Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

GPX1 (Glutathione Peroxidase 1)

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Published in Atlas Database: November 2013

Online updated version : http://AtlasGeneticsOncology.org/Genes/GPX1ID40747ch3p21.html
DOI: 10.4267/2042/53966

Abstract

Review on GPX1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: GPXD, GSHPX1

HGNC (Hugo): GPX1

Location: 3p21.31

Local order

- C3orf62, chr3:49306030-49314508, chromosome 3 open reading frame 62
- USP4, 3p21.31, chr3:49314577-49377536, ubiquitin specific peptidase 4 (proto-oncogene), transcript variant 2
- USP4, 3p21.31, chr3:49314577-49377536, ubiquitin specific peptidase 4 (proto-oncogene), transcript variant 1
- USP4, 3p21.31, chr3:49349218-49377536, ubiquitin specific peptidase 4 (proto-oncogene), transcript variant 3
- **GPX1**, 3p21.31, chr3:49394609-49395791, glutathione peroxidase 1, transcript variant 1
- **GPX1**, 3p21.31, chr3:49394609-49395791, glutathione peroxidase 1, transcript variant 2
- RHOA, 3p21.31, chr3:49396579-49449526, ras homolog family member A
- TCTA, 3p21.31, chr3:49449639-49453909, T-cell leukemia translocation altered
- AMT, 3p21.31, chr3:49454211-49460111, aminomethyltransferase

The colocalization of genes is presented on figure 1.

Note

According to hg19/GRCh37-Feb_2009:
- GPX1 at chr3:49394609-49395791 - (NM_000581) glutathione peroxidase 1 isoform 1
- GPX1 at chr3:49394609-49395791 - (NM_201397) glutathione peroxidase 1 isoform 2

GPX1 is an enzyme that reduces hydrogen and lipid peroxides to water or alcohols by reducing glutathione. Systematic name: glutathione: hydrogen-peroxide oxidoreductase.

Reaction: 2 glutathione + H2O2 = glutathione disulfide + 2 H2O [RN:R00274].

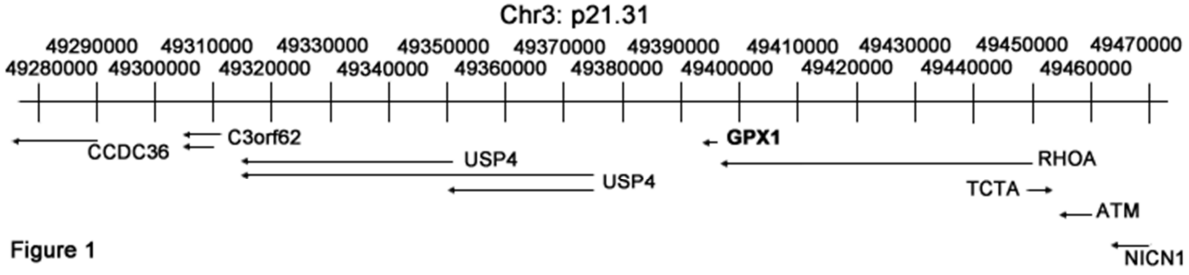

Figure 1

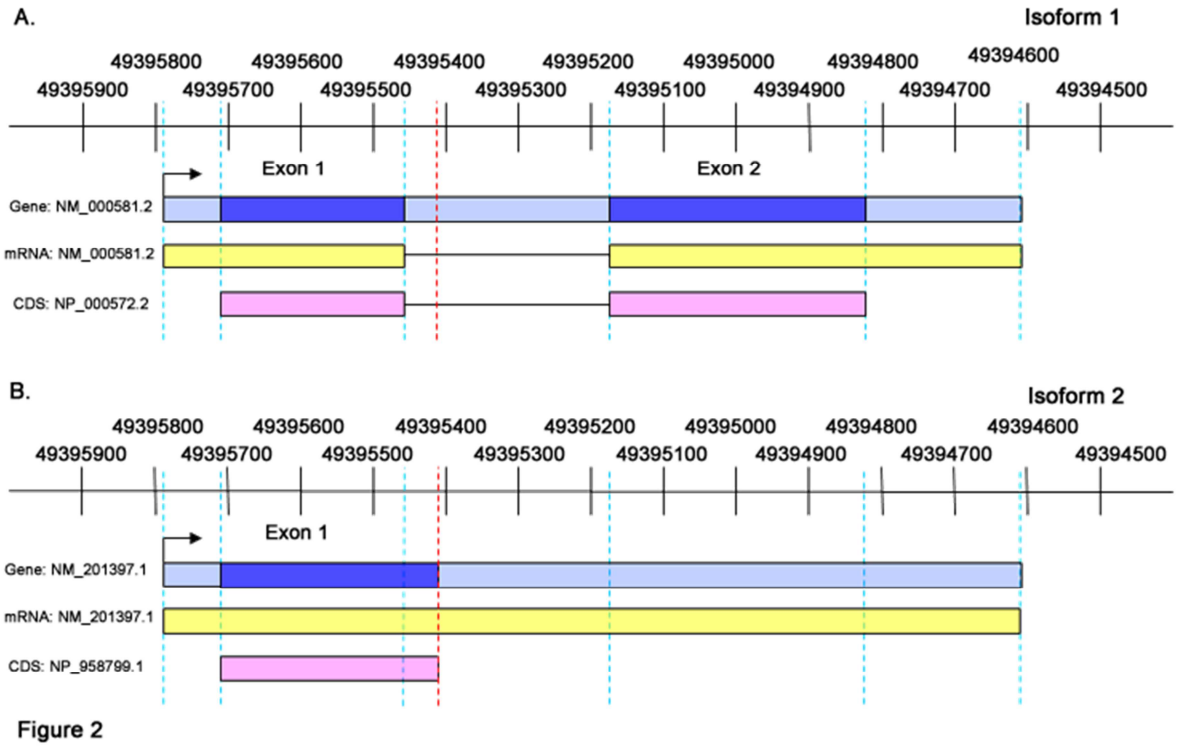

Figure 2

DNA/RNA

Description

According to hg19/GRCh37-Feb_2009:
- Start: chr3:49394609 bp from pter
- End: chr3:49395791 bp from pter
- Size: 1183 bases
- Orientation: minus strand

Transcription

Two alternatively spliced transcript variants encoding distinct isoforms have been shown for this gene (Nucleotide).

Isoform 1 represents the shorter transcript (921 bases), RefSeq: NM_000581.2, which is comprised of 2 exons and coding the longer isoform (Figure 2A).

Isoform 2 is 1200 bases, RefSeq: NM_201397.1, also this variant is intronless.

Due to the fact that this variant is not spliced the open reading frame is shifted and the protein is shorter from C-terminus compared to isoform 1 (Figure 2B).

Pseudogene

Two pseudogenes have been found so far. GPX1P1 glutathione peroxidase pseudogene 1 (other names: GPXL2, GPXP1) is located at the locus Xp22.2 (HGNC:4560). GPX1P2 glutathione peroxidase pseudogene 2 (other names: GPXP2, GPXP2P) is located at the locus 21q21.3 (HGNC:4561).

Protein

Description

203 aa (Accession: NM_000581.2) isoform 1; 98 aa (Accession: NM_201397.1) isoform 2.

GPX1 belongs to the family of glutathione peroxidases (Kryukov et al., 2003).

GPX1, GPX2, GPX3, GPX4 and GPX6 utilize a UGA codon that specifies insertion of a selenocysteine residue which is critical to protein function (Arthur, 2000). Both isoforms contain selenocysteine at the position 49 (Mullenbach et al., 1988).

Expression

GPX1 is found at high levels in tissues exposed to high oxygen tensions such as in the lungs, at the cellular elements of blood, liver, kidney and pancreas, and also at moderate levels in heart, muscle and brain (Esposito et al., 2000; Moscow et al., 1992).

Regulation: Aberrant promotor methylation and consequence silencing has been shown for GPX1 expression during several pathological conditions in breast (Kulak et al., 2012) and gastric cancer (Min et al., 2012); whereas, induction of GPX1 gene expression was associated with transcription factors such TFAP2C in breast cancer (Kulak et al., 2012) and ZNF143 transcription factor under the mitochondrial respiratory dysfunction (Lu et al., 2012).

Localisation

The protein is detected in cytoplasm and mitochondria but the ratio may vary and be dependent on cellular function (Chiu et al., 1976; Timcenko-Youssef et al., 1985; Reeves et al., 2009).

Function

GPX1 is an enzyme of mammals and birds which protects against the damaging effects of various endogenously formed hydroperoxides and hydrogen peroxide as follows: H_2O_2+ 2 GSH - 2 H_2O + GSS and RGOH + 2 GSH - GSSG + ROH + H2O where ROOH represents lipid hydroperoxides, membrane associated phospholipid hydroperoxides (Ursini et al., 1985; Reeves et al., 2009).

Homology

The GPX1 gene is present in vertebrates and across all mammals demonstrates homology of about 70% at the nucleotide level (Mariotti et al., 2012).

Mutations

Note

Single nucleotide and ALA polymorphism have been shown for GPX1.

The 5'-UTR of GPX1 was found to contain a single nucleotide C/T polymorphism rs 1800668 located at the position ch3:49395757. The CC genotype demonstrates relatively high activity of GPX1 compared to CT or TT variant of alleles; however, the polymorphism does not alter the protein structure so differences in activity might be associated with transcriptional regulation since rs 1080668 site is located within promoter of GPX1 (Najafi et al., 2012).

A single nucleotide polymorphism rs 1050450 at the position ch3:49394834 leads to Pro198->Leu (C->T) substitution in GPX1. Many publications suggested an associated increased risk of cancer with the TT (Leu) genotype.

However, extended meta-analysis failed to find a significant correlation of the polymorphism (rs 1050450) with cancer risk, although the TT GPX1 genotype examined in erythrocytes demonstrated significantly lower functional activity (Hong et al., 2012).

ALA N-terminal polymorphism has been shown for the GPX1 gene. In this variant, the number of GCG repeats is altered resulting in a protein with a variable number of alanines 5, 6, or 7 (Shen et al., 1994).

Some association between 5-ALA genotype and high risk of breast cancer have been shown (Knight et al., 2004). However, associations between specific genotypes and the risk of prostate cancer have not been found (Kote-Jarai et al., 2002).

Implicated in

Various cancers

Oncogenesis

GPX1 involvment in certain cancers has been shown by several line of evidence.

Lung cancer

Note

The expression of GPX1 may be altered through LOH (loss of heterozygosity) of GPX1 which leads to decrease gene activity and increased risk of lung cancer (Hardie et al., 2000). Up-regulation of GPX1 in erythrocytes may be seen under several conditions such as hypoxia or with treatment with chemicals such as alcohol (Raaschou-Nielsen et al., 2006) but GPX1 activity tended to be significantly lower in smokers compared to non-smokers (Ravn-Haren et al., 2006) and these differences have been hypothesized to account for increased risk of lung cancer in smokers (Ratnasinghe et al., 2000). However high level of GPX1 was shown in lung cancer compared to non-malignant tissue (Blomquist et al., 2009).

Breast cancer

Note

Decrease GPX1 activity due to LOH (Hu et al., 2003; Hu et al., 2005) or aberrant hypermethylation of the GPX1 gene promotor (Kulak et al., 2012) leads to high risk of breast cancer.

Renal cancer

Note

Selenium consumption plays a dramatic role on GPX1 activity. Selenium in the diet altered both the mRNA and protein levels of GPX1 in mice (Sunde et al., 2009) whereas in pigs selenoprotein gene expression and/or protein production is not dependent on prolonged dietary selenium deficiency or excess (Liu et al., 2012). In humans no association was found between the Se status and breast or colorectal cancer risk (Dennert et al., 2011), but poor Se status was indicative of high mortality rate in renal cancer patients (Jean-Claude et al., 2012; Meyer et al., 2012).

Gastric cancer

Note

Aberrant hypermethylation of the GPX1 gene promotor may decrease GPX1 expression and has been described as a mechanism of GPX1 silencing in gastric cancer (Jee et al., 2009).

Bladder cancer

Note

Relatively high level of GPX1 was observed in bladder cancer (Reszka, 2012).

Anticancer drug resistance

Note

One hypothesis proposes that when damaged cells have progressed to a precancerous status, increased GPX1 activity may become procarcinogenic, presumably due to inhibition of hydroperoxide-mediated apoptosis (Chu et al., 2004) and may be responsible for antitumor drug resistance such as doxorubicin (Gouazé et al., 2001) which acts through increasing ROS products in cells (Wang et al., 2004).

Genetic polymorphisms and cancer

Note

As mentioned above, genetic polymorphisms have been reported for GPX1.

Investigations have attempted to demonstrate an association with cancer incidence, however, no consistent association has been found to date (Lei et al., 2007; Arsova-Sarafinovska et al., 2009; Erdem er al., 2012; Hong et al., 2012).

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This article should be referenced as such:

Kulak MV, Weigel RJ. GPX1 (Glutathione Peroxidase 1). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(7):465-469.