**Atlas of Genetics and Cytogenetics in Oncology and Haematology**

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# Gene Section
**Review**

# PTHLH (parathyroid hormone-like hormone)

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## Identity

**Hugo:** PTHLH
**Other names:** PTHLP (parathyroid hormone-like protein); PTHRP (parathyroid hormone-related protein); PTHrP; PTH-rP (PTH-related protein); PTHR; HHM (humoral hypercalcemia of malignancy); Osteostatin; PLP (parathyroid-like protein); MGC14611
**Location:** 12p11.22

## DNA/RNA

### Description

PTHLP is encoded by a single gene that is highly conserved among species. The gene is composed of 7 exons spanning a region of 13,899 bases (Start: 28,002,284 bp from pter; End: 28,016,183 bp from pter).
Orientation: minus strand.
The genomic DNA for the PTHLP gene was isolated from a human placental genomic library.

### Transcription

The sequence is supported by 3 sequences from 3 cDNA clones.

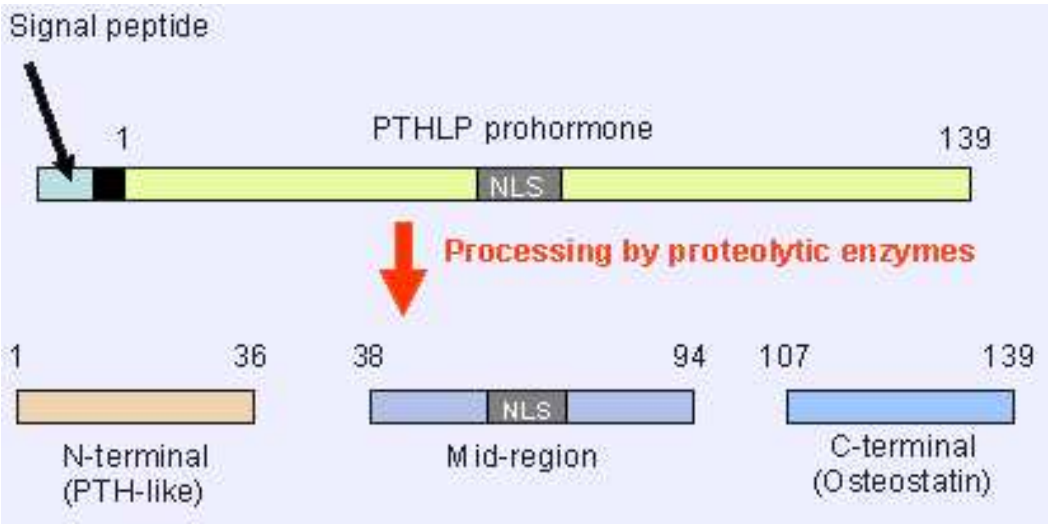
### Pseudogene

None.

## Protein

### Description

Size: 177 amino acids, 20194 Da.




This diagram represents schematically one possible proteolytic processing pattern of PTHLP into 3 bioactive peptides. The mid-region of PTHLP contains the nuclear localization signal (NLS).

The PTHLP gene has seven exons, and its transcripts are processed by alternative splicing into three isoforms, encoding proteins with 139, 173 and 141 amino acids. The pattern of expression of PTHLP mRNA isoforms may be cell type-specific. Although different tumors may have different PTHLP splicing patterns, there are no tumor-specific transcripts.
PTHLP is processed into a set of distinct peptide hormones by endoproteolytic cleavage of the initial translation products: mature N-terminal, mid-region and C-terminal secretory peptides, each having its own distinct function. The distribution of the endopeptidase processing enzymes (PTP (prohormone thiol protease), prohormone convertases 1 and 2 ( PC1 and PC2 )) may vary in different tissues. PTP cleaved the PTHLP precursor at the multibasic, dibasic, and monobasic residue cleavage sites to generate the NH2-terminal peptide (residues 1-37, having PTH-like and growth regulatory activities), the mid-region domain (residues 38-93, regulating calcium transport and cell proliferation), and the COOH-terminal domain (residues 102-141, modulating osteoclast activity).

## Expression

PTHLP is a protein polyhormone produced by most if not all tissues in the body. It is secreted during both fetal and postnatal life. Although PTHLP is found in the circulation, most of its activity appears to be paracrine. A complex of transcription factors and coactivators (CREB, Etsl and CBP) regulates PTHLP transcription and may contribute to the alterations associated with the promotion of carcinogenesis. Disruption of the normal regulation during cancer progression may in part be associated with TGF-beta1 - induced changes in PTHLP mRNA isoform expression and stability. TGF-beta activates PTHLP expression increasing transcription from the P3 promoter through a synergistic interaction of Smad3 and Ets1. ERK1/ERK2 -dependent Ets2/PKCepsilon synergism also appears to regulate PTHLP expression in breast cancer cells.
The PTHLP gene is also under the transcriptional control of glucocorticoids and vitamin D. 1,25-dihydroxy vitamin D3 treatment increases PTHLP mRNA expression and blocks the stimulatory effect of TGF-beta on PTHLP mRNA expression. Glucocortical steroid hormone can suppress PTHLP mRNA expression and release of bioactive PTHLP in certain PTHLP-producing tumors. The regulation of PTHLP expression by female sex steroid hormones is still unclear.
PTHLP is a downstream target for RAS and SRC, K-ras mutation increases PTHLP expression while a farnesyltransferase inhibitor known to inhibit RAS function can decrease PTHLP expression. The von Hippel-Lindau tumor suppressor protein also negatively regulates PTHLP expression at the post-transcriptional level.

## Localisation

PTHLP is a secreted polyhormone and is localized in the Golgi apparatus in the cytoplasm. However, in some cells, PTHLP can be detected in the nucleus by immunochemistry. The growth-inducing effect of NLS-containing mid-region PTHLP peptide in breast cancer is dependent on both internalization into the cytoplasm and subsequent translocation to the nucleus. PTHLP travels from the cytosol to the nucleus with the help of the nuclear transport factor importin beta1. Importin beta1 enhanced the association of PTHLP with microtubules, and the microtubule cytoskeleton plays an important role in protein transport to the nucleus.
The site of recognition of PTHLP is the N-terminal half of importin, which can also bind Ran and nucleoporin, and is sufficient for PTHLP nuclear import.

## Function

PTHLP is a growth factor, a PTH-like calciotropic hormone, a developmental regulatory molecule, and a muscle relaxant. The diverse activities of PTHLP result not only from processing of the precursor into multiple hormones, but from use of multiple receptors.
It is clear that the Type 1 Parathyroid Hormone Receptor (PTH1R), binding both PTH (1-34) and PTHLP (1-36), is the receptor mediating the function of PTHLP (1-36), and it is the only cloned receptor for PTHLP so far.
PTHLP also binds to a type of receptor in some tissues that does not bind PTH. PTHLP (67-86) activates phospholipase C signaling pathways through a receptor distinct from that activated by PTHLP (1-36) in the same cells. Unlike PTH, picomolar concentrations of the PTHLP (107-111) fragment to can activate membrane-associated PKC in osteosarcoma cells. PTHLP (107-139) exerts effects through the PKC/ERK pathway. Thus, it is highly likely that the mid-region and osteostatin peptides bind other, unique receptors, but those receptors have yet to be cloned and identified.
In contrast to the receptor-mediated endrocrine and paracrine action, the mid-region PTHLP peptide contains a classic bipartite nuclear localization signal (NLS) which upon entering the nuclear compartment confers 'intracrine' actions. Details of the nuclear action of PTHLP are still lacking, but overall, nuclear PTHLP appears to be mitogenic. The translation of PTHLP initiates from both the methionine-coding AUG and a leucine-coding CUGs further downstream in its signal sequence. It appeared that when translation was initiated from CUGs, PTHLP accumulated in the nucleoli, and that when translation was initiated from AUG, PTHLP localized in both the Golgi apparatus and nucleoli. Thus, nucleolar PTHLP appears to be derived from translation initiating from both AUG and CUGs. Modulation of cell adhesion by PTHLP localized in the nucleus is a normal physiological action of PTHLP, mediated by increasing integrin gene

transcription. The promotion by PTHLP in cancer growth and metastasis may be mediated by upregulating integrin alpha6beta4 expression and activating Akt.
PTHLP also interacts with beta-arrestin 1B, an important component of MAPK signaling and G-protein-coupled receptor desensitization, and this interaction requires residues 122-141 of PTHLP. Therefore, beta-arrestin 1 may mediate a novel regulatory function of PTHLP in intracellular signaling.
PTHLP also play a major role in development of several tissues and organs. PTHLP stimulates the proliferation of chondrocytes and suppresses their terminal differentiation. PTHLP (107-139) is a substrate for secPHEX, and osteocalcin, pyrophosphate and phosphate are inhibitors of secPHEX activity; thus PHEX activity and PTHLP are part of a complex network regulating bone mineralization. PTHLP plays a central role in the physiological regulation of bone formation, by promoting recruitment and survival of osteoblasts, and probably plays a role in the physiological regulation of bone resorption, by enhancing osteoclast formation. Signaling by fibroblast growth factor receptor 3 and PTHLP coordinate in cartilage and bone development. PTHLP is also an essential physiological regulator of adult bone mass.
PTHLP aids in normal mammary gland development and lactation as well as placental transfer of calcium. Mammary gland development depends upon a complex interaction between epithelial and mesenchymal cells that requires PTHLP. The calcium sensor (CaR) regulates PTHLP production as well as transport of calcium in the lactating mammary gland. In normal animals, mammary epithelial cells secrete a lot of PTHLP, which helps to adjust maternal metabolism to meet the calcium demands of lactation. The mid-region PTHLP peptide has also been shown to control the normal maternal-to-fetal pumping of calcium across the placenta.
PTHLP is secreted from smooth muscle in many organs, usually in response to stretching. PTHLP relaxes smooth muscle. Transgenic mice that express PTHLP in vascular smooth muscle have hypotension, being consistent with a vasodilating effect of PTHLP.
PTHLP is highly expressed in the skin. EGF and other similar ligands can potentially activate PTHLP gene expression in the epidermis. PTHLP can inhibit hair growth and is required for tooth eruption as shown by mouse models that manipulated the PTHLP gene.

# Implicated in

## *Humoral hypercalcemia of malignancy*

**Disease**

Humoral hypercalcemia of malignancy (HHM) was first described by Albright in 1941, and is a well-known complication among cancer patients. This syndrome is commonly encountered in advanced cancer of epithelial origin, especially squamous cell carcinoma of the lung. Studies of the 'humors' secreted by cancer that causes hypercalcemia led to the discovery of 3 classes of peptides: parathyroid-like peptides, growth factor-like peptides, and bone-resorbing factors. Then protein purification led to molecular studies that cloned cDNAs for PTHLH. A study suggested that the PTHLH may be responsible for the abnormal calcium metabolism in HHM.

**Prognosis**

The median survival after the first occurrence of hypercalcemia is 66 days in patients with serum PTHLP inferior or equal to 21 pmol/L and 33 days in patients with PTHLP superior to 21 pmol/L. In hypercalcemia of malignancy, raised serum levels of PTHLP indicate a more advanced tumor state and an extremely poor prognosis.

## *Autocrine promotion of tumor progression*

**Prognosis**

In the absence of hypercalcemia, approximately 17% of patients with gastroesophageal carcinoma have elevated levels of PTHLP, and the increase in PTHLP was associated with a poor prognosis.

**Oncogenesis**

mRNA for the PTH1R was detected many tumors expressing PTHLP; thus the PTHLP produced by these tumors may act in an autocrine or paracrine fashion. PTHLP (1-34) treatment resulted in an increase in proliferation in prostate cancer cells which may require androgen in some cell lines. In breast cancer cells, PTHLP regulates CDC2 and CDC25B via PTH1R in a cAMP-independent manner, and PTHLP promotes cell migration through induction of ITGA6, PAI-1, and KISS-1, and promotes proliferation through induction of KISS-1.
These pieces of evidence together suggest that PTHLP and PTH1R together play an important role in the autocrine/paracrine promotion of tumor proliferation in some cancers.

## *Bone metastasis*

**Disease**

Breast cancer

**Oncogenesis**

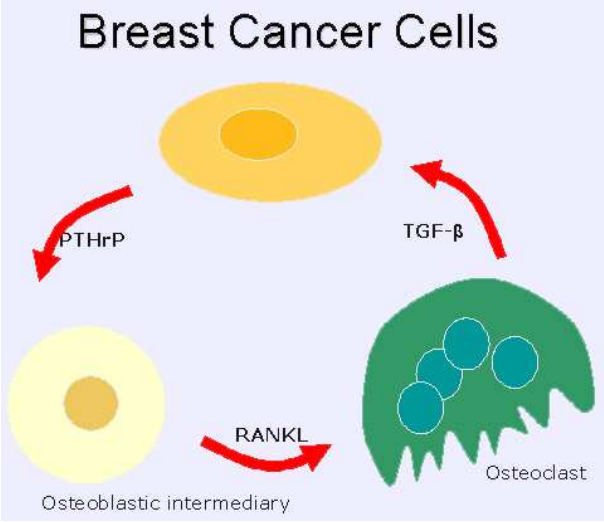
PTHLP is a mediator of the bone destruction associated with osteolytic metastasis. Patients with PTHLP-expressing breast carcinoma are more likely to develop bone metastasis, and bone metastasis expresses PTHLP in more than 90% of cases as compared with less than 20% of cases of metastasis to other sites.
In breast cancer, osteolytic metastases are the most common. PTHLP is a common osteolytic factor, and other osteolytic factors include vascular endothelial

growth factor and interleukin 8 and interleukin 11. Since osteoblasts are the main regulators of osteolytic osteoclasts, stimulation of osteoblasts can paradoxically increase osteoclast function. Simultaneous expression of osteoblastic and osteolytic factors can produce mixed metastases.

PTHLP expression by cancer cells may provide a selective growth advantage in bone because PTHLP stimulates osteoclastic bone resorption to release growth factors such as TGF-beta from the bone matrix. TGF-beta in turn will activate by osteoclastic bone resorption and enhance PTHLP expression and tumor cell growth, thus completing a vicious cycle (See diagram). Taken together, PTHLP expression by breast carcinoma cells enhance the development and progression of breast carcinoma metastasis to bone. Alternatively, cytokines such as IL-8 initiate the process of osteoclastic bone resorption in the early stages of breast cancer metastasis, and PTHLP expression is induced to stimulate the vicious cycle of osteolysis at a later stage.

Certain cancer treatments, especially sex steroid hormone deprivation therapies, stimulate bone loss.

Bone resorption will result in the release of bone growth factors, which may inadvertently facilitate bone metastasis. Treatment with bisphosphonates will prevent bone resorption and reduce the release of bone growth factors.




The interactions among breast cancer cells, osteoblasts and osteoclasts define a feedback loop that promote breast cancer growth in the bone microenvironment.

## *Cachexia in hypercalcemia of malignancy*

### Oncogenesis

PTHLP induces a wasting/cachectic syndrome. PTHLP leads to decreased physical activity and lowered energy metabolism independently of the effects of hypercalcemia and proinflammatory cytokines. In a rodent model, PTHLP induces a cachectic syndrome (in addition to inducing hypercalcemia of malignancy) by changing the mRNA levels of orexigenic and anorexigenic peptides, except leptin and orexin. Expression of cachexia-inducing cytokines such as interleukin-6 and leukemia inhibitory factor is increased by PTHLP. Animal data suggest that humanized antibody against PTHLP may be effective for patients with hypercalcemia and cachexia in patients with humoral hypercalcemia of malignancy.

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