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

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# Gene Section
## Mini Review

# PPP1R1B (protein phosphatase 1, regulatory (inhibitor) subunit 1B (dopamine and cAMP regulated phosphoprotein, DARPP-32))

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## Identity

**Hugo:** PPP1R1B
**Other names:** DARPP-32; DARPP32; FLJ20940; t-DARPP
**Location:** 17q12

## DNA/RNA

### Description

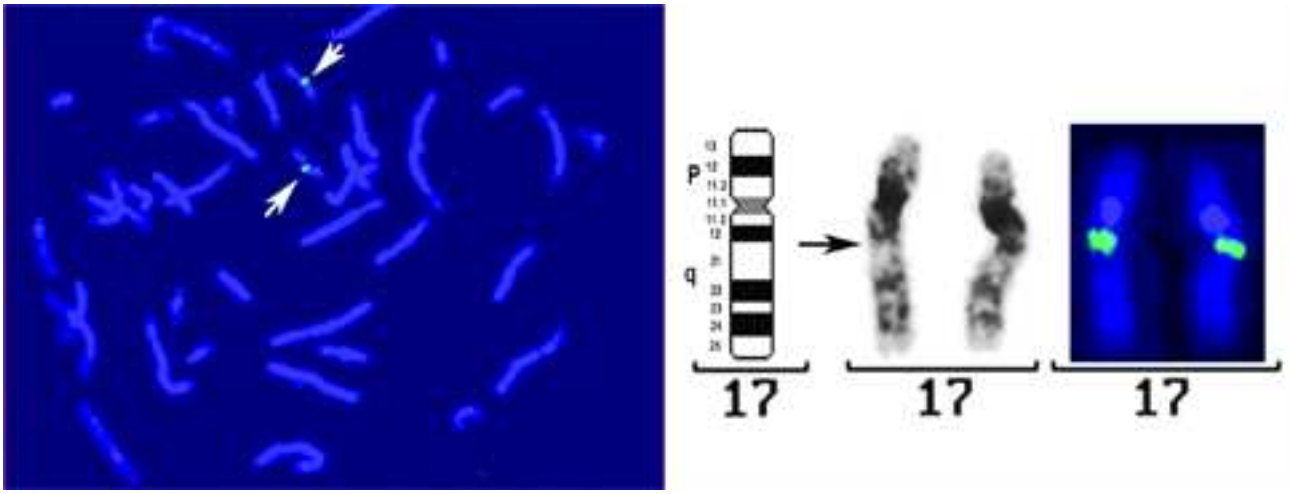
DARPP-32 gene is located at 17q12. Both full length DARPP-32 and its transcriptional splice variant (t-DARPP) consist of seven exons where only exon 1 is unique in each of the two transcripts.

### Transcription

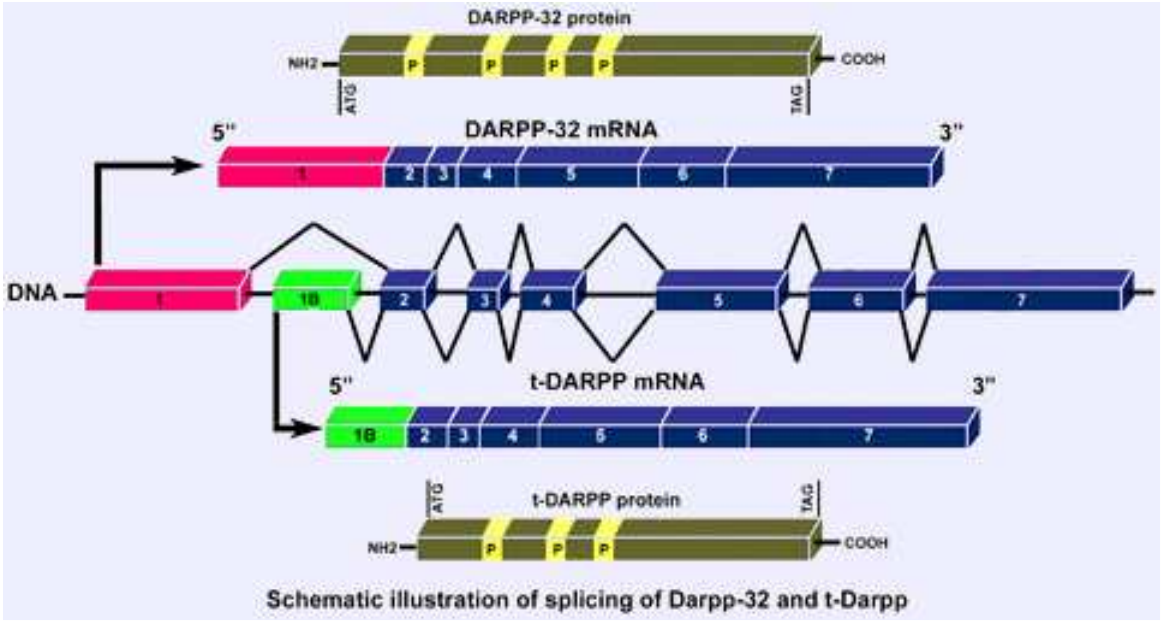
2 alternative transcripts.

### Pseudogene

Unknown.




Genomic localization of DARPP-32, with FISH using BAC clone CTD-2019C10 (Research Genetics) that contains DARPP-32, using fluorescent in situ hybridization (FISH) on a normal metaphase spread. Arrows indicate the green FITC hybridization signals. The ideogram of chromosome 17 together with the inverted DAPI banding and FISH hybridization signals on the two chromosome 17. The FISH signals localize to chromosome band 17q12-q21.




This schematic illustration shows the genomic structure of DARPP-32 and its transcriptional splice variant that encodes a truncated DARPP-32 protein (t-DARPP). The sequence length of the mRNA of DARPP-32 is 1,841 bp, including the untranslated 3' and 5' ends. The length of the transcriptional splice variant of DARPP-32 that encodes a truncated DARPP-32 protein (t-DARPP) is 1,502 bp. DARPP-32 and t-DARPP share an identical sequence from exon 2 to the 3' end. Each of them has seven exons. Each of DARPP-32 and t-DARPP transcripts has its own unique exon 1, where exon1 in DARPP-32 includes 548 bp whereas exon1 in t-DARPP consists of unique 207 bp that does not match with exon1 of DARPP-32.

# Protein

## Description

DARPP-32 encodes a protein of 204 amino acids (about 32 kD), whereas t-DARPP encodes a 168 amino acid protein (about 28 kD). DARPP-32 contains four phosphorylation sites at Thr34, Thr75, Ser102, and Ser137, whereas t-DARPP lacks the Thr34 phosphorylation site of DARPP-32. The schematic illustration, shown above, demonstrates the phosphorylation sites of DARPP-32 and t-DARPP shown in yellow color.

## Expression

DARPP-32 protein is highly expressed in medium-sized spiny neurons of the neostriatum. DARPP-32 was characterized as a major target for dopamine and protein kinase A signaling. Modulation of DARPP-32 phosphorylation state provides a molecular mechanism for integrating signals through several neurotransmitters and steroid hormones that stimulate dopaminoceptic neurons in various regions of the brain. Activation of PKA or PKG leads to phosphorylation of DARPP-32 at Thr34 and subsequently converts DARPP-32 into a potent inhibitor of protein phosphatase-1 (PP-1). Cdk5 can also phosphorylate DARPP-32 at Thr75 and this converts DARPP-32 into a PKA inhibitor. Expression of t-DARPP in the brain was not reported.
Protein and mRNA expression of both DARPP-32 and t-DARPP are expressed at varying levels in several types of normal epithelial tissues outside the brain. DARPP-32 and t-DARPP are over-expressed in carcinomas of the breast, prostate, colon, and stomach compared with normal tissue samples. The observation that DARPP-32 and t-DARPP are frequently over-expressed in common subtypes of human cancers suggests that these proteins may play a role in tumorigenesis. The expression of t-DARPP has been shown to increase the AKT kinase activity and regulate the levels of BCL2 in cancer cells. This effect is believed to mediate resistance to drug-induced apoptosis.

## Localisation

Cytosolic.

## Homology

Unknown.

# Mutations

**Note:** Unknown

# Implicated in

## Dopaminergic disorders

**Disease**

DARPP-32 plays a key role in cognitive function, and multiple brain functions. DARPP-32 is a key mediator of the biochemical, electrophysiological, transcriptional, and behavioral effects of dopamine. In this respect, DARPP-32 plays a critical role in

dopaminoceptive neurons in the neostriatum (and likely in other brain regions) in signal transduction pathways regulated by a variety of neurotransmitters, neuromodulators, and neuropeptides. Abnormal signaling through DARPP-32 has been implicated in several major neurologic and psychiatric disorders. DARPP-32 may be involved in the pathogenesis of schizophrenia and plays a role in mediating the actions of a broad range of drugs of abuse.

## *Cancers*

### Oncogenesis

Over-expression of DARPP-32 and t-DARPP are associated with gastric cancer, and confer a potent anti-apoptotic function in cancer cells through a p53 - independent mechanism that involves preservation of mitochondrial membrane potential and increased Bcl2 expression levels. t-DARPP transcriptionally up-regulates Bcl2 by an Akt-dependent mechanism through activation of CREB/ATF-1 transcription factors in gastric cancer. DARPP-32 is frequently over-expressed in multiple human adenocarcinomas suggesting that DARPP-32 proteins may be important in tumorigenesis. Decreased expression of DARPP-32, however, in oral premalignant and malignant lesions was observed, and thereby suggested that DARPP-32 may be a tumor suppressor in this particular malignancy. In addition, phosphorylation of DARPP-32 at Thr34 or Thr75 appears to regulate breast cancer cell migration downstream of the receptor tyrosine kinase DDR1.

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