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Gene Section
Review

PAEP (progestagen-associated endometrial protein)

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Identity

Other names: GD; GdA; GdF; GdS; MGC138509; MGC142288; PAEG; PEP; PP14

HGNC (Hugo): PAEP

Location: 9q34.3

Local order: Several other lipocalin genes have been mapped on the same chromosomal region. From centromere to telomere (GeneLoc database): lipocalin 1 (tear prealbumin, LCN1) - ENSG00000221613 - odorant binding protein 2A (OBP2A) - **progestagen-associated endometrial protein (PAEP)** - ENSG00000237339 - LOC138159 - ENSG00000236543 - glycosyltransferase 6 domain containing 1 (GLT6D1) - lipocalin 9 (LCN9).

DNA/RNA

Note
Many other lipocalin genes have similar exon/intron organization.

Description

Maps to chromosome 9: 138453602-138458801 on forward (plus) strand (5200 bases). Gene consists of 7 exons. Promoter region contains, by sequence similarity, 2 forward and two reverse Sp1-like binding sites, four putative glucocorticoid/progesterone response elements (PREs), cAMP responsive element (CRE) and activator protein-1 (AP-1) element.

Transcription

PAEP mRNA (NM_001018049) has 857 bp. Several alternatively spliced mRNA forms have been described, but for most of these evidence for the corresponding protein lacks. Alternative Splicing and Transcript Diversity database (ASTD) reports 16 different transcripts.

Pseudogene

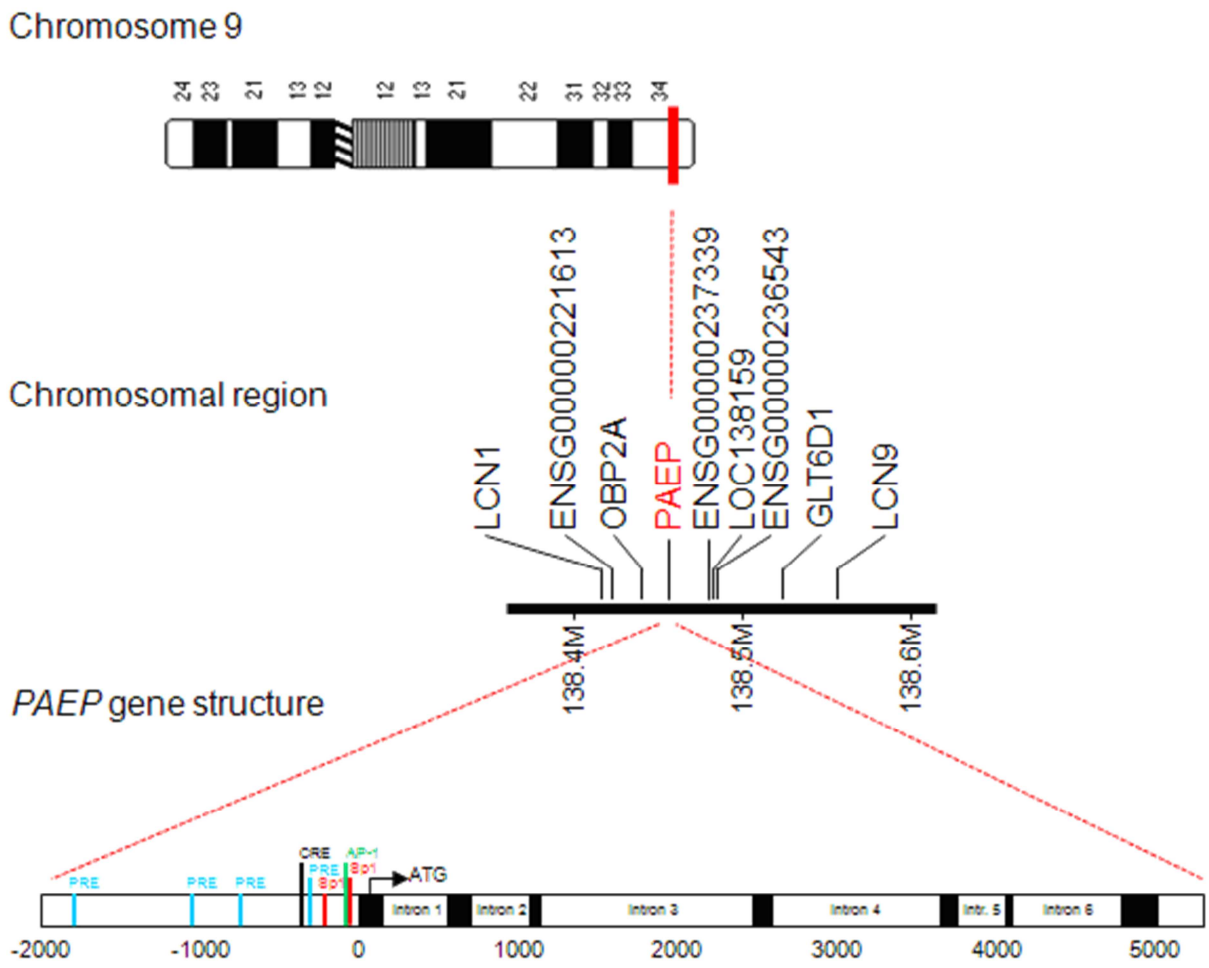
Not known.

Protein

Note
Some of the localization studies have employed antibodies, the specificity of which is questionable. Some of the biological studies have utilized short peptides derived from PAEP sequence. It is unclear whether such peptides are present in vivo. Glycosylation plays an important part in modulating/dictating the activity of PAEP. In the literature, PAEP is widely referred to as PP14 and glycodelin.

Description

PAEP (180 amino acids, of which 18 corresponds to signal sequence) is a 28 kDa secreted glycoprotein, belonging to the kernel lipocalin family. Most family members share three conserved sequence motifs. Although sequence similarity between the family members is low, their three dimensional structures are similar.



Chromosomal location and gene structure of PAEP. Promoter region shows some of the potential regulatory elements. After translation-initiating codon (ATG) exons of the major transcript are shown in black. Some splicing variants contain also parts outside of these exons. PRE: glucocorticoid/progesterone response element; CRE: cAMP responsive element; Sp1: Sp1 transcription factor binding site; AP-1: activator protein-1 element.

Lipocalins are small extracellular proteins, many of which bind small hydrophobic molecules, such as retinol and steroids. There is no evidence that PAEP exhibits similar binding properties. PAEP is a glycoprotein with three potential glycosylation sites. Two of them are glycosylated. Many differentially glycosylated forms have been characterized in these sites. Glycosylation modulates/dictates the biological activity of PAEP. Some of the alternatively spliced mRNAs lack the sequences encoding glycosylation sites and/or the lipocalin signature sequence.

Expression

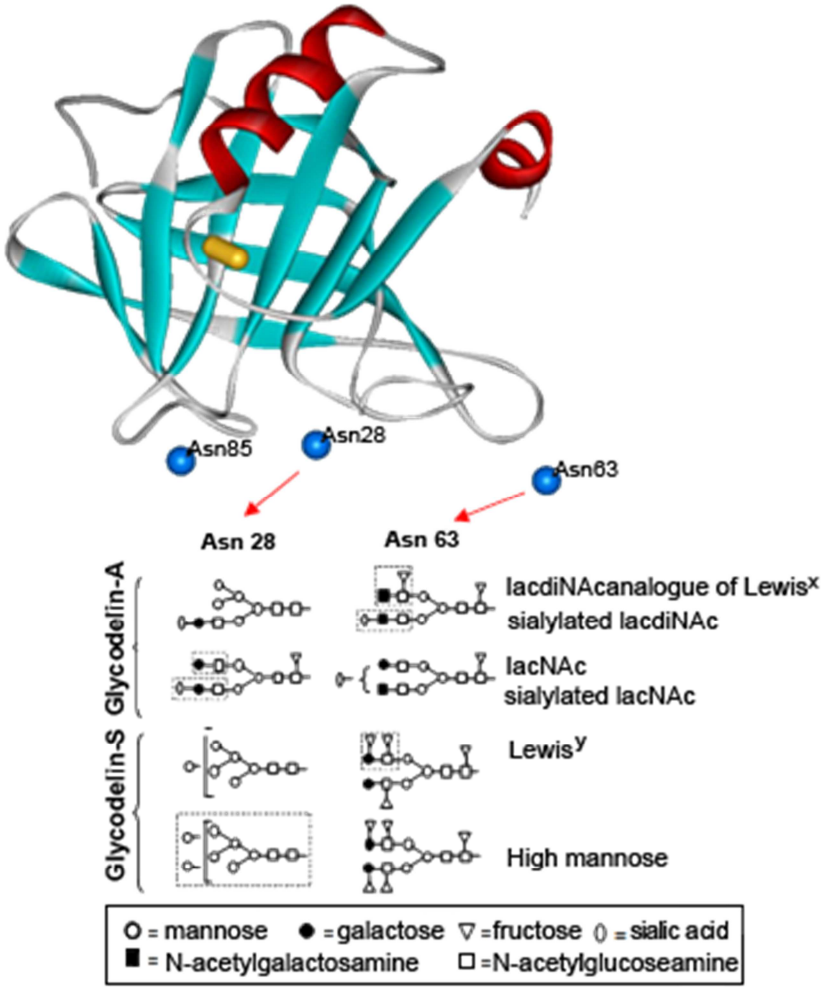
The expression of PAEP is highly regulated in a spatiotemporal fashion. In the female, PAEP is mainly expressed in secretory/decidualized endometrial glands after progesterone exposure. In secretory endometrium, expression becomes detectable four days after ovulation and reaches maximum at the end of the menstrual cycle unless pregnancy ensues. PAEP is one of the major proteins in endometrial secretions. In the male, the highest expression has been reported in seminal vesicles. PAEP is also expressed in other epithelial cells of reproductive tissues, such as fallopian tubes, ovary and the breast. In addition, other secretory epithelia, such as eccrine sweat glands and the bronchus epithelium express PAEP. It is also expressed in differentiated areas of breast cancer, ovarian tumors, endometrial adenocarcinoma, and synovial sarcoma. In addition to epithelial tissues, PAEP has been found in megakaryocytes and erythroid precursor cells. Experimental evidence suggests that PAEP expression is regulated by progesterone/progestins, relaxin, and histone deacetylase inhibitors.

Localisation

PAEP is mostly found in exocrine epithelial cells, from which it is secreted into the gland lumen. In breast cancer, PAEP has been found also in paranuclear vacuoles of lobular carcinoma cells.

Function

PAEP/PP14/glycodelin regulates the functions of spermatozoa during fertilization in a glycosylation dependent manner.



Swiss model-deduced tertiary structure of the PAEP monomer. The S-S bridge is shown as cylinder and side chain nitrogen atoms of asparagines of potential glycosylation sites are shown as balls. Below are representative examples of the major complex-type glycans present at the N-glycosylation sites Asn 28 and Asn 63 of amniotic fluid glycodelin-isoform (glycodelin-A) and seminal plasma glycodelin-isoform (glycodelin-S). Some of the characteristic epitopes are marked by broken line.

The various glycoforms of PAEP have different, sometimes even opposite, biological actions at different phases of the fertilization process. Seminal fluid glycodelin-S binds to the sperm head and inhibits premature capacitation. In the female reproductive tract, spermatozoa come into contact with various PAEP glycoforms, that modulate sperm function, e.g., by preventing premature, progesterone-induced acrosome reaction (glycodelin-F). Glycodelin-A inhibits binding of spermatozoa to the zona pellucida, whereas another glycoform (glycodelin-C) stimulates the same. All these actions are glycosylation-dependent.

PAEP also regulates immune cell functions, which too are, at least in part, regulated by glycosylation. Different PAEP glycoforms contain diverse bi-, tri-, and tetra-antennary complex-type glycans with varying levels of fucose and sialic acid substitution. Glycodelin-A and -F are the most heavily sialylated and inhibit cell proliferation, induce cell death, and suppress interleukin-2 secretion of Jurkat cells and peripheral blood mononuclear cells. No such immunosuppressive effect has been observed for glycodelin-C and -S carrying less or no sialic acids, or for desialylated glycodelin-A and -F. By its immunosuppressive properties one of the PAEP glycoforms (glycodelin-A) may contribute to immunotolerance at the fetomaternal interface and prevent rejection of the fetal semi-allograft.

In early pregnancy, glycodelin-A restrains inappropriate invasion of extravillous cytotrophoblasts by suppressing activity of some key metalloproteinases. In breast and endometrial cancer cell lines, PAEP has been found to revert the malignant phenotype in vitro by inducing morphological differentiation and specific gene expression changes. In a preclinical mouse model, transgenic PAEP expression in breast cancer cells has reduced tumor growth.

Homology

Most lipocalins do not share high sequence similarity, but they are likely to be homologous.

Functional PAEP gene has been found in higher primates. Beta-lactoglobulins represent orthologs of

PAEP, but they are likely to be functionally different from human PAEP, not least because of their differences in glycosylation. No convincing evidence of a PAEP ortholog in mouse or rat has been reported.

Mutations

Note
NCBI SNP database reports 128 PAEP SNPs (Homo sapiens, 13 September 2010). Also HinfI restriction enzyme polymorphism has been reported in Finnish population with 5% frequency for allele A1 and 95% frequency for allele A2. No disease associations for mutations have been described.

Implicated in

Ovarian carcinoma

Note
PAEP is expressed in both normal and malignant ovarian tissue. PAEP has been localized to the cytoplasm of tumor cells and its staining is more frequent in well-differentiated than in poorly differentiated carcinomas. Nuclear progesterone receptors (PRA and PRB) are often coexpressed with cytoplasmic PAEP.

Disease
In 2002, ovarian cancer was the 6th most common cancer in women, and 7th most common cause of cancer death. Most malignant neoplasms of the ovary originate from the coelomic epithelium.

Prognosis
In ovarian serous carcinoma, PAEP expression is associated with a more favorable prognosis, even in patients with the same tumor grade and clinical stage.

Breast cancer

Note
In breast cancer tissue, PAEP staining has been found in both estrogen and progesterone receptor negative and positive cancers. PAEP is also present in normal breast tissue. Transfection of PAEP in MCF-7 breast cancer cells reverted the malignant phenotype of the cells by inducing morphological differentiation and specific gene expression changes. Furthermore, these cells showed reduced tumor growth in a preclinical xenograft tumor mouse model.

Disease
Breast cancer is the most common cancer among women worldwide. Although the prognosis has improved following improved diagnosis and therapies, breast cancer remains an important cause of death among women. Most of the neoplasms of the breast originate from the ductal epithelium, while a minority originates from the lobular epithelium. Family history of breast cancer is associated with a 2-3-fold higher risk of the disease.

Prognosis
In sporadic breast cancer, PAEP is associated with low proliferation rate and well-differentiated tumors, whereas in familial "non BRCA1/BRCA2" patients, PAEP expression is associated with a less favorable phenotype and increased risk of metastases.

Reproductive failure

Note
During the period of endometrial receptivity for implantation, reduced PAEP secretion/serum levels have been observed in reproductive failure, e.g. in unexplained infertility or recurrent early pregnancy loss.

Disease
Unexplained infertility or recurrent miscarriage may result from inadequate implantation and/or placentation.

Polycystic ovary syndrome (PCOS)

Note
Pregnant women with PCOS who subsequently miscarry show subnormal rise of PAEP serum concentration during the first trimester.

Disease
PCOS is a common endocrine disorder in fertile-aged women. It is associated with ovulatory disturbance, insulin resistance and androgen excess, and is a frequent cause of menstrual disorders and infertility in women.

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