

Gene Section

Mini Review

PTGIS (prostaglandin I2 (prostacyclin) synthase)

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Identity

Other names: CYP8; CYP8A1; EC 5.3.99.4; MGC126858; MGC126860; PGIS; PTGI

HGNC (Hugo): PTGIS

Location: 20q13.13

DNA/RNA

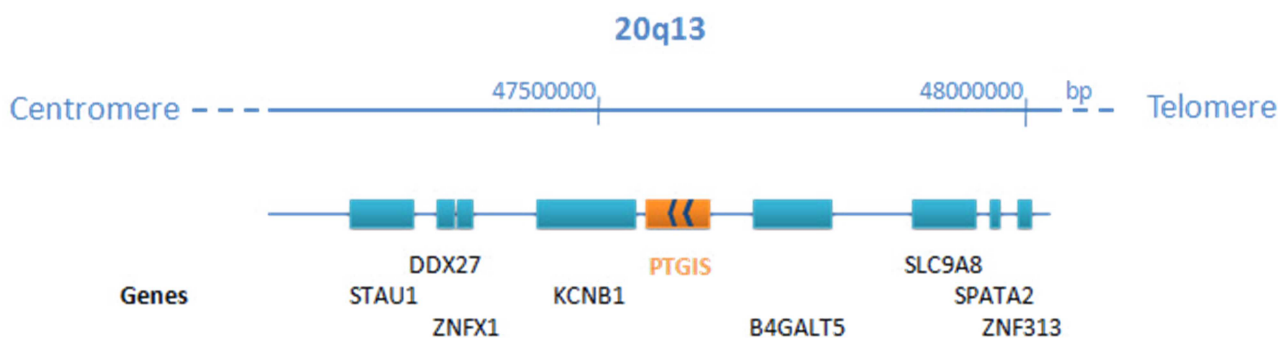
Description

64297 bases (chr20:47553818-47618114); 10 exons; telomere to centromere orientation.

Transcription

Two alternative splicing products; 5624bp (coding, 1578bp ORF) and 313bp (non-coding). A 1.5kb upstream sequence presents CG-rich and pyrimidine-rich regions and contains consensus sequences for the recognition sites of Sp-1, AP-2, INF-gamma responsive element, GATA, NF-kB, glucocorticoid responsive element and a CACCC box.

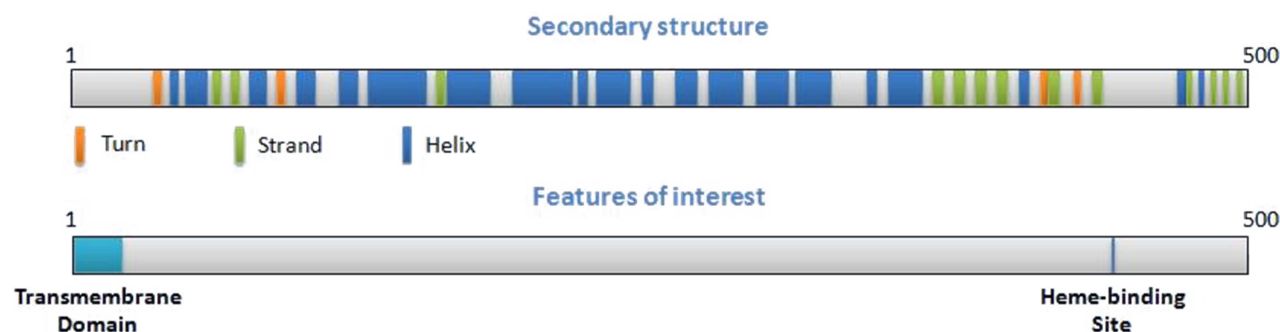
It has been demonstrated that PTGIS transcription is regulated via Sp1 binding, which may be affected by polymorphisms in the promoter region. The CG-rich region presents significant promoter activity.



Map of 20q13 chromosomal region.



Schematic diagram of PTGIS genomic region.



PTGIS protein structure: secondary structure composition and features of interest.

Protein

Description

PTGIS is a protein from the cytochrome P450 superfamily that consists of 500 amino acids and has a molecular weight of 57kDa. Is a single-pass membrane protein with a single transmembrane domain (1-20) and presents a heme-binding site at position 441. No post-translational modifications have been described for this protein.

Expression

Abundant in heart, lung, skeletal muscle, ovary and prostate. PTGIS is found underexpressed in most colorectal carcinomas and in several lung carcinomas and hypertensive subjects.

Localisation

At cellular level can be found in the endoplasmatic reticulum membrane and in microsomes as a peripheral membrane protein.

Function

Catalyses the isomerization of prostaglandin H2 to prostacyclin (prostaglandin I2), a potent vasodilator and inhibitor of platelet aggregation.

Homology

Pan troglodytes - Prostaglandin I2 (prostacyclin) Synthase.

Canis lupus familiaris - Prostaglandin I2 (prostacyclin) Synthase.

Bos taurus - Prostaglandin I2 (prostacyclin) Synthase.

Mus musculus - Prostaglandin I2 (prostacyclin) Synthase.

Rattus norvegicus - Prostaglandin I2 (prostacyclin) Synthase.

Danio rerio - Prostaglandin I2 (prostacyclin) Synthase like.

Mutations

Note

One splicing mutation has been associated with essential hypertension.

Implicated in

Colorectal cancer

Note

PTGIS promoter is silenced by through promoter hypermethylation in a large subset of colorectal carcinomas (also observed in colorectal adenomas and in several colorectal cancer cell lines). The PTGIS silencing is an early event on tumor progression and age and sex-independent. A PTGIS promoter VNTR polymorphism has been associated with the risk of colorectal polyps, being the risk increased when both alleles present less than 6 repeats.

Non-small cell lung cancer

Disease

PTGIS promoter is hypermethylated in lung cancer cell lines. The VNTR polymorphism has also been associated with gene silencing in lung cancer cells.

Breast cancer

Disease

The combination of the SNPs PTGIS(11)rs477627, PTGIS(21)rs476496 and PTGIS(20)rs1066894, located in the 5' region and first intron, confers reduced susceptibility to breast cancer.

Essential hypertension

Disease

A splicing mutation (T->C at the +2 position of the donor site of the intron 9) alters the reading frame and results in the production of a truncated protein with the heme-binding region deleted. The subjects found with this mutation presented lower levels of prostacyclin and hypertension.

The polymorphism C1117A has been significantly associated with hypertension, being the allele C associated with higher risk the condition, although it does not change the aminoacid sequence.

A polymorphism in the 5' region with a variable number of repeats of a 9-bp sequence (CCGCCAGCC) is associated with hypertension. The alleles less repeats possess less Sp1 sites and present lower promoter activity, being related with

higher pulse pressure in women and higher systolic blood pressure in older individuals.

Cerebral infarction

Disease

Association between cerebral infarction and the PTGIS promoter VNTR alleles with less repeats.

Myocardial infarction

Disease

A synonymous SNP at codon 373 (Arg373Arg) in exon 8 has been associated with risk of myocardial infarction in the Japanese population.

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