KLK8 is differentially expressed in a number of malignancies, including ovarian, cervical, head and neck, breast and salivary gland cancers (Kishi et al., 2003; Cane et al., 2004; Borgono et al., 2006; Darling et al., 2008; Liu et al., 2008; Kountourakis et al., 2009), but the mechanisms of its involvement in these cancer have yet to be determined. In lung cancer, KLK8 suppress tumor cell invasiveness in vitro and in vivo (Sher et al., 2006).

Homology

The human KLK8 protein sequence shares 40-70% homology with other members of the human tissue kallikreins, and 70% identity with that of the mouse orthologue.

Mutations

Note

Genomewide DNA linkage analysis identified a susceptibility locus for intracranial aneurysm (IA) on chromosome 19q13 in the Finnish population. Two SNPs located in the intronic region of KLK8 were found significantly associated with IA (Weinsheimer et al., 2007). A significant allelic association between several KLK8 SNPs and bipolar disorder has recently been reported (Izumi et al., 2008).

No germinal or somatic mutations are identified to be associated with cancer so far.

Implicated in

Carcinomas

Note

Several carcinomas (ovarian, cervical, oral, salivary glands and lung cancers) show high expression of the KLK8 gene. Depending on the cancer type, KLK8 acts as tumor promoting or tumor suppressing factor.

Ovarian cancer

Disease

Expression of KLK8 was not detected on the surface epithelium of normal ovaries by immunohistochemistry. In contrast, KLK8 protein was detected in ovarian carcinomas with a significantly higher detection rate of KLK8 expression in early stage disease compared to advanced stage disease (Shigemasa et al., 2004). Other analyses using sandwich-type immunoassays found KLK8 protein in

cancer tissue extracts, serum and ascites fluid of ovarian cancer patients (Kishi et al., 2003; Shigemasa et al., 2004; Borgono et al., 2006).

Prognosis

It had been proposed that KLK8 is an independent marker of favorable prognosis in ovarian cancer at both the mRNA and protein levels. For example, KLK8 mRNA levels were found associated with longer disease-free survival (PFS) (Magklara et al., 2001; Shigemasa et al., 2004). The tissue concentration of KLK8 was also described as an independent marker of favorable prognosis in ovarian cancer. Patients with KLK8-positive tumors had a significantly longer PFS and overall survival than KLK8-negative patients (Borgono et al., 2006). Higher ascites fluid KLK8 concentration was also associated with better ovarian cancer PFS (Kishi et al., 2003). Using another approach, Kountourakis et al. showed significant correlations between tumour mask KLK8 protein expression levels and clinicopathological variables, including grade, residual disease and clinical response to chemotherapy. There was also a significant correlation between KLK8 tumour mask expression and five years progression-free survival (Kountourakis et al., 2009).

Non-small cell lung cancer

Disease

In non-small cell lung cancer (NSCLC), KLK8 appears to suppress tumor cell invasiveness by degrading fibronectin, thereby suppressing integrin signaling, and also retards cancer cell motility by inhibiting actin polymerization. In a mouse model, KLK8 suppresses tumor growth and invasion in vivo (Sher et al., 2006). Compared with sera from normal subjects, sera of patients with NSCLC had lower levels of KLK8. Using a KLK8 ELISA on 51 patients with NSCLC and 50 normal controls, it was shown that KLK8 may have utility as a lung cancer biomarker when used in conjunction with KLK4, KLK10, KLK11, KLK12, KLK13, and KLK14 (Planque et al., 2008).

Prognosis

In patients with non-small cell lung cancer, the time to postoperative recurrence was longer for early-stage patients with high KLK8 gene expression than for patients with low KLK8 gene expression (Sher et al., 2006). Another study has revealed that the Type 4 KLK8 alternative splice variant, alone or in combination with other KLK mRNAs, may be a new independent marker of unfavorable prognosis in lung cancer (Planque et al., 2010).

Breast cancer

Disease

KLK8 is downregulated in breast cancer tissues and cell lines (Yousef et al., 2004). On the other hand, KLK8, along with several other kallikrein genes, could be primarily up-regulated by 17b-estradiol and, to a lesser degree, by other steroid hormones in hormone receptor-positive breast cancer cell lines MCF-7 and T-47D, suggesting a coordinated kallikrein expression as part of a complex regulatory mechanism that controls the expression of these genes and also their downstream physiological function (Paliouras and Diamandis, 2007).

Cervical cancer

Disease

At the mRNA level, KLK8 was found to be highly expressed in 82% primary cervical cancer cell lines and in 87% established cervical cancer cell lines. In addition, immunohistochemistry staining of paraffin-embedded cervical cancer specimens showed KLK8 expression in tumor cells and its absence on normal cervical epithelial cells (Cane et al., 2004).

Bladder cancer

Disease

Reverse transcription-polymerase chain reaction analysis of 42 primary bladder tumor samples revealed an higher expression level of KLK8 mRNA in invasive tumors than in superficial tumors (Shinoda et al., 2007).

Salivary gland cancers

Disease

The KLK8 immunoreactivity was determined in normal salivary gland tissue and in malignant salivary gland tumors. In general, all the tumors showed a relatively high overall staining for both ductal and non-ductal cells, particularly mucoepidermoid carcinomas and adenocarcinoma NOS (Darling et al., 2008).

Oral squamous cell carcinoma

Disease

Comparison of oral squamous carcinoma (OSC) cell lines with either overexpression or silencing of uPAR revealed that the more aggressive phenotype is associated with a co-overexpression of KLK5, KLK7, KLK8 and KLK10. Furthermore, immunohistochemical analysis demonstrated strong reactivity for KLKs 5, 7, 8 and 10 in both orthotopic murine tumors and human OSC tissues. These results suggest that KLK8 along with other KLKs is involved in malignant progression of oral squamous cell carcinoma (Pettus et al., 2009).

Skin diseases

Note

KLK8 involvement in normal skin barrier formation and inflammatory skin disease pathology has recently become apparent. Work done in Klk8/neuropsin-null mice suggested that Klk8/neuropsin is involved in skin barrier homeostasis, whereby healing of chemically wounded or UV-irradiated mouse skin is largely impaired in its absence (Kitayoshi et al., 1999; Kirihara et al., 2003; Kishibe et al., 2012). Additionally, the dramatic increase of KLK8 mRNA in hyperkeratotic

skin of psoriasis vulgaris, seborrheic keratosis, lichen planus, and squamous cell carcinoma patients, compared with normal and basal cell carcinoma skin, suggested that human KLK8 is involved in keratinocyte differentiation and skin barrier formation (Kuwae et al., 2002; Shingaki et al., 2010; Shingaki et al., 2012). KLK8 protein overexpression was also detected in psoriasis, atopic dermatitis, and peeling skin syndrome skin tissues (Komatsu et al., 2006; Komatsu et al., 2007a; Komatsu et al., 2007b). KLK8 together with KLK5, KLK6, KLK7, KLK10 and KLK12 was upregulated in normal human keratinocytes following SP1 silencing. Moreover, thymic stromal lymphopoietin (TSLP), an epithelial-derived T(H)2-promoting cytokine, was induced in Sp1-silenced keratinocytes because of elevated KLK activity. This observation suggests that KLKs may contribute to T(H)2 immune responses in the skin by inducing TSLP (Bin et al., 2011).

Brain diseases

Note

Under non-pathological conditions, KLK8 protein is localized mainly to the neurons of the cerebral cortex and hippocampus. Immunohistochemistry for KLK8 also demonstrated signals in cerebellum (The Human Protein Atlas). A variety of transcriptional controls through both physiological and nonphysiological activity, such as long-term potentiation, chemically induced plasticity, kindling epileptogenesis, and experimental encephalitis, have been shown to positively regulate Klk8 gene expression in mice (Momota et al., 1998; Komai et al., 2000; He et al., 2001; Ishikawa et al., 2011). Increased anxiety like response was also observed in Klk8/neuropsin-deficient mice (Horii et al., 2008). Recently, Attwood et al. (Attwood et al., 2011) have shown that Klk8/neuropsin is involved in stress-related plasticity in the amygdala by the cleavage of EphB2 during stress and the reduction of EphB2-NMDA binding. So currently, accumulating evidence supports pivotal roles of Klk8 in the early phase of synaptic plasticity, late associativity, and behavioral memory (Shiosaka and Ishikawa, 2011). Further studies are required to determine if KLK8 is involved in human brain diseases, however an overexpression of KLK8 has yet been observed in Alzheimer's disease hippocampus (Shimizu-Okabe et al., 2001).

References

Chen ZL, Yoshida S, Kato K, Momota Y, Suzuki J, Tanaka T, Ito J, Nishino H, Aimoto S, Kiyama H. Expression and activity-dependent changes of a novel limbic-serine protease gene in the hippocampus. J Neurosci. 1995 Jul;15(7 Pt 2):5088-97

Inoue N, Kuwae K, Ishida-Yamamoto A, Iizuka H, Shibata M, Yoshida S, Kato K, Shiosaka S. Expression of neuropsin in the keratinizing epithelial tissue-immunohistochemical analysis of wild-type and nude mice. J Invest Dermatol. 1998 Jun;110(6):923-31

Momota Y, Yoshida S, Ito J, Shibata M, Kato K, Sakurai K, Matsumoto K, Shiosaka S. Blockade of neuropsin, a serine protease, ameliorates kindling epilepsy. Eur J Neurosci. 1998 Feb;10(2):760-4

Yoshida S, Taniguchi M, Hirata A, Shiosaka S. Sequence analysis and expression of human neuropsin cDNA and gene. Gene. 1998 Jun 15;213(1-2):9-16

Kitayoshi H, Inoue N, Kuwae K, Chen ZL, Sato H, Ohta T, Hosokawa K, Itami S, Yoshikawa K, Yoshida S, Shiosaka S. Effect of 12-O-tetradecanoyl-phorbol ester and incisional wounding on neuropsin mRNA and its protein expression in murine skin. Arch Dermatol Res. 1999 Jun;291(6):333-8

Komai S, Matsuyama T, Matsumoto K, Kato K, Kobayashi M, Imamura K, Yoshida S, Ugawa S, Shiosaka S. Neuropsin regulates an early phase of schaffer-collateral long-term potentiation in the murine hippocampus. Eur J Neurosci. 2000 Apr;12(4):1479-86

Mitsui S, Yamada T, Okui A, Kominami K, Uemura H, Yamaguchi N. A novel isoform of a kallikrein-like protease, TLSP/hippostasin, (PRSS20), is expressed in the human brain and prostate. Biochem Biophys Res Commun. 2000 May 27;272(1):205-11

He XP, Shiosaka S, Yoshida S. Expression of neuropsin in oligodendrocytes after injury to the CNS. Neurosci Res. 2001 Apr;39(4):455-62

Magklara A, Scorilas A, Katsaros D, Massobrio M, Yousef GM, Fracchioli S, Danese S, Diamandis EP. The human KLK8 (neuropsin/ovasin) gene: identification of two novel splice variants and its prognostic value in ovarian cancer. Clin Cancer Res. 2001 Apr;7(4):806-11

Shimizu-Okabe C, Yousef GM, Diamandis EP, Yoshida S, Shiosaka S, Fahnestock M. Expression of the kallikrein gene family in normal and Alzheimer's disease brain. Neuroreport. 2001 Aug 28;12(12):2747-51

Kuwae K, Matsumoto-Miyai K, Yoshida S, Sadayama T, Yoshikawa K, Hosokawa K, Shiosaka S. Epidermal expression of serine protease, neuropsin (KLK8) in normal and pathological skin samples. Mol Pathol. 2002 Aug;55(4):235-41

Oka T, Akisada M, Okabe A, Sakurai K, Shiosaka S, Kato K. Extracellular serine protease neuropsin (KLK8) modulates neurite outgrowth and fasciculation of mouse hippocampal neurons in culture. Neurosci Lett. 2002 Mar 22;321(3):141-4

Kirihara T, Matsumoto-Miyai K, Nakamura Y, Sadayama T, Yoshida S, Shiosaka S. Prolonged recovery of ultraviolet B-irradiated skin in neuropsin (KLK8)-deficient mice. Br J Dermatol. 2003 Oct;149(4):700-6

Kishi T, Grass L, Soosaipillai A, Scorilas A, Harbeck N, Schmalfeldt B, Dorn J, Mysliwiec M, Schmitt M, Diamandis EP. Human kallikrein 8, a novel biomarker for ovarian carcinoma. Cancer Res. 2003 Jun 1;63(11):2771-4

Kishi T, Grass L, Soosaipillai A, Shimizu-Okabe C, Diamandis EP. Human kallikrein 8: immunoassay development and identification in tissue extracts and biological fluids. Clin Chem. 2003 Jan;49(1):87-96

Matsumoto-Miyai K, Ninomiya A, Yamasaki H, Tamura H, Nakamura Y, Shiosaka S. NMDA-dependent proteolysis of presynaptic adhesion molecule L1 in the hippocampus by neuropsin. J Neurosci. 2003 Aug 27;23(21):7727-36

Cané S, Bignotti E, Bellone S, Palmieri M, De las Casas L, Roman JJ, Pecorelli S, Cannon MJ, O'brien T, Santin AD. The novel serine protease tumor-associated differentially expressed gene-14 (KLK8/Neuropsin/Ovasin) is highly overexpressed in cervical cancer. Am J Obstet Gynecol. 2004 Jan;190(1):60-6

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

Li Y, Qian YP, Yu XJ, Wang YQ, Dong DG, Sun W, Ma RM, Su B. Recent origin of a hominoid-specific splice form of neuropsin, a gene involved in learning and memory. Mol Biol Evol. 2004 Nov;21(11):2111-5

Shigemasa K, Tian X, Gu L, Tanimoto H, Underwood LJ, O'Brien TJ, Ohama K. Human kallikrein 8 (hK8/TADG-14) expression is associated with an early clinical stage and favorable prognosis in ovarian cancer. Oncol Rep. 2004 Jun;11(6):1153-9

Yousef GM, Yacoub GM, Polymeris ME, Popalis C, Soosaipillai A, Diamandis EP. Kallikrein gene downregulation in breast cancer. Br J Cancer. 2004 Jan 12;90(1):167-72

Komatsu N, Saijoh K, Toyama T, Ohka R, Otsuki N, Hussack G, Takehara K, Diamandis EP. Multiple tissue kallikrein mRNA and protein expression in normal skin and skin diseases. Br J Dermatol. 2005 Aug;153(2):274-81

Rajapakse S, Ogiwara K, Takano N, Moriyama A, Takahashi T. Biochemical characterization of human kallikrein 8 and its possible involvement in the degradation of extracellular matrix proteins. FEBS Lett. 2005 Dec 19;579(30):6879-84

Borgoño CA, Kishi T, Scorilas A, Harbeck N, Dorn J, Schmalfeldt B, Schmitt M, Diamandis EP. Human kallikrein 8 protein is a favorable prognostic marker in ovarian cancer. Clin Cancer Res. 2006 Mar 1;12(5):1487-93

Kishi T, Cloutier SM, Kündig C, Deperthes D, Diamandis EP. Activation and enzymatic characterization of recombinant human kallikrein 8. Biol Chem. 2006 Jun;387(6):723-31

Komatsu N, Suga Y, Saijoh K, Liu AC, Khan S, Mizuno Y, Ikeda S, Wu HK, Jayakumar A, Clayman GL, Shirasaki F, Takehara K, Diamandis EP. Elevated human tissue kallikrein levels in the stratum corneum and serum of peeling skin syndrome-type B patients suggests an over-desquamation of corneocytes. J Invest Dermatol. 2006 Oct;126(10):2338-42

Nakamura Y, Tamura H, Horinouchi K, Shiosaka S. Role of neuropsin in formation and maturation of Schaffer-collateral L1cam-immunoreactive synaptic boutons. J Cell Sci. 2006 Apr 1;119(Pt 7):1341-9

Sher YP, Chou CC, Chou RH, Wu HM, Wayne Chang WS, Chen CH, Yang PC, Wu CW, Yu CL, Peck K. Human kallikrein 8 protease confers a favorable clinical outcome in non-small cell lung cancer by suppressing tumor cell invasiveness. Cancer Res. 2006 Dec 15;66(24):11763-70

Kishibe M, Bando Y, Terayama R, Namikawa K, Takahashi H, Hashimoto Y, Ishida-Yamamoto A, Jiang YP, Mitrovic B, Perez D, Iizuka H, Yoshida S. Kallikrein 8 is involved in skin desquamation in cooperation with other kallikreins. J Biol Chem. 2007 Feb 23;282(8):5834-41

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. 2007a 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. 2007b May;156(5):875-83

Lu ZX, Peng J, Su B. A human-specific mutation leads to the origin of a novel splice form of neuropsin (KLK8), a gene involved in learning and memory. Hum Mutat. 2007 Oct;28(10):978-84

Paliouras M, Diamandis EP. Coordinated steroid hormone-dependent and independent expression of multiple kallikreins in breast cancer cell lines. Breast Cancer Res Treat. 2007 Mar;102(1):7-18

Scott FL, Sun J, Whisstock JC, Kato K, Bird PI. SerpinB6 is an inhibitor of kallikrein-8 in keratinocytes. J Biochem. 2007 Oct;142(4):435-42

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

Shinoda Y, Kozaki K, Imoto I, Obara W, Tsuda H, Mizutani Y, Shuin T, Fujioka T, Miki T, Inazawa J. Association of KLK5 overexpression with invasiveness of urinary bladder carcinoma cells. Cancer Sci. 2007 Jul;98(7):1078-86

Terayama R, Bando Y, Murakami K, Kato K, Kishibe M, Yoshida S. Neuropsin promotes oligodendrocyte death, demyelination and axonal degeneration after spinal cord injury. Neuroscience. 2007 Aug 10;148(1):175-87

Weinsheimer S, Goddard KA, Parrado AR, Lu Q, Sinha M, Lebedeva ER, Ronkainen A, Niemelä M, Khusnutdinova EK, Khusainova RI, Helin K, Jääskeläinen JE, Sakovich VP, Land S, Kuivaniemi H, Tromp G. Association of kallikrein gene polymorphisms with intracranial aneurysms. Stroke. 2007 Oct;38(10):2670-6

Darling MR, Tsai S, Jackson-Boeters L, Daley TD, Diamandis EP. Human kallikrein 8 expression in salivary gland tumors. Head Neck Pathol. 2008 Sep;2(3):169-74

Horii Y, Yamasaki N, Miyakawa T, Shiosaka S. Increased anxiety-like behavior in neuropsin (kallikrein-related peptidase 8) gene-deficient mice. Behav Neurosci. 2008 Jun;122(3):498-504

Izumi A, Iijima Y, Noguchi H, Numakawa T, Okada T, Hori H, Kato T, Tatsumi M, Kosuga A, Kamijima K, Asada T, Arima K, Saitoh O, Shiosaka S, Kunugi H. Genetic variations of human neuropsin gene and psychiatric disorders: polymorphism screening and possible association with bipolar disorder and cognitive functions. Neuropsychopharmacology. 2008 Dec;33(13):3237-45

Liu CJ, Liu TY, Kuo LT, Cheng HW, Chu TH, Chang KW, Lin SC. Differential gene expression signature between primary and metastatic head and neck squamous cell carcinoma. J Pathol. 2008 Mar;214(4):489-97

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

Kountourakis P, Psyrri A, Scorilas A, Markakis S, Kowalski D, Camp RL, Diamandis EP, Dimopoulos MA. Expression and prognostic significance of kallikrein-related peptidase 8 protein levels in advanced ovarian cancer by using automated quantitative analysis. Thromb Haemost. 2009 Mar;101(3):541-6

Lu ZX, Huang Q, Su B. Functional characterization of the human-specific (type II) form of kallikrein 8, a gene involved in learning and memory. Cell Res. 2009 Feb;19(2):259-67

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

Planque C, Choi YH, Guyetant S, Heuzé-Vourc'h N, Briollais L, Courty Y. Alternative splicing variant of kallikrein-related

peptidase 8 as an independent predictor of unfavorable prognosis in lung cancer. Clin Chem. 2010 Jun;56(6):987-97

Shingaki K, Matsuzaki S, Taniguchi M, Kubo T, Fujiwara T, Kanazawa S, Yamamoto A, Tamura H, Maeda T, Ooi K, Matsumoto K, Shiosaka S, Tohyama M. Molecular mechanism of kallikrein-related peptidase 8/neuropsin-induced hyperkeratosis in inflamed skin. Br J Dermatol. 2010 Sep;163(3):466-75

Yoshida S. Klk8, a multifunctional protease in the brain and skin: analysis of knockout mice. Biol Chem. 2010 Apr;391(4):375-80

Attwood BK, Bourgognon JM, Patel S, Mucha M, Schiavon E, Skrzypiec AE, Young KW, Shiosaka S, Korostynski M, Piechota M, Przewlocki R, Pawlak R. Neuropsin cleaves EphB2 in the amygdala to control anxiety. Nature. 2011 May 19;473(7347):372-5

Bin L, Kim BE, Hall CF, Leach SM, Leung DY. Inhibition of transcription factor specificity protein 1 alters the gene expression profile of keratinocytes leading to upregulation of kallikrein-related peptidases and thymic stromal lymphopoietin. J Invest Dermatol. 2011 Nov;131(11):2213-22

Eissa A, Amodeo V, Smith CR, Diamandis EP. Kallikrein-related peptidase-8 (KLK8) is an active serine protease in human epidermis and sweat and is involved in a skin barrier proteolytic cascade. J Biol Chem. 2011 Jan 7;286(1):687-706

Ishikawa Y, Tamura H, Shiosaka S. Diversity of neuropsin (KLK8)-dependent synaptic associativity in the hippocampal pyramidal neuron. J Physiol. 2011 Jul 15;589(Pt 14):3559-73

Oumeraci T, Schmidt B, Wolf T, Zapatka M, Pich A, Brors B, Eils R, Fleischhacker M, Schlegelberger B, von Neuhoff N. Bronchoalveolar lavage fluid of lung cancer patients: mapping the uncharted waters using proteomics technology. Lung Cancer. 2011 Apr;72(1):136-8

Shiosaka S, Ishikawa Y. Neuropsin--a possible modulator of synaptic plasticity. J Chem Neuroanat. 2011 Sep;42(1):24-9

Kishibe M, Bando Y, Tanaka T, Ishida-Yamamoto A, Iizuka H, Yoshida S. Kallikrein-related peptidase 8-dependent skin wound healing is associated with upregulation of kallikrein-related peptidase 6 and PAR2. J Invest Dermatol. 2012 Jun;132(6):1717-24

Qin W, Zhang K, Kliethermes B, Ruhlen RL, Browne EP, Arcaro KF, Sauter ER. Differential expression of cancer associated proteins in breast milk based on age at first full term pregnancy. BMC Cancer. 2012 Mar 21;12:100

Ramachandran R, Eissa A, Mihara K, Oikonomopoulou K, Saifeddine M, Renaux B, Diamandis E, Hollenberg MD. Proteinase-activated receptors (PARs): differential signalling by kallikrein-related peptidases KLK8 and KLK14. Biol Chem. 2012 Apr 1;393(5):421-7

Shingaki K, Taniguchi M, Kanazawa S, Matsuzaki S, Maeda T, Miyata S, Kubo T, Torii K, Shiosaka S, Tohyama M. NGF-p75 and neuropsin/KLK8 pathways stimulate each other to cause hyperkeratosis and acanthosis in inflamed skin. J Dermatol Sci. 2012 Jul;67(1):71-3

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