Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

PHLPP2 (PH domain leucine-rich repeat protein phosphatase 2)

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Identity

Other names: PHLPPL; KIAA0931

HGNC (Hugo): PHLPP2

Location: 16q22.3

DNA/RNA

Description

The gene for PHLPP2 is located at 16q22.3 and spans approximately 70 kb. The most recent version of the Ensembl database predicts four splice variants of PHLPP2, whose sizes range from 69.8 to 73.9 kb (see diagram).

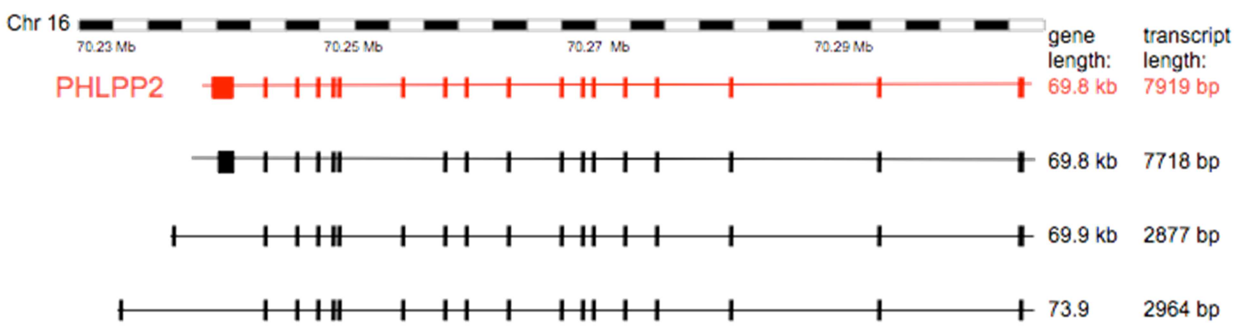
Transcription

The predicted PHLPP2 transcripts have between 2877 and 7919 bp. Three of these predicted variants have 18 exons; the 7718 bp variant has only 17 exons. All of the variants have similar exon structures; only exon 1 and exon 7 (which is missing in the 7718 bp variant) differ. Of these putative transcripts, only the largest of these transcripts (labeled "PHLPP2" in the diagram) has been cloned and characterized.

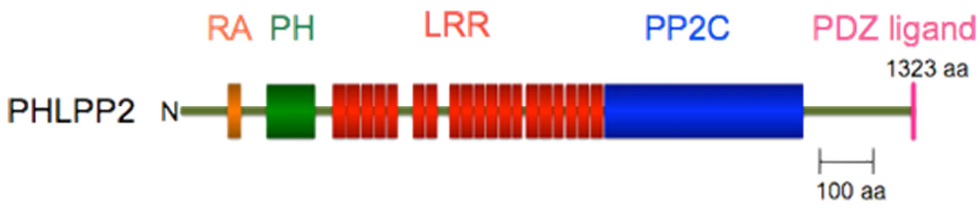
Protein

Description

Like the related isoform PHLPP1beta, the PHLPP2 protein contains a Ras association (RA) domain, a pleckstrin homology (PH) domain, a series of leucine-rich repeats (LRR), a PP2C phosphatase domain, and a C-terminal PDZ (post synaptic density protein [PSD95], Drosophila disc large tumor suppressor [DlgA], and zonula occludens-1 protein [zo-1]) binding motif. The characterized PHLPP1 protein has 1323 amino acids and a predicted molecular weight of approximately 147 kDa. Of the uncharacterized shorter transcripts, the longer (1256 aa) variant has a similar structure, while the two shorter variants (792 and 956 amino acids respectively) lack the RA and PH domains.



Genomic organization of the PHLPP2 transcripts. Exons are represented by boxes, and position along chromosome 16 is indicated by the scale bar at the top.



PHLPP2 protein structure.

Expression

PHLPP2 is expressed in many human cancer cell lines and in all mouse tissues examined so far.

Localisation

PHLPP2 appears to be predominantly expressed in the cytosolic and nuclear fractions.

Function

PHLPP2, like PHLPP1, dephosphorylates Akt and conventional/novel protein kinase C (PKC) isoforms at their hydrophobic motifs (HM). Both kinases are regulated by phosphorylation at this site, which corresponds to serine 473 in Akt1 and serine 660 in PKCbetaII. HM motif phosphorylation of Akt occurs under agonist-stimulated conditions and allows full activation of the kinase. Phosphorylation of PKC's HM motif, on the other hand, is constitutive and regulates PKC stability. HM dephosphorylation by PHLPP renders PKC susceptible to dephosphorylation at two other important regulatory sites on the kinase (the activation loop and the turn motif). The fully-dephosphorylated form of PKC is shunted to the detergent-insoluble pellet and degraded. Thus, PHLPP functions to decrease Akt's activity and PKC's stability, effectively dowregulating both kinases.
While PHLPP2 and its family member PHLPP1 have similar functions, their specificity for Akt isoforms differs. PHLPP1 preferentially binds and dephosphorylates Akt2 and Akt3, resulting in decreased phosphorylation of a set of Akt targets that includes GSK-3beta, TSC2, and FoxO, as well as HDM2 and GSK3a. PHLPP2, on the other hand, binds and dephosphorylates Akt1 and Akt3, resulting in downregulation of an overlapping yet distinct set of downstream targets: GSK-3beta, TSC2, and FoxO, as well as TSC2 and p27.
PHLPP2 regulates cellular survival and proliferation, partially by regulating Akt. PHLPP2 overexpression increases apoptosis in cancer cell lines under low serum conditions; this effect is partially blocked by overexpressing an Akt mutant that is resistant to dephosphorylation by PHLPP. Conversely, siRNA-mediated knockdown of PHLPP2 decreases basal and etoposide-stimulated apoptosis and increases cellular proliferation.
PHLPP2 may also be involved in cAMP signaling to Akt. PHLPP2 binds adenylyl cyclase type 6 in cardiac myocytes, and treatments that raise cAMP levels decrease Akt HM phosphorylation, possibly through activation of PHLPP.

Homology

PHLPP is a highly conserved phosphatase; its earliest orthologue is the yeast protein CYR1. In addition to a PP2C phosphatase domain, a leucine-rich repeat, and a Ras association domain, CYR1 contains an adenylate cyclase domain near its C terminus. Though invertebrates have only one PHLPP gene, most vertebrates have genes for both PHLPP1 and PHLPP2.

Mutations

Somatic

A common single nucleotide polymorphism (SNP) in the PP2C phosphatase domain of PHLPP2 may be involved in breast cancer progression. This SNP, a T->C nucleotide change at base pair position 3047, results in a Leu->Ser amino acid change at position 1016 in the PHLPP2 protein. Heterozygosity at this position is present in approximately 30% of the population, although Ser/Ser homozygosity has not yet been observed.
The L1016S variant of PHLPP2 may be involved in breast cancer. Although most breast cancer cell lines are homozygous for the Leucine allele, some are homozygous for the Serine allele. In addition, the normal breast cell line Hs578Bst is heterozygous (Leu/Ser) at position 1016, while its pair-matched tumor cell line Hs578t has only the Serine allele, suggesting that the gene has undergone loss of heterozygosity in this tumor. Similar results were obtained upon comparing normal and tumor tissues from breast cancer patients who are heterozygous at position 1016. High-grade breast tumors from some of these patients exhibited loss of the Leucine allele, but no tumors exhibited loss of the Serine allele. Further characterization of the L1016S mutant has revealed that its phosphatase activity (as measured by activity toward Akt) and its ability to promote apoptosis are defective. Moreover, siRNA-mediated knockdown of PHLPP2 in Ser/Ser breast cancer cell lines has no effect on Akt phosphorylation or PKCalpha levels, while knocking down PHLPP2 in cell lines with at least one Leucine allele increases Akt phosphorylation and PKCalpha levels. All in all, the data indicate that the version of PHLPP2 with Serine at position 1016 is less functional towards Akt and PKC than the wildtype version, and

that loss of the wildtype allele in heterozygous (Leu/Ser) breast cancer patients may be involved in the progression of breast cancer.

Implicated in

Various cancer

Cytogenetics

16q22.3, the chromosomal locus containing PHLPP2, commonly undergoes loss of heterozygosity in breast and ovarian cancers, Wilms tumors, prostate cancer and hepatocellular carcinomas.

Oncogenesis

siRNA-mediated reduction of PHLPP2 in breast cancer cell lines results in decreased apoptosis and increased proliferation, suggesting that PHLPP2 may act as a tumor suppressor. In addition, wildtype PHLPP2 may be lost in breast tumors with a less-functional PHLPP2 (PHLPP2 L1016S; see "Mutations" section), resulting in impaired Akt dephosphorylation and accelerating tumor development.

Colorectal cancer

Oncogenesis

Overexpression of PHLPP1 or PHLPP2 in the human colon cancer cell lines HCT-116 and HT29 causes decreased expression of PKC and decreased phosphorylation of Akt. Cells overexpressing PHLPP exhibit decreased proliferation and were less able to induce tumors in nude mice. Conversely, DLD1 cells, which express high levels of PHLPP, respond to PHLPP1 or PHLPP2 knockdown with increased Akt phosphorylation, PKC stability, and proliferation.

Chronic myelogenous leukemia

Oncogenesis

PHLPP mRNA levels may be decreased in chronic myelogenous leukemia (CML). Bcr-Abl, the fusion protein responsible for CML, downregulates PHLPP1 and PHLPP2 mRNA levels; decreasing PHLPP levels interferes with the efficacy of Bcr-Abl inihibitors, including Gleevec, in CML cell lines.

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