Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

PPP1R9B (protein phosphatase 1, regulatory subunit 9B)

Amancio Carnero

Instituto de Biomedicina de Sevilla, (IBIS/HUVR), Consejo Superior de Investigaciones Cientificas (CSIC), Edificio IBIS, Campus Hospital Universitario Virgen del Rocio, Avda, Manuel Siurot s/n, 41013, Sevilla, Spain (AC)

Published in Atlas Database: March 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/PPP1R9BID51558ch17q21.html
DOI: 10.4267/2042/47487

Identity

Other names: PPP1R6, PPP1R9, SPINO, Spn

HGNC (Hugo): PPP1R9B

Location: 17q21.33

DNA/RNA

See the scheme of the 17q21 locus below.

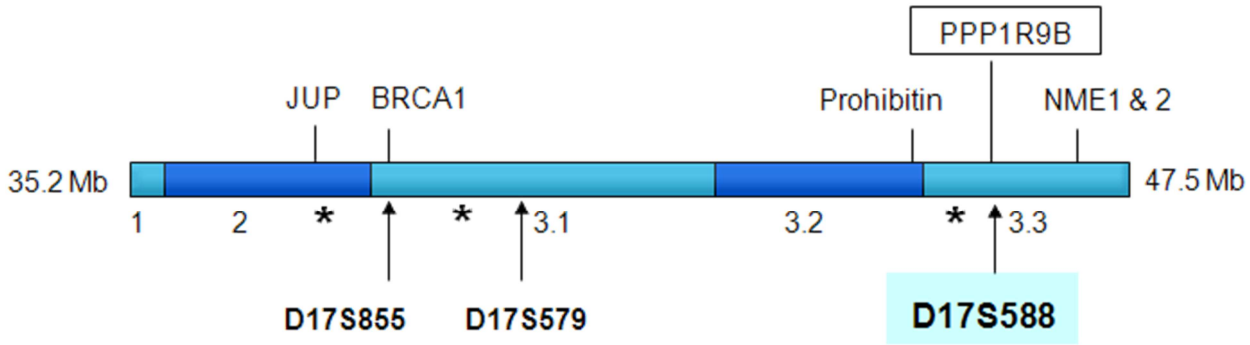
Protein

Description

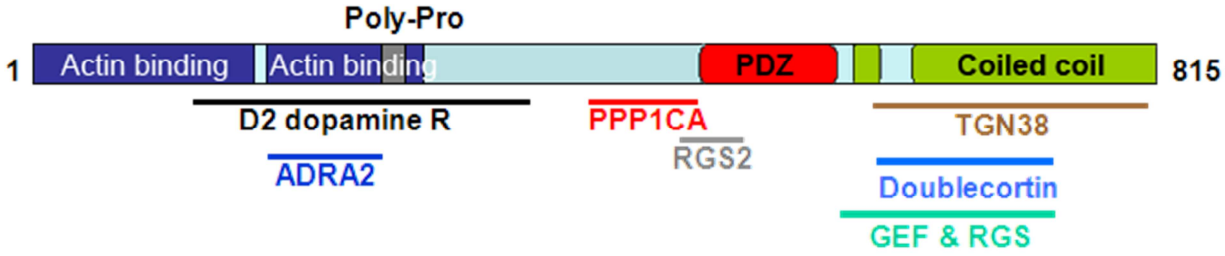
PPP1R9B protein have different modular domains that govern protein-protein interactions (Sarrouilhe et al., 2006). These domains include two F-actin-, three potential Src homology 3 (SH3)-, one receptor- and one PP1-binding domains, one PDZ binding domain, three coiled-coil domains, and one potential leucine/isoleucine zipper motif.

Many partner proteins of PPP1R9B have been described, including enzymes, guanine nucleotide exchange factors, cytoskeletal and cell adhesion molecules, membrane receptors, ion channels and G-protein signaling protein regulators.

PPP1R9B also regulates seven-transmembrane receptor signaling and may link these receptors to intracellular mitogenic signaling dependent on p70S6k and the Rac-GEF. Accordingly, PPP1R9B may serve as a linker between actin cytoskeleton and transmembrane proteins, targeting PP1 to its targets and facilitating the coordination of the external signaling with the downstream pathway (Brady et al., 2003; Küntziger et al., 2011; Sarrouilhe et al., 2006; Vivo et al., 2001; Wang et al., 2004; Carnero, 2012).



Scheme of the 17q21 locus. Adapted from Carnero, 2012.



Scheme of the PPP1R9B protein. Below bars indicate binding regions for proteins indicated. Adapted from Carnero, 2012.

Expression

PPP1R9B was detected predominantly in dendritic spines in prefrontal cortex and is enriched in cerebral cortex, caudatoputamen, hypocampal formation and cerebellum. But expression in most normal tissues is also clearly detected (Muly et al., 2004; Ouimet et al., 2004).
PPP1R9B protein is downrelulated in a great variety of human carcinomas but in a low percentage of tumors.
Immunohistochemical analysis of PPP1R9B during cancer progression shows some correlation with tumoral progression and p53 mutations (Carnero, 2012).

Localisation

In most tissues, with higher levels in neural system.

Function

The structure of PPP1R9B suggests that functions as a protein scaffold that regulates both membrane and cytoskeletal functions. PPP1R9B performs important functions in the nervous system where it is implicated in the regulation of spine morphology and density, synaptic plasticity and neuronal migration.
PPP1R9B could serve as a link between excitatory synapse transmission and changes in spine morphology and density (Allen et al., 2006; Hsieh-Wilson et al., 1999; Sarrouilhe et al., 2006).
PPP1R9B is a key modulator of the opiate action. PPP1R9B also promotes endocytosis of the mu-opioid receptor (Charlton et al., 2008).
PPP1R9B has been implicated through PP1 binding in the regulation of AMPA-type glutamate receptor. PPP1R9B may serve to regulate excitatory synaptic transmission and plasticity by targeting PP1 to its cellular substrates, promoting their downregulation by dephosphorylation regulating the post-synaptic glutaminergic neurotransmission.
PKA modulation of the localization of the PPP1R9B/PP1 complex could contribute to this effect.
Plasticity in dendritic spines may underlie learning and memory, and observations in PPP1R9B null mice shown that PPP1R9B plays a role in learning in vivo (Hsieh-Wilson et al., 2003; Stafstrom-Davis et al., 2001; Yan et al., 1999).
PPP1R9B also has a role in the regulation of blood pressure and cardiac function (da Costa-Goncalves et al., 2008). Since PPP1R9B can control the intensity and duration of the G-protein receptor signaling influencing synaptic activity, PPP1R9B affects blood pressure through central mechanisms. In adult cardiomyocytes it has been proposed that PPP1R9B is an upstream regulator required for normal growth and excitation-contraction coupling, but is dispensable for b-adrenergic stimulation (Petzhold et al., 2011).
Association of PPP1R9B with the α2-AR leads to alteration of α2-AR phosphorylation following agonist stimulation, suggesting that Spn acts mainly as an antagonist of arrestin. Thus, PPP1R9B participates in the regulation of signaling duration and sensitivity of the α2-AR response therefore regulating smooth muscle contraction. Following agonist treatment, PPP1R9B competition with GRK for α2-AR also prevents α2-AR endocytosis.
Finally, a role for PPP1R9B in the formation of immunological synapses in dendritic cells has also been proposed, and PPP1R9B may be involved in the maintenance of cellular architecture by regulating actin assembly (Meng et al., 2009; Shaw and Filbert, 2009).

Implicated in

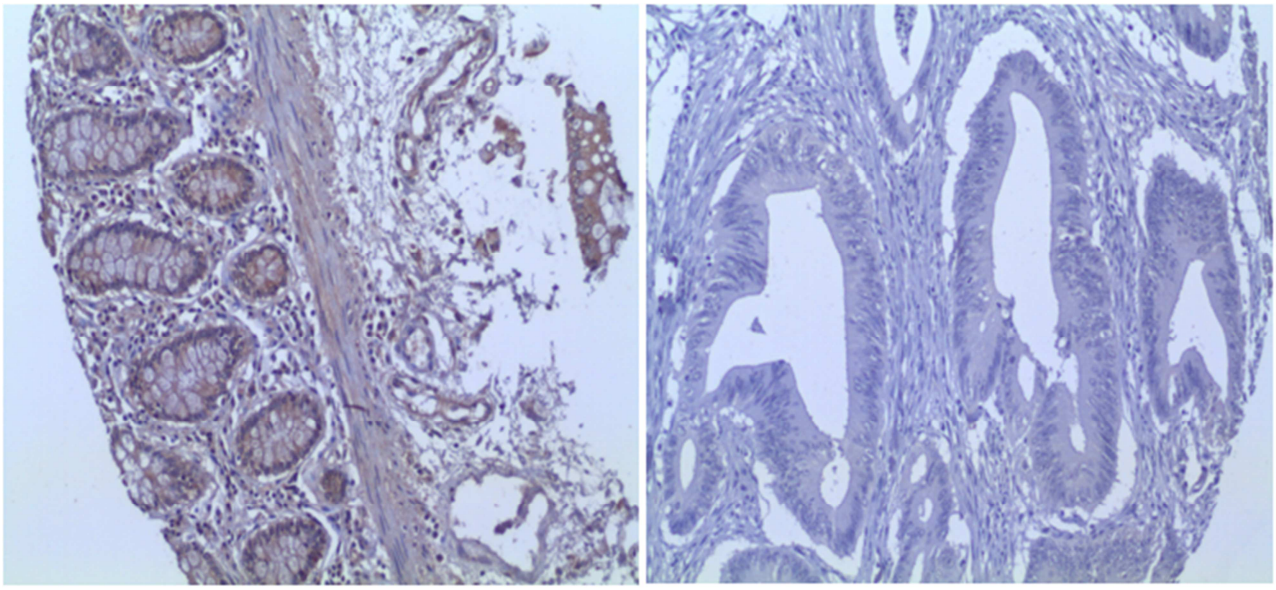
Various cancers

Prognosis

Expression levels decrease in some carcinomas.

Oncogenesis

PPP1R9B mRNA is lost in a percentage of renal carcinomas and lung adenocarcinomas (Carnero, 2012). More interestingly, analysis of normal vs tumoral samples of tumors of the CNS showed clear downregulation of PPP1R9B in tumoral samples.
Furthermore, lower levels of PPP1R9B mRNA correlates with higher grade of ovarian carcinoma and chronic myelogenous leukaemia (Carnero, 2012).
PPP1R9B is also lost in 20% and reduced in another 37% of human lung tumors (Molina-Pinelo et al., 2011).
PPP1R9B reduction correlates with malignant grade and p53 mutations (Carnero, 2012).



PPP1R9B expression in colon: left, normal epithelia with high levels PPPR1B; right, PPP1RB downregulation in carcinoma.

The PPP1R9B gene is located in chromosome 17, at position 17q21.33, and in a cytogenetic area frequently associated with microsatellite instability and loss of heterozygosity.

This region is comprised of a relatively high density of tumor suppressor genes, including known (BRCA1, NME1), putative (JUP, prohibitin), and unidentified candidates distal to the BRCA1 locus (Carnero, 2012).

Most of the studies on the 17q21 locus have focused on BRCA1, which exhibits a variable frequency in LOH depending on the type of tumor, stage and marker employed, and has been extensively studied in breast carcinomas (Caduff et al., 1999; Maitra et al., 1999; Querzoli et al., 2001). However, there are few studies that suggest the existence of unknown tumor suppressor genes for breast tumors in an area that includes the locus of PPP1R9B.

LOH in chromosome 17q21.3 has been observed in different tumors, including breast, ovarian, prostate, colorectal, gastric, renal and lung carcinomas, as well as in salivary gland carcinosarcoma, an extremely aggressive neoplasm (Caduff et al., 1999; Maitra et al., 1999; Querzoli et al., 2001).

The markers used in some of these studies with no linkage to BRCA1 point to NME1 as a tumor suppressor gene candidate to justify the functional impact of the allelic loss.

However, in different LOH studies an unidentified tumor suppressor gene nearby NME1 has been proposed.

PPP1R9B is located in close proximity to NME1, at only 1 Mb, probably sharing the allelic loss in these studies.

The most relevant data according to PPP1R9B LOH came from a study on primary lung carcinoma (Abujiang et al., 1998). This group performed an extensive LOH mapping in human lung cancers, using 15 highly polymorphic markers, 7 of which span 17q11-24 region. The higher LOH value appeared with the D17S588 marker, showing a 53% of loss. The D17S588 marker locates exactly within the PPP1R9B locus. These data provided the first robust data implicating PPP1R9B LOH in cancer. Closer tumor suppressor genes, such as BRCA1, were not seriously affected (6-13% LOH), nor other lung proliferative pathologies (squamous cell carcinoma and small cell carcinoma only showed minimal LOH, below 14%, for both PPP1R9B and BRCA1 markers).

Several genetic linkage studies using the marker D17S588 have suggested the existence of a tumor suppressor gene distal to BRCA1 (Porter et al., 1993; Porter et al., 1994). The maximum LOD scores obtained for D17S588 were of 5,44 in an Edinburgh study of 15 families (Cohen et al., 1993) and 21,68 in an analysis of 271 breast and breast-ovarian cancer families (Easton et al., 1993, Smith et al., 1993), indicating the importance of this locus in the pathology of cancer. The D17S588 marker lies inside the PPP1R9B gene.

Another study that investigated the correlation between p53 abnormalities and allelic loss of BRCA1, BRCA2 and adjacent loci in breast cancer found a strong correlation when using the D17S588 marker (Querzoli et al., 2001; Tseng et al., 1997). Again, PPP1R9B may be involved in the tumorigenic process by functioning, in association with a loss of p53 functionality, as a tumor suppressor (47,1% LOH) (Tseng et al., 1997).

Learning and memory, regulation of blood pressure and cardiac function

Disease

Learning and memory defects, problems in the regulation of blood pressure and cardiac function, tumors of different origin.

References

Cohen BB, Porter DE, Wallace MR, Carothers A, Steel CM. Linkage of a major breast cancer gene to chromosome 17q12-21: results from 15 Edinburgh families. Am J Hum Genet. 1993 Apr;52(4):723-9

Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1993 Apr;52(4):678-701

Porter DE, Steel CM, Cohen BB, Wallace MR, Carothers A, Chetty U, Carter DC. Genetic linkage analysis applied to unaffected women from families with breast cancer can discriminate high- from low-risk individuals. Br J Surg. 1993 Nov;80(11):1381-5

Smith SA, Easton DF, Ford D, Peto J, Anderson K, Averill D, Stratton M, Ponder M, Pye C, Ponder BA. Genetic heterogeneity and localization of a familial breast-ovarian cancer gene on chromosome 17q12-q21. Am J Hum Genet. 1993 Apr;52(4):767-76

Porter DE, Cohen BB, Wallace MR, Smyth E, Chetty U, Dixon JM, Steel CM, Carter DC. Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 gene mutation in families linked to BRCA1 on chromosome 17q12-21. Br J Surg. 1994 Oct;81(10):1512-5

Tseng SL, Yu IC, Yue CT, Chang SF, Chang TM, Wu CW, Shen CY. Allelic loss at BRCA1, BRCA2, and adjacent loci in relation to TP53 abnormality in breast cancer. Genes Chromosomes Cancer. 1997 Dec;20(4):377-82

Abujiang P, Mori TJ, Takahashi T, Tanaka F, Kasyu I, Hitomi S, Hiai H. Loss of heterozygosity (LOH) at 17q and 14q in human lung cancers. Oncogene. 1998 Dec 10;17(23):3029-33

Caduff RF, Svoboda-Newman SM, Ferguson AW, Frank TS. Comparison of alterations of chromosome 17 in carcinoma of the ovary and of the breast. Virchows Arch. 1999 Jun;434(6):517-22

Hsieh-Wilson LC, Allen PB, Watanabe T, Nairn AC, Greengard P. Characterization of the neuronal targeting protein spinophilin and its interactions with protein phosphatase-1. Biochemistry. 1999 Apr 6;38(14):4365-73

Maitra A, Tavassoli FA, Albores-Saavedra J, Behrens C, Wistuba II, Bryant D, Weinberg AG, Rogers BB, Saboorian MH, Gazdar AF. Molecular abnormalities associated with secretory carcinomas of the breast. Hum Pathol. 1999 Dec;30(12):1435-40

Yan Z, Hsieh-Wilson L, Feng J, Tomizawa K, Allen PB, Fienberg AA, Nairn AC, Greengard P. Protein phosphatase 1 modulation of neostriatal AMPA channels: regulation by DARPP-32 and spinophilin. Nat Neurosci. 1999 Jan;2(1):13-7

Querzoli P, Albonico G, di Iasio MG, Ferretti S, Rinaldi R, Cariello A, Pedriali M, Matteuzzi M, Maestri I, Nenci I. Biophenotypes and survival of BRCA1 and TP53 deleted breast cancer in young women. Breast Cancer Res Treat. 2001 Mar;66(2):135-42

Stafstrom-Davis CA, Ouimet CC, Feng J, Allen PB, Greengard P, Houpt TA. Impaired conditioned taste aversion learning in spinophilin knockout mice. Learn Mem. 2001 Sep-Oct;8(5):272-8

Vivo M, Calogero RA, Sansone F, Calabrò V, Parisi T, Borrelli L, Saviozzi S, La Mantia G. The human tumor suppressor arf interacts with spinophilin/neurabin II, a type 1 protein-phosphatase-binding protein. J Biol Chem. 2001 Apr 27;276(17):14161-9

Brady AE, Wang Q, Colbran RJ, Allen PB, Greengard P, Limbird LE. Spinophilin stabilizes cell surface expression of alpha 2B-adrenergic receptors. J Biol Chem. 2003 Aug 22;278(34):32405-12

Hsieh-Wilson LC, Benfenati F, Snyder GL, Allen PB, Nairn AC, Greengard P. Phosphorylation of spinophilin modulates its interaction with actin filaments. J Biol Chem. 2003 Jan 10;278(2):1186-94

Muly EC, Smith Y, Allen P, Greengard P. Subcellular distribution of spinophilin immunolabeling in primate prefrontal cortex: localization to and within dendritic spines. J Comp Neurol. 2004 Feb 2;469(2):185-97

Ouimet CC, Katona I, Allen P, Freund TF, Greengard P. Cellular and subcellular distribution of spinophilin, a PP1 regulatory protein that bundles F-actin in dendritic spines. J Comp Neurol. 2004 Nov 22;479(4):374-88

Wang Q, Zhao J, Brady AE, Feng J, Allen PB, Lefkowitz RJ, Greengard P, Limbird LE. Spinophilin blocks arrestin actions in vitro and in vivo at G protein-coupled receptors. Science. 2004 Jun 25;304(5679):1940-4

Allen PB, Zachariou V, Svenningsson P, Lepore AC, Centonze D, Costa C, Rossi S, Bender G, Chen G, Feng J, Snyder GL, Bernardi G, Nestler EJ, Yan Z, Calabresi P, Greengard P. Distinct roles for spinophilin and neurabin in dopamine-mediated plasticity. Neuroscience. 2006 Jul 7;140(3):897-911

Sarrouilhe D, di Tommaso A, Métayé T, Ladeveze V. Spinophilin: from partners to functions. Biochimie. 2006 Sep;88(9):1099-113

Charlton JJ, Allen PB, Psifogeorgou K, Chakravarty S, Gomes I, Neve RL, Devi LA, Greengard P, Nestler EJ, Zachariou V. Multiple actions of spinophilin regulate mu opioid receptor function. Neuron. 2008 Apr 24;58(2):238-47

da Costa-Goncalves AC, Tank J, Plehm R et al.. Role of the multidomain protein spinophilin in blood pressure and cardiac function regulation. Hypertension. 2008 Oct;52(4):702-7

Meng X, Kanwar N, Du Q, Goping IS, Bleackley RC, Wilkins JA. PPP1R9B (Neurabin 2): involvement and dynamics in the NK immunological synapse. Eur J Immunol. 2009 Feb;39(2):552-60

Shaw AS, Filbert EL. Scaffold proteins and immune-cell signalling. Nat Rev Immunol. 2009 Jan;9(1):47-56

Küntziger T, Landsverk HB, Collas P, Syljuåsen RG. Protein phosphatase 1 regulators in DNA damage signaling. Cell Cycle. 2011 May 1;10(9):1356-62

Molina-Pinelo S, Ferrer I, Blanco-Aparicio C, Peregrino S, Pastor MD, Alvarez-Vega J, Suarez R, Verge M, Marin JJ, Hernandez-Losa J, Ramon y Cajal S, Paz-Ares L, Carnero A. Down-regulation of spinophilin in lung tumours contributes to tumourigenesis. J Pathol. 2011 Sep;225(1):73-82

Petzhold D, da Costa-Goncalves AC, Gross V, Morano I. Spinophilin is required for normal morphology, Ca(2+) homeostasis and contraction but dispensable for β-adrenergic stimulation of adult cardiomyocytes. J Muscle Res Cell Motil. 2011 Dec;32(4-5):243-8

Carnero A. Spinophilin: a new tumor suppressor at 17q21. Curr Mol Med. 2012 Jun;12(5):528-35

This article should be referenced as such:

Carnero A. PPP1R9B (protein phosphatase 1, regulatory subunit 9B). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(8):545-548.