

## Gene Section

### Review

# MUC6 (mucin 6, oligomeric mucus/gel-forming)

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### Identity

**Other names:** MUC-6; mucin 6

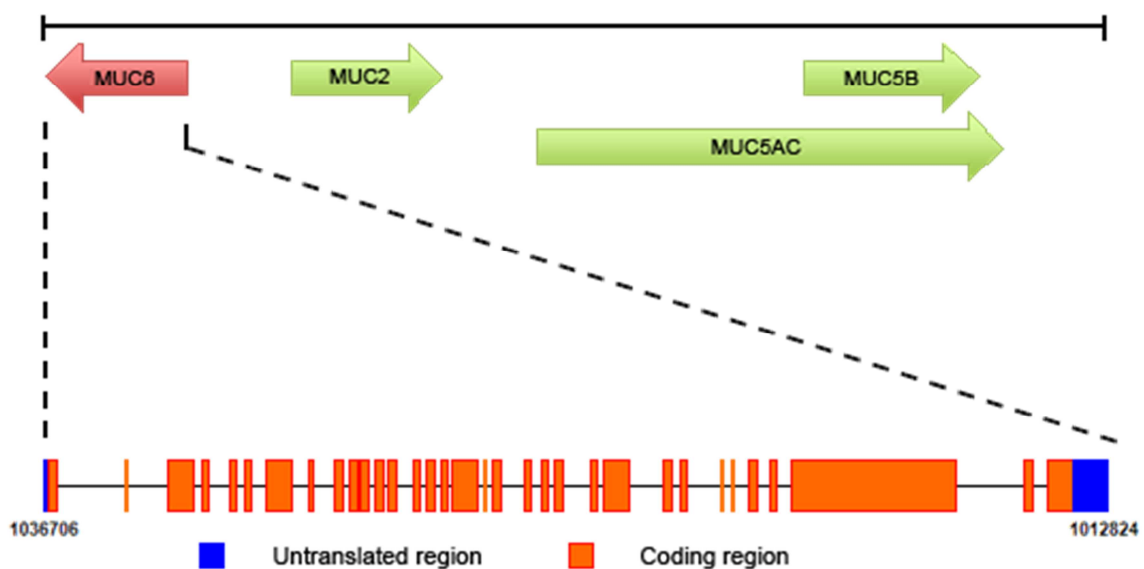
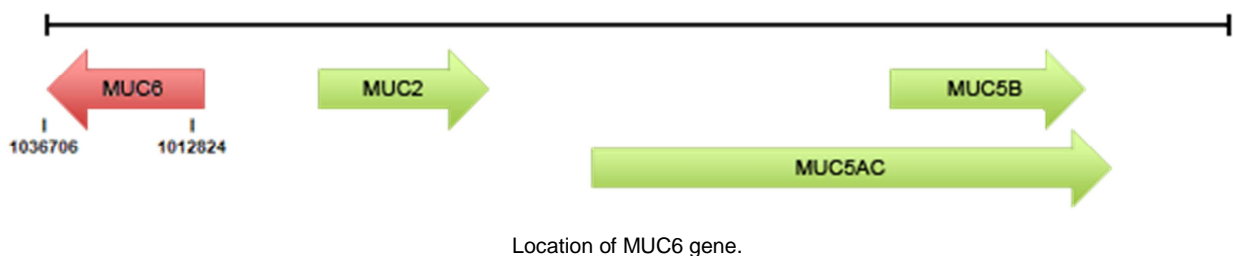
**HGNC (Hugo):** MUC6

**Location:** 11p15.5

### DNA/RNA

#### Description

MUC6 gene approximately extends 24 kb-long on the chromosome 11 in the region p15.5.



The central region has sequences repeated in tandem (TR) with a consensus motif composed of 507 pb. The variable number of TR (VNTR) diverges between 15 and 26, and the difference in distinct alleles is 5 kb long. Some data suggest that short MUC6 alleles are associated with *Helicobacter pylori* infection and gastric cancer.

### Transcription

MUC6 gene is composed of 33 exons and the mRNA length is approximately 8 kb. The 5' flanking region of the MUC6 gene contains a TATA box at -35/-29 and potential transcription factor binding sites are described for NFκB and Sp family members. Although MUC6 promoter contains a high percentage of CpG dinucleotides (up to 75%) and a CpG island, its regulation is not influenced by epigenetics.

At present no splice variants forms have been reported.

## Protein

### Description

At the N-terminal region D1, D2, D' and D3 domains similar to von Willebrand factor (vWF) are present.

The TR domain composes the central region. The 169 amino acid consensus sequence has a high content of Thr-Ser-Pro containing numerous potential O-glycosylation sites.

The C-terminal region consists in two distinct regions. One with a high Thr-Ser-Pro content (STP domain), very similar to the tandem repeat region in amino acid composition, and the other region that has a high content of cystein residues. This domain has approximately 25% similarity to the CK domain of the 11p15 human mucins MUC2, MUC5AC, MUC5B and the vWF.

### Expression

MUC6 was initially isolated from a gastric cDNA library, and it is expressed in the deep gland cells. It is the only mucin produced by acinar cells of the duodenal Brünner's glands and it is also expressed in pancreas, endocervix and gallbladder.

Under pathological conditions, MUC6 expression can be altered, as it is reported below.

### Function

MUC6, together with MUC5AC, is the major component of the protective layer over the gastric surface where it acts as a selective diffusion barrier for HCl. Furthermore, the O-glycans found in the MUC6 TR have antimicrobial activity against *Helicobacter pylori*, inhibiting the biosynthesis of cholesteryl-alpha-D-glucopyranoside, a major cell wall component.

### Homology

Several orthologues of MUC6 have been identified in *Mus musculus*, *Rattus norvegicus*, *Pan troglodytes* and *Equus caballus*. The chicken and mouse Muc6 have similar domain structures with human MUC6. Furthermore, the tissue-specific expression is conserved in murine organisms.

## Implicated in

### Gastric cancer

#### Disease

Gastric cancer remains the second leading cause related death and the fourth most common cancer in the world, although its incidence is gradually decreasing.

#### Prognosis

MUC6 is highly expressed in gastric mucosa and in intestinal metaplasia MUC6 levels are decreased: In incomplete metaplasia and type I complete metaplasia MUC6 is not detected, whereas it is found in type II and type III complete intestinal metaplasia. MUC6 expression is lower in intestinal-type of gastric carcinomas than in adenomas or normal mucosa suggesting that the downregulation of MUC6 may contribute to the malignant transformation of gastric epithelial cells.

MUC6 is expressed in diffuse-type gastric carcinoma and its levels are greater in early carcinomas than in advanced carcinomas, showing no relationship with the depth of the carcinoma cells invasion.

### Colon cancer

#### Disease

Colorectal cancer is one of the commonest cancers and the third leading cause of cancer death.



Schematic representation of MUC6 peptide structure (not to scale).

However, its incidence has decreased due to a most effective intervention and life-style changes in the western countries.

#### **Prognosis**

Although in normal colon mucosa MUC6 is not expressed, it is upregulated through the adenoma-carcinoma sequence, together with the downregulation of MUC2.

### **Salivary glands tumors**

#### **Disease**

Salivary gland tumors are relatively uncommon. However, mucoepidermoid carcinoma is the most frequent malignant tumor of salivary glands.

#### **Prognosis**

Normal salivary glands do not express MUC6 whereas in mucoepidermoid carcinomas MUC6 is detected preferentially in mucous cells.

### **Esophagus adenocarcinoma**

#### **Disease**

The frequency of adenocarcinoma of the esophagus is increasing in the western world from a result of a higher prevalence in Barrett's mucosa.

#### **Prognosis**

MUC6 showed a decrease in expression with progression from Barrett's esophagus to dysplasia and to adenocarcinoma.

### **Pancreatic cancer**

#### **Disease**

Pancreas cancer is a very aggressive tumor with a 5-year survival of less than 5%, and approximately 85% of them correspond to ductal adenocarcinomas.

#### **Prognosis**

In normal pancreatic epithelium MUC6 is only expressed in ductal and in a minority of centroacinar cells. However, it is upregulated at early stages of pancreatic carcinogenesis and in pancreatic cancer. MUC6 expression has been related to clinicopathological factors and patient prognosis and survival in invasive ductal carcinoma.

### **Biliary tract cancer**

#### **Disease**

Biliary tract carcinomas are uncommon tumors that include cholangiocarcinomas and gallbladder carcinomas. These tumors have a poor prognosis: more than 80% of the patients are unresectable with a 6-9 month survival, and this rate is increased to 5 year after surgery.

#### **Prognosis**

MUC6 is expressed in normal gallbladder mucosa. However in adenomas, dysplasias and carcinomas, MUC6 tends to decrease and its expression is

related to non-invasive growth. MUC6 is expressed frequently in pseudopyloric gland metaplasia as well as dysplasia and carcinoma.

### **Lung cancer**

#### **Disease**

Lung cancer is the leading cause of cancer-related mortality worldwide. Despite of this its incidence is decreasing.

#### **Prognosis**

MUC6 is not expressed in normal respiratory epithelium, but it has been focally detected in normal and distal epithelium from cancer patients. MUC6 levels increase significantly in the progression from atypical adenomatous hyperplasia, through bronchio alveolar carcinoma, to adenocarcinoma with mixed subtypes, suggesting that its expression might be associated with the progression of the lung adenocarcinoma. No expression of MUC6 is found in squamous lesions.

### **Breast cancer**

#### **Disease**

Breast cancer is the most common cancer worldwide and the leading cause of cancer mortality in women.

#### **Prognosis**

MUC6 is generally not detected in normal breast epithelium but it is overexpressed in benign breast disease (fibrocystic disease without atypia and atypical fibrocystic disease) and in breast carcinoma.

### **Endometrial adenocarcinoma**

#### **Disease**

Endometrial carcinoma is the most common malignant neoplasm of the female genital tract in developed countries, and it occurs predominantly after menopause.

#### **Prognosis**

MUC6 is not expressed in normal endometrial epithelium. However during endometrial neoplasia transformation, increased levels of MUC6 are detected: from simple hyperplasia, to complex hyperplasia, and in endometrial adenocarcinomas a MUC6 upregulation is found.

### **Uterine cervix adenocarcinoma**

#### **Disease**

Adenocarcinoma is the second most common malignancy of the uterine cervix. Its incidence has been increasing and constitutes 10-20% of invasive cervical cancers.

#### **Prognosis**

Although MUC6 is not expressed in normal cervical epithelium, in adenocarcinomas from uterine cervix; MUC6 can be detected at different levels associated to the histological type.

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