

# Gene Section

## Review

# PTPN6 (protein tyrosine phosphatase, non-receptor type 6)

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Published in Atlas Database: November 2012

Online updated version : <http://AtlasGeneticsOncology.org/Genes/PTPN6ID41920ch12p13.html>  
DOI: 10.4267/2042/49700

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## Identity

**Other names:** HCP, HCPH, HPTP1C, PTP-1C, SH-PTP1, SHP-1, SHP-1L, SHP1

**HGNC (Hugo):** PTPN6

### Note

Orientation: plus strand.

## DNA/RNA

### Description

The human PTPN6 gene is divided in 17 exons spanning a length of 14740 bp. A notable feature of the PTPN6 gene is that it has two promoter regions. Whereas the distal promoter, P1, located upstream of the very short exon 1 (also known as exon 1a) is active in epithelial cells, the proximal promoter P2 that initiates gene transcription from exon 2 (known as exon 1b), is utilized by the hematopoietic cells. The function of P1 promoter has been partially elucidated, while the structure and regulatory mechanism of the P2 promoter remain essentially unknown.

Recent findings, characterized the hematopoietic cell-specific P2 promoter of PTPN6 gene as well as identified the PU.1 transcription factor as the activator of the P2 promoter.

## Transcription

There are three transcript variants:

The variant 1 represents the predominant variant and encodes the shortest isoform.

The variant 2 originates by an alternate 5' terminal exon compared to transcript variant 1, resulting in an isoform (2) with a distinct and longer (by 2 aa) N-terminus, compared to isoform 1.

The variant 3 uses an alternate 5' terminal exon, and an alternate acceptor splice site at the penultimate exon, compared to transcript variant 1, resulting in a longer isoform (3, also known as 70 kDa SHP-1L protein) with distinct N and C termini, compared to isoform 1.

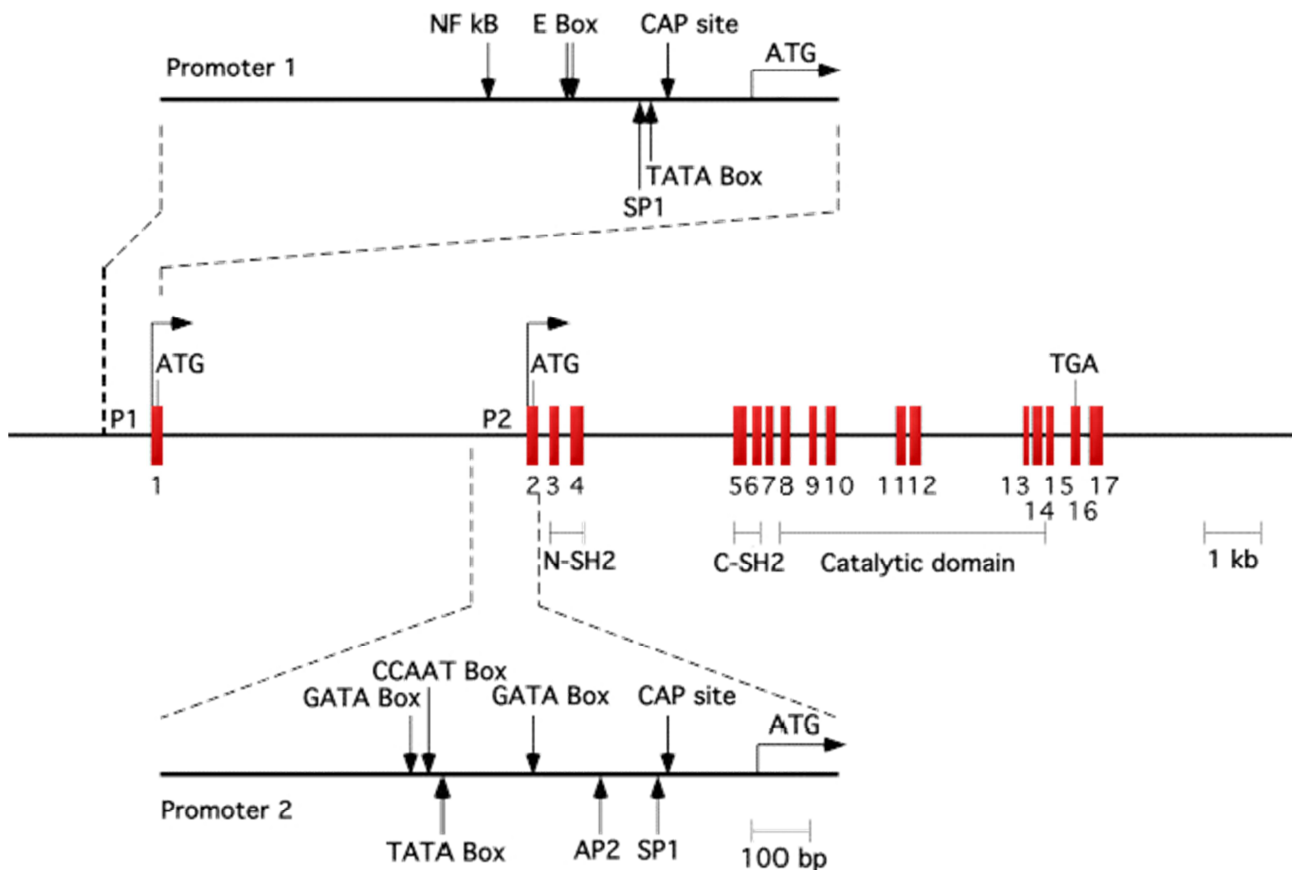
## Protein

### Description

PTPN6 contain two adjacent NH<sub>2</sub> - terminal SH2 domains, two tandem Src homology (SH2) domains, a catalytic domain, and a -COOH terminal tail of 100 amino-acid residues.

### Expression

PTPN6 tyrosine phosphatase is encoded by the PTPN6 gene and expressed primarily in the hematopoietic and epithelial cells.



Schematic representation of the human PTPN6 gene. Adapted from Wu et al., 2003.

## Function

PTPN6 plays a peculiar role in the maturation and functional differentiation of lymphoid and myeloid cells as underlined by the aberrant proliferation and impaired hematopoiesis in the "motheaten" (me) mice that display defects in the Shp-1 gene expression.

The role of PTPN6 in hematopoiesis has been shown in motheaten and viable motheaten (me<sup>v</sup>) mice, characterized by mutations at the Shp-1 locus. The Shp-1 mRNA from me bone marrow cells have a 101 bp frameshift deletion in the coding region of the N-terminal SH2 domain, while me<sup>v</sup> bone marrow cells have an in-frame 15 bp deletion or a 69 bp in-frame insertion within the PTPase catalytic domain.

Shp-1 acts in the immune and other hematopoietic cells by inhibiting signaling through receptors for cytokines, growth factors and chemokines as well as receptors involved in the immune responses and programmed cell death.

Moreover, PTPN6 acts as tumor suppressor and loss of its expression has been identified in the whole spectrum of myeloid and lymphoid malignancies.

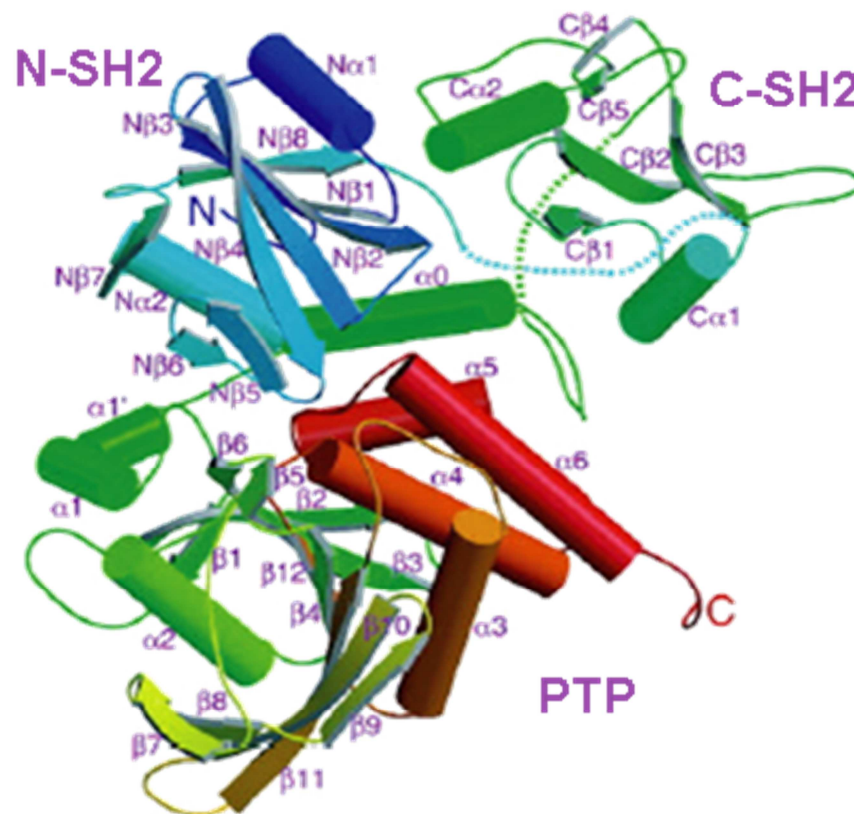
According to Gilfillan, PTPN6 is found to be

constitutively associated with FcεRI, with an opposing roles in FcεRI-mediated mast cell signaling. The study demonstrated that PTPN6 caused the decreased phosphorylation of FcεRI and Syk, but, also, an enhanced phosphorylation of JNK and an increased of the TNF production is observed. This study, suggests that PTPN6 may play a negative role proximal to FcεRI.

It was also demonstrated that the PTPN6 protein tyrosine phosphatase negatively modulates the glucose homeostasis and insulin activity, through a dephosphorylation of transmembrane glycoprotein Carcinoembryonic Antigen-related Cell Adhesion Molecule-1 (CEACAM-1).

The data obtained from in vitro studies, suggested that the deficiency of PTPN6 was associated with the increase in insulin-evoked tyrosin phosphorylation of the insulin receptor, IRS-1 and IRS-2, as well as enhanced activation of PI3K and Akt in liver and skeletal muscle.

Moreover, the activation of PTPN6, through a PKC-δ and p38α MAPK actions on PDGFRβ is involved in hyperglycemia and causes an increase vascular cell apoptosis and diabetic vascular complications.



**Crystal structure of human protein tyrosine phosphatase SHP-1.** The blue region represents the N-terminal of protein, while the red region represents the C-terminal of protein.

## Mutations

### Note

The absence or impaired function of PTPN6 in the homozygous state causes the development of the motheaten phenotype in mice, an autosomal recessive condition with focal skin inflammation and the absence of hair. Failure of neutrophils to undergo apoptosis results in the accumulation of these cells in the peripheral blood, skin, lung and spleen of affected mice.

### Somatic

A pathologically similar extensive skin infiltration by neutrophils is present in Pyoderma gangrenosum (PG) and Sweet's syndrome (SW), two uncommon neutrophilic dermatoses of unknown origin. Isoforms resulting from deletions of exons 2, 5, 11, and 15 and retention of intron 1 or 5 were identified in a patient with a familial case of SW, who had a neonatal onset of an inflammatory disorder with skin lesions and a biopsy specimen consistent with SW. These isoforms were associated with a heterozygous E441G mutation and a heterozygous 1,7-kbp deletion in the promoter region of the PTPN6 gene. The E441G mutation changes the hydrophilic, negatively charged amino acid glutamate to the hydrophobic nonpolar, aliphatic amino acid glycine, thereby potentially affecting the tertiary

structure of PTPN6. SW an acute febrile neutrophilic dermatoses appears in several clinical forms as idiopathic, tumor associated, postinfectious and drug induced (for example after an administration of granulocyte macrophage colony stimulating factor). SW and PG have strong associations with hematological tumors. Recent studies have shown that patient with leukemia and lymphoma had methylated a P2 promoter in the PTPN6 gene, causing the absence of PTPN6 protein.

PTPN6 is expressed at low level in non-hematopoietic cells while higher levels of this protein are found in hematopoietic precursors. PTPN6 promoter methylation causes loss of expression in leukemias, which results in the activation of the JAK/STAT pathway. PTPN6 plays a role in chronic myelogenous leukemia transformation and progression: it seems to be physically associated with BCR-ABL being able both to block BCR-ABL-dependent transformation and to mediate PP2A induced BCR-ABL proteasome-degradation. The tyrosine phosphatase PTPN6 plays a prominent role as resistance determinant of Imatinib (IMA) treatment response in Chronic Myelogenous Leukemia cell lines (sensitive/KCL22-S and resistant/KCL22-R).

The lack of PTPN6 expression is frequent in malignant T cells and results from methylation of the PTPN6 gene promoter. Loss of PTPN6 enhances JAK3/STAT3

signaling and decreases proteasome degradation of JAK3 and NPM-ALK in ALK + anaplastic large-cell lymphoma.

According to Wu's research, in most human Burkitt's lymphoma cell lines, the expression of SHP-1 is decreased suggesting a role of SHP-1 in a developing of Burkitt's lymphoma, a non-Hodgkin's lymphoma, associated with EBV infection.

Moreover the activity of PTPN6, is also implicated in a breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer.

## Implicated in

### T-cell lymphomas

#### Disease

Cutaneous T-cell lymphoma (CTCL) is generally classified as a type of non-Hodgkin's lymphoma, and it represents a spectrum of diseases composed of malignant clonal helper T lymphocytes of the CD4 phenotype. Widely known variants include Sezary syndrome, Worringer-Kolopp disease (Pagetoid Reticulosis), CD8+ T-cell lymphoma, granulomatous slack skin, peripheral T-cell lymphoma, angiocentric lymphoma, adult T-cell leukemia/lymphoma, large-cell or anaplastic lymphoma, and lymphomatoid granulomatosis. Poikiloderma atrophicum vasculare, small and large plaque parapsoriasis, alopecia mucinosa, and lymphomatoid papulosis likely represent early forms of CTCL, but there is a problem to whether these represent CTCL or separate premalignant entities. Accurate diagnosis of early CTCL is difficult because of the varied clinical and histologic expressions of the disease and because of a lack of uniformity regarding diagnosis and treatment.

#### Prognosis

Treatment regimens in CTCL include skin-directed therapies with UVA irradiation, topical chemotherapy with mechlorethamine (nitrogen mustard) and carmustine, and electron beam radiation, as well as systemic therapies such as chemotherapy and interferons.

### Acute myeloid leukemia

#### Note

The first hint that A-to-I RNA editing has fundamental implications in leukemic disorders derives from Beghini and co-authors, who detected altered editing events in the protein tyrosine phosphatase (PTPN6/SHP-1) transcript of patients affected by AML (Galeano et al., 2012).

The analysis of PTPN6 mRNA revealed a multiple A-I editing conversion of A<sup>7866</sup>, a branch site in IVS3 of PTPN6 mRNA causing the retention of IVS1.

#### Disease

Adult acute myeloid leukemia (AML) is a type of cancer in which the bone marrow makes abnormal myeloblasts (a type of white blood cell), red blood

cells, or platelets. Adult acute myeloid leukemia (AML) is a cancer of the blood and bone marrow. This type of cancer usually gets worse quickly if it is not treated. It is the most common type of acute leukemia in adults. AML is also called acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia. Most AML subtypes are based on how mature (developed) the cancer cells are at the time of diagnosis and how different they are from normal cells. Acute promyelocytic leukemia (APL) is a subtype of AML that occurs when parts of two genes stick together. APL usually occurs in middle-aged adults. Symptoms of APL may include both bleeding and forming blood clots.

#### Prognosis

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the spinal column (intrathecal chemotherapy), an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). Intrathecal chemotherapy may be used to treat adult AML that has spread, or may spread to the brain and spinal cord. Combination chemotherapy is treatment using more than one anticancer drug.

Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. Stem cell transplant is a method of giving chemotherapy and replacing blood-forming cells that are abnormal or destroyed by the cancer treatment. Stem cells (immature blood cells) are removed from the blood or bone marrow of the patient or a donor and are frozen and stored. After the chemotherapy is completed, the stored stem cells are thawed and given back to the patient through an infusion. These reinfused stem cells grow into (and restore) the body's blood cells.

### Pyoderma gangrenosum (PG)

#### Disease

Pyoderma gangrenosum (PG) is a rare noninfectious neutrophilic dermatosis first described in 1930. Clinically it begins with sterile pustules that rapidly progress and turn into painful ulcers of variable depth and size with undermined violaceous borders. The legs are most commonly affected but other parts of the skin and mucous membranes may also be involved. Extracutaneous manifestations include involvement of



upper airway mucosa, eye, sterile pulmonary neutrophilic infiltrates, and neutrophilic myositis. The ulcer starts as a follicular pustule with rapid growth, tissue necrosis and enlargement of the area. The surrounding skin is erythematous with infiltration and edema.

Ulcerative colitis is found in 10-15% of cases. Another associated disease is Crohn's regional enteritis with a frequency close to that of ulcerative colitis. Hepatitis C, seronegative polyarticular arthritis, spondylitis, and a broad spectrum of lymphoproliferative disorders including monoclonal gammopathies, leukemia, lymphoma, and myelodysplastic syndrome have been described in association with PG. Two main variants of PG exist: classic and atypical.

Classic PG: characterized by a deep ulceration with a violaceous border that overhangs the ulcer bed. May occur anywhere on the body; but most commonly found on the legs.

Atypical PG: has a vesiculopustular component only at the border, is erosive or superficially ulcerated, and most often occurs on the dorsal surface of the hands, the extensor parts of the forearms, or the face.

### Prognosis

Local care: debridement, intralesional injection of steroids or cyclosporin, topical agents to alter immune response (nitrogen mustard, steroids, acetic acid, 5-aminosalicylic acid) or inhibit infection. Systemic care: glucocorticoids (prednisone). These agents have anti-inflammatory properties and cause metabolic effects. In addition, these agents modify the body's immune response to diverse stimuli. Immunosuppressive agents (Cyclosporine, Azathioprine, Mycophenolate, Cyclophosphamide, Tacrolimus, Chlorambucil) have immunomodulatory effects. These agents are used to improve the clinical and immunologic aspects of the disease. They may decrease autoantibody production and increase solubilization and removal of immune complexes. Immunomodulators (Thalidomide, Clofazimine).

### Sweet's syndrome (SW)

#### Disease

Sweet's syndrome (acute febrile neutrophilic dermatosis) is characterized by physical features, and pathologic findings which include fever, neutrophilia, tender erythematous skin lesions (papules, nodules, and plaques), and a diffuse infiltrate consisting predominantly of mature neutrophils that are typically located in the upper dermis. Sweet's syndrome presents in three clinical settings:

Classical Sweet's syndrome (CSS) usually presents in women between the age of 30 to 50 years, it is often preceded by an upper respiratory tract infection and may be associated with inflammatory bowel disease and pregnancy.

The malignancy-associated Sweet's syndrome (MASS) can occur as a paraneoplastic syndrome in patients with

an established cancer or individuals whose Sweet's syndrome-related hematologic dyscrasia or solid tumor was previously undiscovered; MASS is most commonly related to acute myelogenous leukemia. The dermatosis can precede, follow, or appear concurrent with the diagnosis of the patient's cancer.

Drug-induced Sweet's syndrome (DISS) most commonly occurs in patients who have been treated with granulocyte-colony stimulating factor, however, other medications may also be associated with DISS.

### Prognosis

The pathogenesis of Sweet's syndrome may be multifactorial and still remains to be definitively established. Systemic corticosteroids are the therapeutic gold standard for Sweet's syndrome. Horio et al. originally described the dramatic improvement in patients with Sweet's syndrome who were treated with potassium iodide in 1980. He confirmed his earlier observations with a larger study in 1983. Subsequently, several other investigators have also observed similar improvement when using potassium iodide to treat patients with Sweet's syndrome. Vasculitis and hypothyroidism are potential drug-induced side effects of potassium iodide. Other agents are: colchicine, indomethacin, clofazimine, cyclosporin, dapsone.

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*This article should be referenced as such:*

Beghini A, Lazzaroni F. PTPN6 (protein tyrosine phosphatase, non-receptor type 6). *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(5):327-332.

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