Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

PTPRA (protein tyrosine phosphatase, receptor type, A)

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Published in Atlas Database: May 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/PTPRAID41923ch20p13.html
DOI: 10.4267/2042/56297

Abstract

Review on PTPRA, with data on DNA/RNA expression, on the protein encoded, and the functional importance of the gene.

Identity

Other names: HEPTP, HLPR, HPTPA, HPTPalpha, LRP, PTPA, PTPRL2, R-PTP-alpha, RPTPA

HGNC (Hugo): PTPRA

Location: 20p13

DNA/RNA

Description

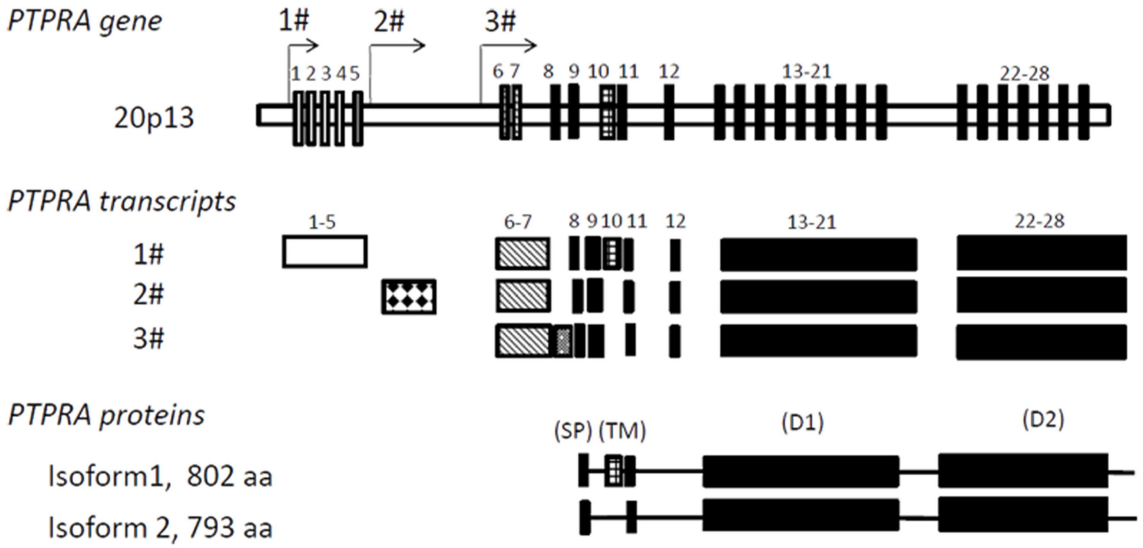
Human PTPRA is located at Chromosome 20: 2844830-3019722 bp.
Its Entrez gene ID is 5786 (NCBI) or 9664 (HGNC).
PTPRA consists of 21 coding exons (protein isoform 1) or 20 coding exons (protein isoform 2). 82 organisms have orthologs with human gene PTPRA.
The PTPRA gene is conserved across species including chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and C. elegans.

Transcription

Three transcript variants encoding different isoforms have been found for PTPRA gene. Transcript variant 1 (NM_002836.3) represents the longest transcript and encodes the longer isoform1 including 802 aa residues. Transcript variant 2 (NM_080840.2) contains an alternate 5' UTR exon which is different from transcript variant 1, and lacks exons one to five and coding exon ten, when compared to variant 1. Transcript variant 3 (NM_080841.2) contains an additional exon within the 5' UTR, when compared to variant 2. Transcript variant 2 and transcript variant 3 encode the short isoform 2. Isoform 2 lacks a 9 aa internal segment, because exon ten missing, compared to Isoform 1. It is known that the expression of RPTPa mRNA is increased by 2 to 10-fold in 70% (10 of 14) of late-stage colon tumors compared to normal colonic mucosa (Tabiti et al., 1995). Another study demonstrated that RPTPa mRNA was increased in 29% (15 of 51) of primary breast carcinomas and correlated with its protein overexpression (Ardini et al., 2000). Recently, PTPRA mRNA splice mutants were described from Chinese colon, breast, and liver tumors (Huang et al., 2011).

Pseudogene

One pseudogene (ID: PGOHUM00000236674) for PTPRA described on the website Pseudogenes.org.



Schematic depiction of human gene PTPRA (upper panel), derived alternative transcripts (middle panel) and corresponding protein isoforms (lower panel). Arrows in the upper panel indicate the three distinct transcriptional start sites within chromosome 20p13. 28 exon numbers according to transcript variant 1 (NM_002836.3) are indicated above the corresponding boxes. In the middle panel the build-up of the three different PTPRA transcripts, deduced based on cDNA deposits in public databases, is depicted. Transcript variant 1 (NM_002836.3) represents the longest transcript and encodes the longer isoform 1. Transcript variant 2 (NM_080840.2) contains an alternate 5' UTR exon which is different from transcript variant 1, and lacks coding exons one to five and exon ten, when compared to variant 1. Transcript variant 3 (NM_080841.2) contains an additional exon within the 5' UTR, and lacks an coding exon and exon one to five, when compared to variant 1. Transcript variant 2 and transcript variant 3 encode the short isoform 2. The N-terminal, the protein domain reflects the signal peptide (SP). The transmembrane spanning regions (TM) and protein tyrosine phosphatase catalytic domain (D1 and D2) are shown respectively. Isoform 2 lacks a 9 aa internal segment, because of exon ten missing, compared to Isoform 1.

Protein

Description

The protein encoded by PTPRA gene is a member of the protein tyrosine phosphatase (PTP) family. This PTP contains an extracellular domain, a single transmembrane segment and two tandem intracytoplasmic catalytic domains, and thus represents a receptor-type PTP. Three alternatively spliced variants of this gene are well known to encode two distinct isoforms differing only in their extracellular region. The shorter form, expressed in most tissues, has 793 aa of which 123 are extracellular. The longer form, RPTPa802, has nine extra amino acids located just before the transmembrane region and is expressed only in a few tissues, especially in brain. It is noted that extensive N- and O-linked glycosylation of RPTPa gives rise to a mature 130 kD form of the protein (Daum et al., 1994).

Expression

PTPRA gene was originally isolated by PCR-based PTP identification and cloning from several groups (Sap et al., 1990; Kaplan et al., 1990; Matthews et al., 1990). The protein, RPTPa, is a widely distributed transmembrane molecule that is particularly highly expressed in the brain and kidney (Sap et al., 1990). RPTPa is highly expressed in the developing central and peripheral nervous system of mouse, especially in the dorsal root ganglia, cranial ganglia and adrenal gland (den Hertog et al., 1996). During chicken development, chicken RPTPa (ChPTPa) is expressed in pre-migratory and migrating granule cells, and in Bergmann glia and their radial processes as determined by in situ hybridization and immunostaining (Fang et al., 1996). Taken together, these studies demonstrate that RPTPa is highly expressed in the developing brain of various species (Shock et al., 1995; Yang and Friesel, 1998; den Hertog et al., 1999).

Localisation

Membrane. A typical single-pass type I membrane protein.

Function

Generally, RPTPa has been shown to dephosphorylate and activate Src family kinases (SFKs), and is implicated in the regulation of integrin signaling, cell adhesion and proliferation. Studies involving overexpression of RPTPa were the first to demonstrate that PTP can dephosphorylate tyrosine 527 of Src and activate c-Src in vivo and in vitro. This activation causes cellular transformation (Zheng et al., 1992). Dephosphorylation of tyrosine 527 of c-Src in RPTPa overexpressing P19 embryonal carcinoma cells activates c-Src and induces neuronal differentiation (den Hertog et al., 1993). This

observation has been independent validated in studied involving RPTPa knockout mice that exhibit a dramatic decrease (50-70%) in c-Src activity in the brain (Ponniah et al., 1999; Su et al., 1999).
In addition to Src, RPTPa regulates other Src family kinases.
As an example, Fyn dephosphorylation and activation is observed in cells co-expressing RPTPa and Fyn (Bhandari et al., 1998).
Additionally, dephosphorylation of c-Src, Fyn and Yes, but not Lyn, was observed in A431 cells expressing RPTPa (Harder et al., 1998), indicating some degree of specificity of RPTPa.
It is noteworthy that there is no evidence of gross physical abnormalities in the RPTPa-deficient mice, indicating that RPTPa is not essential for embryonic development.
One explanation is that certain functions of RPTPa are compensated for by other PTPs in mice deficient in RPTPa (Pallen, 2003).
RPTPa is involved in promoting integrin signaling through activation of SFKs.
An earlier study shows that c-Src activation by RPTPa can increase the association of c-Src with focal adhesion kinase (FAK), and enhance tyrosine phosphorylation of the Src/FAK substrate paxillin (Harder et al., 1998). Recently, Sun et al. described a novel molecular complex of RPTPa-BCAR3-Cas-Src that is important in integrin signaling (Sun et al., 2012). This complex forms in response to RPTPaTyr789 phosphorylation and mediates Cas localization to focal adhesions and Cas downstream signaling to promote cell migration (Sun et al., 2012).
More recently, Cheng et al. identified two roles of Grb2 in integrin signaling: one as a regulator of paxillin stability and upstream promoter of FAKTyr397 phosphorylation that is required for Src-FAK complex activation and another as an essential coordinator of RPTPa and activation of the Src-FAK interaction thus enabling the phosphorylation of RPTPaTyr789 (Cheng et al., 2014).

Mutations

Note

Huang et al. sequence RPTPa cDNAs from five types of Chinese human tumors and paired normal samples. They observed three sequences encoding truncated proteins, designated RPTPa245, RPTPa445, or RPTPa652, lacking the D1 domain or both the D1 and D2 domains. One mutant, RPTPa245, widely expressed in colon, breast, and liver tumors from individuals of Chinese origin, can form an RPTPa-RPTPa245 heterodimer and activate c-Src. (Huang et al., 2011).

Implicated in

Breast cancer

Note

It is clear that RPTPa functions as an activator of c-Src family kinases, and thus was considered to be an oncogene. However, the first study on human breast tumors by Ardini et al. revealed an unexpected and interesting role of RPTPa. RPTPa protein levels are found significantly overexpressed in 29% of 51 samples. High RPTPa protein levels correlated with low tumor grade and positive estrogen receptor status.
Overexpression of RPTPa in MCF-7 breast cancer cells (ER+) resulted in growth inhibition while activating c-Src (Ardini et al., 2000). In a later study, Zheng reported that knockdown of RPTPa and c-Src using RNAi induced apoptosis in estrogen receptor-negative breast cancer cells, but not in immortalized noncancerous breast cells and ER-positive breast cancer cells (including MCF-7). It is noted by Zheng that correlation between ER status and c-Src/RPTPa dependence in breast cancer may be important for planning therapeutic strategy (Zheng et al., 2008). Recently, Wang J and colleagues reported that EGF-induced RPTPa phosphorylation at Ser180 and Ser204 in BT-20 and SKBR3 breast cancer cell lines results in increased c-Src kinase activity, due to a decrease in RPTPa binding with Grb2 and an increase in RPTPa binding with c-Src. These observations reveal novel aspects of integration of an EGF/PKC/RPTPa/Src pathway in breast cancer cell lines (Wang et al., 2013). Currently, Meyer et al. demonstrate that RPTPa functions as a positive mediator of tumor initiation and maintenance in both HER2/Neu-positive breast tumors (Meyer et al., 2014).

Colorectal cancer

Note

The first report correlation with RPTPa and colonic tumors was reported by Tabiti et al. in 1995. They quantified mRNA levels of RPTPa from 14 colon carcinomas and compared these levels to adjacent healthy colon mucosa. They observed a 2 to 10-fold increase in mRNA levels in advanced (Dukes' stage D) carcinoma. Another study from Zheng et al. reported that RNAi knockdown of RPTPa reduced c-Src kinase activity in several colon cancer cell lines (HCT-15, HCT-116 and HT-29), which suppresses anchorage-independent growth and induces apoptosis (Zheng et al., 2008). Recently, tissue-arrays containing 50 colorectal cancer specimens and 10 normal colon samples were analysed by immunohistochemistry for RPTPa expression. In normal tissue samples, RPTPa expression was restricted to smooth muscle cells.

None of the normal colonocyte expressed RPTPa in measurable quantities. However, over 70% of the colon cancer samples demonstrated expression of RPTPa (Krndija et al., 2010). These data provide evidence for an oncogenic role of RPTPa in colorectal cancer.

Gastric cancer

Note

To date, only one study has revealed an association between RPTPa expression and gastric cancer. RPTPa expression is observed in 44% of gastric samples and was the most widely expressed of the five PTPs. Several clinicopathological features were significantly linked with the expression of RPTPa, including gross appearance, lymphovascular invasion, lymph node metastasis, liver metastasis and peritoneal dissemination. (Wu et al., 2006).

Oral squamous cell carcinoma (OSCC)

Note

In an earlier study, Berndt et al. evaluated RPTPa expression in 12 oral squamous cell carcinoma (OSCC) samples. Interestingly, not only the tumor cells but also the stromal fibro/myofibroblasts as well as inflammatory cells account for RPTPa expression in OSCC. In particular, immunostaining revealed a predominantly intracellular pattern of RPTPa expression, which may be due to an incompletely glycosylated form (Berndt et al., 1999) and/or to proteolytic cleavage of RPTPa in vivo (Gil-Henn et al., 2001).

Diffuse large B-cell lymphoma

Cytogenetics

A dup(20)(p13p13) was found in a case of diffuse large B-cell lymphoma (Morin et al., 2013).

Hybrid/Mutated gene

TMC2/PTPRA.

References

Kaplan R, Morse B, Huebner K, Croce C, Howk R, Ravera M, Ricca G, Jaye M, Schlessinger J. Cloning of three human tyrosine phosphatases reveals a multigene family of receptor-linked protein-tyrosine-phosphatases expressed in brain. Proc Natl Acad Sci U S A. 1990 Sep;87(18):7000-4

Matthews RJ, Cahir ED, Thomas ML. Identification of an additional member of the protein-tyrosine-phosphatase family: evidence for alternative splicing in the tyrosine phosphatase domain. Proc Natl Acad Sci U S A. 1990 Jun;87(12):4444-8

Sap J, D'Eustachio P, Givol D, Schlessinger J. Cloning and expression of a widely expressed receptor tyrosine phosphatase. Proc Natl Acad Sci U S A. 1990 Aug;87(16):6112-6

Zheng XM, Wang Y, Pallen CJ. Cell transformation and activation of pp60c-src by overexpression of a protein tyrosine phosphatase. Nature. 1992 Sep 24;359(6393):336-9

den Hertog J, Pals CE, Peppelenbosch MP, Tertoolen LG, de Laat SW, Kruijer W. Receptor protein tyrosine phosphatase alpha activates pp60c-src and is involved in neuronal differentiation. EMBO J. 1993 Oct;12(10):3789-98

Daum G, Regenass S, Sap J, Schlessinger J, Fischer EH. Multiple forms of the human tyrosine phosphatase RPTP alpha. Isozymes and differences in glycosylation. J Biol Chem. 1994 Apr 8;269(14):10524-8

Shock LP, Bare DJ, Klinz SG, Maness PF. Protein tyrosine phosphatases expressed in developing brain and retinal Müller glia. Brain Res Mol Brain Res. 1995 Jan;28(1):110-6

Tabiti K, Smith DR, Goh HS, Pallen CJ. Increased mRNA expression of the receptor-like protein tyrosine phosphatase alpha in late stage colon carcinomas. Cancer Lett. 1995 Jul 13;93(2):239-48

den Hertog J, Overvoorde J, de Laat SW. Expression of receptor protein-tyrosine phosphatase alpha mRNA and protein during mouse embryogenesis. Mech Dev. 1996 Aug;58(1-2):89-101

Fang KS, Martins-Green M, Williams LT, Hanafusa H. Characterization of chicken protein tyrosine phosphatase alpha and its expression in the central nervous system. Brain Res Mol Brain Res. 1996 Apr;37(1-2):1-14

Bhandari V, Lim KL, Pallen CJ. Physical and functional interactions between receptor-like protein-tyrosine phosphatase alpha and p59fyn. J Biol Chem. 1998 Apr 10;273(15):8691-8

Harder KW, Moller NP, Peacock JW, Jirik FR. Protein-tyrosine phosphatase alpha regulates Src family kinases and alters cell-substratum adhesion. J Biol Chem. 1998 Nov 27;273(48):31890-900

Yang CQ, Friesel R. Identification of a receptor-like protein tyrosine phosphatase expressed during Xenopus development. Dev Dyn. 1998 Jul;212(3):403-12

Berndt A, Luo X, Böhmer FD, Kosmehl H. Expression of the transmembrane protein tyrosine phosphatase RPTPalpha in human oral squamous cell carcinoma. Histochem Cell Biol. 1999 May;111(5):399-403

den Hertog J, Blanchetot C, Buist A, Overvoorde J, van der Sar A, Tertoolen LG. Receptor protein-tyrosine phosphatase signalling in development. Int J Dev Biol. 1999;43(7):723-33

Ponniah S, Wang DZ, Lim KL, Pallen CJ. Targeted disruption of the tyrosine phosphatase PTPalpha leads to constitutive downregulation of the kinases Src and Fyn. Curr Biol. 1999 May 20;9(10):535-8

Su J, Muranjan M, Sap J. Receptor protein tyrosine phosphatase alpha activates Src-family kinases and controls integrin-mediated responses in fibroblasts. Curr Biol. 1999 May 20;9(10):505-11

Ardini E, Agresti R, Tagliabue E, Greco M, Aiello P, Yang LT, Ménard S, Sap J. Expression of protein tyrosine phosphatase alpha (RPTPalpha) in human breast cancer correlates with low tumor grade, and inhibits tumor cell growth in vitro and in vivo. Oncogene. 2000 Oct 12;19(43):4979-87

Gil-Henn H, Volohonsky G, Elson A. Regulation of protein-tyrosine phosphatases alpha and epsilon by calpain-mediated proteolytic cleavage. J Biol Chem. 2001 Aug 24;276(34):31772-9

Pallen CJ. Protein tyrosine phosphatase alpha (PTPalpha): a Src family kinase activator and mediator of multiple biological effects. Curr Top Med Chem. 2003;3(7):821-35

Wu CW, Kao HL, Li AF, Chi CW, Lin WC. Protein tyrosine-phosphatase expression profiling in gastric cancer tissues. Cancer Lett. 2006 Oct 8;242(1):95-103

Zheng X, Resnick RJ, Shalloway D. Apoptosis of estrogen-receptor negative breast cancer and colon cancer cell lines by PTP alpha and src RNAi. Int J Cancer. 2008 May 1;122(9):1999-2007

Krndija D, Schmid H, Eismann JL, Lother U, Adler G, Oswald F, Seufferlein T, von Wichert G. Substrate stiffness and the receptor-type tyrosine-protein phosphatase alpha regulate spreading of colon cancer cells through cytoskeletal contractility. Oncogene. 2010 May 6;29(18):2724-38

Huang J, Yao L, Xu R, Wu H, Wang M, White BS, Shalloway D, Zheng X. Activation of Src and transformation by an RPTPα splice mutant found in human tumours. EMBO J. 2011 Jul 1;30(15):3200-11

Sun G, Cheng SY, Chen M, Lim CJ, Pallen CJ. Protein tyrosine phosphatase α phosphotyrosyl-789 binds BCAR3 to position Cas for activation at integrin-mediated focal adhesions. Mol Cell Biol. 2012 Sep;32(18):3776-89

Morin RD, Mungall K, Pleasance E, Mungall AJ, Goya R, Huff RD, Scott DW, Ding J, Roth A, Chiu R, Corbett RD, Chan FC, Mendez-Lago M, Trinh DL, Bolger-Munro M, Taylor G, Hadj Khodabakhshi A, Ben-Neriah S, Pon J, Meissner B, Woolcock B, Farnoud N, Rogic S, Lim EL, Johnson NA, Shah S, Jones S, Steidl C, Holt R, Birol I, Moore R, Connors JM, Gascoyne RD, Marra MA. Mutational and structural analysis of diffuse large B-cell lymphoma using whole-genome sequencing. Blood. 2013 Aug 15;122(7):1256-65

Wang J, Yu L, Zheng X. PTPα-mediated Src activation by EGF in human breast cancer cells. Acta Biochim Biophys Sin (Shanghai). 2013 Apr;45(4):320-9

Cheng SY, Sun G, Schlaepfer DD, Pallen CJ. Grb2 promotes integrin-induced focal adhesion kinase (FAK) autophosphorylation and directs the phosphorylation of protein tyrosine phosphatase α by the Src-FAK kinase complex. Mol Cell Biol. 2014 Feb;34(3):348-61

Meyer DS, Aceto N, Sausgruber N, Brinkhaus H, Müller U, Pallen CJ, Bentires-Alj M. Tyrosine phosphatase PTPα contributes to HER2-evoked breast tumor initiation and maintenance. Oncogene. 2014 Jan 16;33(3):398-402

This article should be referenced as such:

Huang J, Lai X, Zheng X. PTPRA (protein tyrosine phosphatase, receptor type, A). Atlas Genet Cytogenet Oncol Haematol. 2015; 19(2):121-125.