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Gene Section
Review

PTPN14 (protein tyrosine phosphatase, non-receptor type 14)

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Identity

Other names: PEZ, PTP36

HGNC (Hugo): PTPN14

Location: 1q41

DNA/RNA

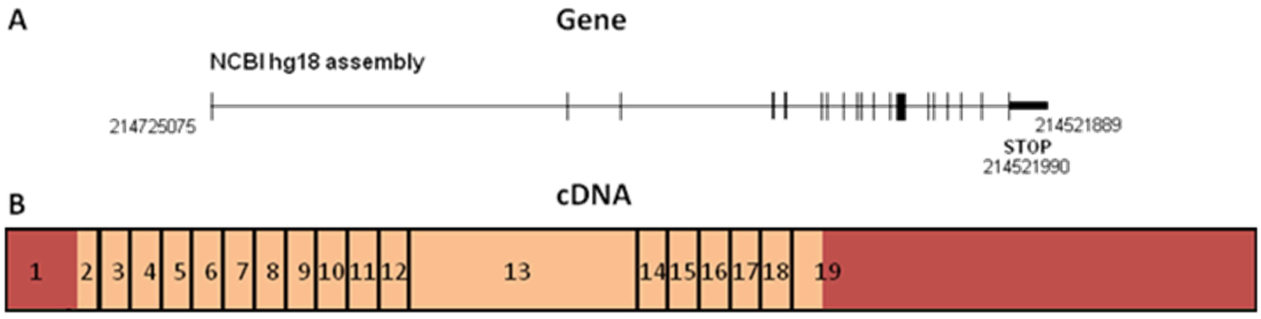
Description

The PTPN14 gene consists of 19 exons and 21 introns divided over 203 kb, including a coding region and 5' and 3' non-coding regions.

Transcription

The PTPN14 transcript is processed into a mature mRNA in excess of 10 kb, estimated by Northern blot analysis (Smith et al., 1995). The mature transcript has a 3561 nucleotide open reading frame and ~9,2 kb 3' UTR followed by a polyadenylation site. No transcript variants have been identified.

Little investigation has been undertaken to elucidate the factors regulating PTPN14 transcription. However, real-time PCR and ChIP sequencing have shown that p63 induces PTPN14 expression by binding to a p63 consensus sequence within intron 3 of PTPN14 (Perez et al., 2007).



Genomic and transcript structure of human PTPN14. A. The genomic arrangement of PTPN14 with vertical bars depicting the location and relative size of exons. Space between exons depicts relative sizes of introns/non-coding regions. **B.** The mature transcript arrangement of PTPN14. Exons are numbered and coding regions are depicted in light brown, with non-coding regions depicted in red.

C

Exon #	Length(bp)	Coding/non-coding
1	451	non-coding
2	320	both (153 coding)
3	183	coding
4	98	coding
5	68	coding
6	71	coding
7	87	coding
8	89	coding
9	88	coding
10	82	coding
11	57	coding
12	58	coding
13	1477	coding
14	143	coding
15	218	coding
16	128	coding
17	235	coding
18	170	coding
19	9354	both (129 coding)

C. PTPN14 exon length and coding status.

Protein

Description

PTPN14 is an 1187 amino acid non-receptor protein tyrosine phosphatase of approximately 135 kDa. It possesses an N-terminal FERM (band **4**.1, **e**zrin, **r**adixin, **m**oesin homology) domain and C-terminal catalytic domain, as well as acidic and proline-rich regions in its central uncharacterised region (Smith et al., 1995).

FERM domain: the FERM domain has been shown in other proteins to be important for cytoskeletal association; however a role for the FERM domain in the PTPN14 protein has yet to be described.

Catalytic PTP domain: the crystal structure of the PTPN14 catalytic C-terminal PTP domain has been solved (Barr et al., 2006).

PPxY motifs: Pez contains two PPxY motifs in its central region. These motifs are known to facilitate binding to proteins containing WW domains. Indeed, both PPxY motifs in PTPN14 are critical for binding KIBRA and YAP, components of the Hippo signalling pathway that contain WW domains (Liu et al., 2013; Poernbacher et al., 2012).

Mitochondrial localisation signal: PTPN14 contains a putative mitochondrial localisation signal (MitoProt II), and may be localised to mitochondria in some cell types (Chao et al., 2011).

Localisation

PTPN14 protein has been reported to localise to adherens junctions in confluent human umbilical vein endothelial cells (HUVEC) and translocate to the nucleus in sub-confluent, proliferating HUVEC (Wadham et al., 2000; Wadham et al., 2003). Localisation to the golgi apparatus in epithelial cell types (Wyatt and Khew-Goodall, 2008) and mitochondria in human sperm has also been reported (Chao et al., 2011).

Function

PTPN14 intracellular signaling pathways/processes

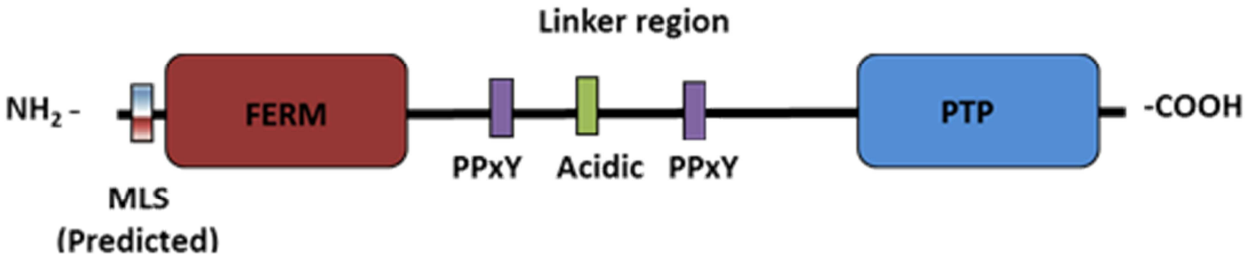
Adherens junction integrity: PTPN14 protein has been reported to dephosphorylate the adherens junction protein beta-catenin. Over-expression of a dominant-negative form of PTPN14 caused an increase in phosphorylation at adherens junctions (Wadham et al., 2003), an event linked to adherence junction destabilisation.

TGF-β: PTPN14 promotes epithelial-mesenchymal transition (EMT) via increased TGF-beta production in MDCK epithelial cells (Wyatt et al., 2007)

Lymphangiogenesis: PTPN14 forms a complex with VEGFR3 and is required for normal lymphangiogenesis in human and mouse models (Au et al., 2010).

Hippo signalling: PTPN14 has been shown to interact with Kibra/WWC1 (Poernbacher et al., 2012; Wang et al., 2012) and YAP (Liu et al., 2013; Huang et al., 2012; Wang et al., 2012), two members of the Hippo signalling pathway.

In Drosophila, PTPN14 interacts with Kibra via a PPxY:WW domain interaction, to negatively regulate the transcriptional activity of the downstream effector Yorkie, resulting in a decrease in intestinal stem cell proliferation (Poernbacher et al., 2012).



Protein structure of PTPN14. A schematic of PTPN14 protein highlighting putative nuclear / mitochondrial localisation signals (red/grey box), the band **4**.1 **e**zrin, **r**adixin, **m**eosin (FERM) homology domain (red), and the tyrosine-phosphatase (PTP) catalytic domain (blue). The linker region also contains an acidic region as well as two PPxY motifs.

EXPRESSION		
Location	Organism	Reference
Breast	Human	Smith et al, 1995
Kidney	Human	
Skeletal Muscle	Human	
Lung	Human	
Placenta	Human	
Heart	Human	
Pancreas	Human	
Sperm	Human	Chao et al, 2011
Mast cells	Mouse	Zhang et al, 2010
Endothelial cells	Mouse	Benzinou et al, 2012
Lymphatic endothelial cells	Mouse	Au et al, 2010
Intestinal stem cells	Drosophila	Poernbacher et al, 2012
Pharyngeal arches	Zebra fish	Wyatt et al, 2007
Somites	Zebra fish	
Brain	Zebra fish	
Heart	Zebra fish	
Pectoral Fins	Zebra fish	

Expression of PTPN14.

Pez interacts with YAP (the mammalian homolog of Drosophila Yorkie), also via a PPxY:WW domain interaction, and regulates its activity by controlling YAP cytoplasmic retention (resulting in a loss of transcription of YAP target genes) (Liu et al., 2013, Huang et al., 2012, Wang et al., 2012).

Mast cell degranulation: PTPN14 siRNA mediated knock-down in mast cells caused a decrease in IgE dependent mast cell degranulation (Zhang et al., 2010).

Homology

PTPN14 belongs to a FERM domain-containing family of non-receptor protein tyrosine phosphatases including PTPN3 (PTPH1), PTPN4 (PTP-MEG1), PTPN13 (PTP-BAS / FAP-1) and PTPN21 (PTPD2). PTPN14 displays a higher degree of homology to PTPN21 than other members of this sub-family (Smith et al., 1995; Alonso et al., 2004).

Mutations

Germinal

A deletion in PTPN14 has been described in a kindred with inherited lymphedema-choanal atresia syndrome, characterised by defects in lymphatic vasculature (Au et al., 2010).

Somatic

Missense mutations in PTPN14 have been reported in sporadic human colorectal cancers (Wang et al., 2004), breast cancers (Sjöblom et al., 2006), and HCV-associated hepatocellular carcinoma (Li et al., 2011).

Implicated in

Various cancers

Note

Several studies have identified mutations associated with PTPN14 in colorectal (Wang et al., 2004), breast (Sjöblom et al., 2006) and liver cancers (Li et al., 2011), although the functional consequences of these mutations are yet to be determined.

Colorectal cancer

Note

PTPN14 has been shown to interact with and de-phosphorylate residue Y128 of p130 Crk-associated substrate (p130Cas) in colorectal cancer cells (CRC) (Zhang et al., 2012). CRC homozygous for a non-phosphorylatable Y128F mutant form of p130Cas display a reduction in migration,anchorage-independent growth and xenograft tumor growth in nude mice, suggesting that Pez, via p130Cas Y128 dephosphorylation, may function as a tumour suppressor in colorectal cancer.

Pancreatic cancer

Note

PTPN14 expression was found to be lower in liver metastases compared to primary tumours in an orthotopic transplantation model of pancreatic adenocarcinoma (Niedergethmann et al., 2007), implicating PTPN14 as a suppressor of metastasis in this model.

Epithelial-mesenchymal transition

Note

Over-expression of PTPN14 in epithelial cells (MDCK) resulted in increased TGF-beta secretion and subsequent induction of epithelial-mesenchymal transition (EMT) (Wyatt et al., 2007).

Sperm motility

Note

PTPN14 expression in human sperm was correlated with motility, where moderate-motility sperm had less PTPN14 expression than highly-motile sperm (Chao et al., 2011).

Lymphedema-choanal atresia syndrome

Note

Analyses of a kindred with autosomal-recessive lyphedema-choanal atresia syndrome showed a loss of function mutation in PTPN14. $PTPN14^{-/-}$ mice developed lymphatic hyperplasia with lymphedema.

PTPN14 was also shown to interact with VEGFR3, a signalling receptor essential to lymphangiogenesis (Au et al., 2010).

Hereditary haemorrhagic telangiectasia

Note

PTPN14 maps to a chromosomal region that modifies the penetrance of a vascular dysgenesis phenotype in $Tgfb1^{-/-}$ mice, and can modulate angiogenesis in 3D primary endothelial cell culture (Benzinou et al., 2012), suggesting that Pez contributes to angiogenesis, possibly an interaction with the TGF-beta signalling pathway.

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