Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

PTPN11 (Protein tyrosine phosphatase, non-receptor type, 11)

Marco Tartaglia, Bruce D Gelb

Dipartimento di Biologia Cellulare e Neuroscienze, Istituto Superiore di Sanitá, Rome, Italy (MT);
Departments of Pediatrics and Human Genetics, Mount Sinai School of Medicine, New York, USA (BDG)

Published in Atlas Database: February 2005

Online updated version: http://AtlasGeneticsOncology.org/Genes/PTPN11ID41910ch12q24.html
DOI: 10.4267/2042/38180

Identity

Other names: SHP-2; SH-PTP2 (Src homology 2 domain-containing protein tyrosine phosphatase 2); PTP2C (Protein tyrosine phosphatase 2C); BPTP3

HGNC (Hugo): PTPN11

Location: 12q24.1

Local order: centromere - FLJ34154 - RPL6 - PTPN11 - RPH3A - OAS1 – telomere.

DNA/RNA

Description

The PTPN11 gene is divided in 16 exons. Exon 1 contains the 5' untranslated region and the translation initiation ATG, and a few additional codons. Exon 15 contains the stop codon and exon 16 contains a major portion of the 3' untranslated region. Other features of the PTPN11 gene, such as the promoter region and enhancer elements have not been delineated.

Transcription

A 7.0-kb transcript is detected in several tissues (heart, brain, lung, liver, skeletal muscle, kidney, and pancreas) with highest steady-state levels in heart and skeletal muscle. The predominant human PTPN11 mRNA contains an open reading frame of 1,779 bases, resulting in a predicted protein of 593 amino acid residues. A second mRNA containing 12 additional base pairs (exon 11) has been identified. Little additional information is available about this alternative transcript.

Pseudogene

A number of PTPN11-related processed pseudogenes, i.e. with no apparent exon structure, have been documented in the human genome. All the pseudogenes share >92% nucleotide identity with the PTPN11 cDNA (including the 5'-UTR and 3'-UTR), but harbour frameshift mutations and multiple stop codons. Three of the five pseudogenes appear to be expressed with distinct tissue distributions and expression levels.

Protein

Description

SHP-2 is a member of a small subfamily of cytoplasmic Src homology 2 (SH2) domain-containing protein tyrosine phosphatases. Both the N-SH2 and C-SH2 domains selectively bind to short amino acid motifs containing a phosphotyrosyl residue and promote SHP-2 association with activated receptors and other signaling partners. Crystallographic data indicate that the N-SH2 domain also interacts with the PTP domain using a separate site. As these subdomains show negative cooperativity, the N-SH2 domain functions as an intramolecular switch controlling SHP-2 catalytic activation. Specifically, the N-SH2 domain interacts with the PTP domain basally, blocking the catalytic site. Binding of the N-SH2 phosphopeptide-binding site to the phosphotyrosyl ligand promotes a conformational change of the domain that weakens the auto-inhibiting intramolecular interaction, making the catalytic site available to substrate, thereby activating the phosphatase.

Expression

Widely expressed in both embryonic and adult tissues.

Localisation

Cytoplasmic. It binds to activated cell surface receptors, cell adhesion molecules and scaffolding adapters.

Function

SHP-2 functions as an intracellular signal transducer. It positively modulates signal flow in most circumstances, but can also function as negative regulator depending upon its binding partner and interactions with downstream signaling networks. SHP-2 positively controls the activation of the RAS/MAPK cascade induced by several growth factors, and negatively regulates JAK/STAT signaling. In most cases, SHP-2's function in intracellular signaling appears to be immediately proximal to activated receptors and upstream to RAS. The mechanisms of SHP-2's action and its physiological substrates are still poorly defined. However, both membrane translocation and PTPase activity are required for SHP-2 function. SHP-2 is required during development. Embryos nullizygous for Shp-2 have defects in gastrulation and mesodermal patterning resulting in severe abnormalities in axial and paraxial mesodermal structures. Shp-2 function is also required for development of terminal and skeletal structures, semilunar valvulogenesis in the heart, and hematopoiesis.

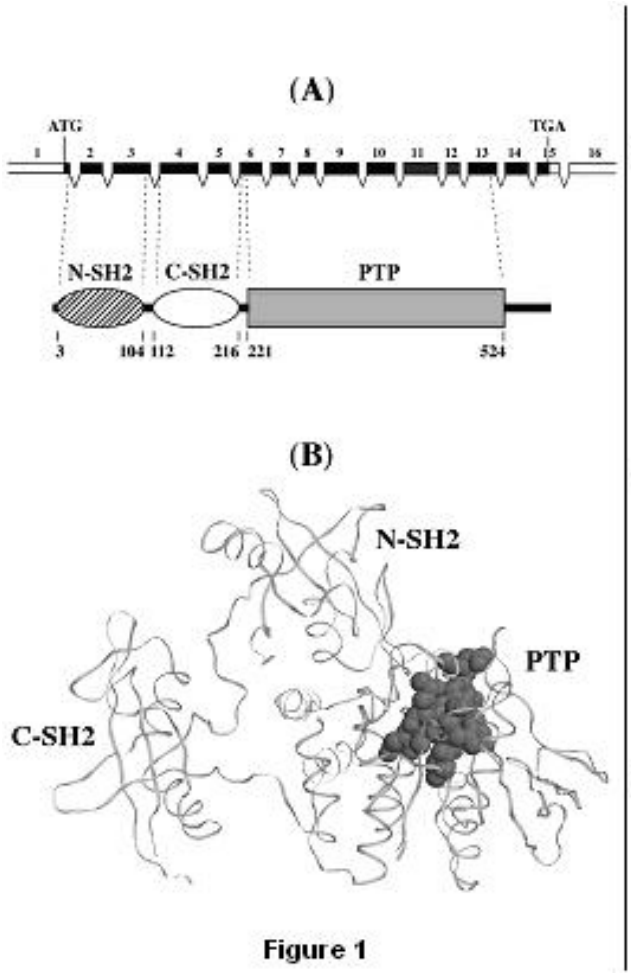

Figure 1

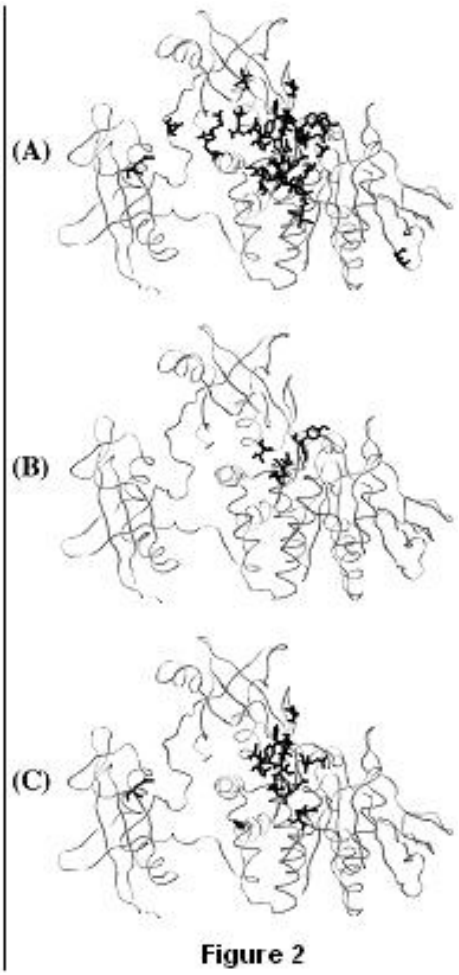

Figure 2

PTPN11 genomic organization and SHP-2 domain structure:

Figure 1 : (A) The PTPN11 gene and SHP-2 domain characterization. The coding exons are shown as numbered filled boxes. The functional domains of the protein, comprising two tandemly arranged SH2 domains at the N terminus (N-SH2 and C-SH2) followed by a protein tyrosine phosphatase (PTP) domain, are shown below. Numbers below the domain structure indicate the amino-acid boundaries of those domains. (B) Three-dimensional structure of SHP-2 in its catalytically inactive conformation, as determined by Hof et al. (1998). Residues involved in catalysis are shown (space fill).

Figure 2 : Location of SHP-2 mutated residues in human disease. (A) Noonan syndrome and LEOPARD syndrome (germ-line origin; N=224); (B) Noonan syndrome with juvenile myelomonocytic leukemia (germ-line origin; N=11); (C) hematologic malignancies, including juvenile myelomonocytic leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes and chronic myelomonocytic leukemia (somatic origin; N=97). The pictures show the C trace of SHP-2 in its catalytically inactive conformation. Affected residues are indicated with their side chains as black sticks.

Homology

PTPN6 (protein tyrosine phosphatase, non-receptor type, 6) previously known as SHP1 or SHP-1 (Src homology 2 domain-containing protein tyrosine phosphatase, 1).

Mutations

Note

At least two distinct classes of PTPN11 mutations have been identified in humans.

The first group, which has germ-line origin, causes Noonan syndrome and closely related developmental disorders.

The second group, acquired as a somatic event, has been documented in a heterogeneous group of hematologic malignancies and pre-leukemic disorders, and rarely in certain solid tumors.

The vast majority of mutations affect residues residing at or close to the interface between the N-SH2 and PTP domains. Increasing evidence supports that both germ-line and somatic mutations promote SHP-2 gain-of-function by destabilizing the catalytically inactive conformation of the protein, and prolong signal flux through the RAS/MAPK pathway in a ligand-dependent manner.

A mouse model bearing the NS-causative D61G mutation in the Ptpn11 gene has been recently generated and characterized. The $Ptpn11^{D61G/D61G}$ genotype is embryonic lethal. At day E13.5, these embryos are grossly edematous and hemorrhagic, have diffuse liver necrosis and severe cardiac defects. Heterozygous embryos exhibit cardiac defects, proportionate growth failure and perturbed craniofacial development. Hematologic anomalies include a mild myeloproliferative disease. $Ptpn11^{D61G/+}$ embryonic fibroblasts exhibit a three-fold increased Shp-2 activity and increased association of Shp-2 with Gab1 after stimulation with EGF. Cell culture and whole embryo studies reveal that increased RAS/MAPK signaling is variably present, appearing to be cell-context specific.

Germinal

Selection: 124A>G (T42A), 179-181delGTG (delGly60), 181-183delGAT (delAsp61), 182A>G (D61G), 184T>G (Y62D), 188A>G (Y63C), 214G>T (A72S), 215C>G (A72G), 218C>T (T73I), 228G>T,C (E76D), 236A>G (N79R), 317A>C (D106A), 836A>G (Y279C), 922A>G (N308D), 1403C>T (T468M), 1510A>G (M504V).

Somatic

Selection: 181G>T (D61Y), 182A>T (D61V), 205G>A (E69K), 211-213TTT>AAA (F71K), 214G>A (A72T), 215C>T (A72V), 226G>A (E76K), 226G>C (E76Q), 227A>T (E76V), 227A>G (E76G), 227A>C (E76A), 1471C>T (P491S), 1472C>T (P491L), 1504T>C (S502P), 1504T>G (S502A), 1520C>A (T507K), 1528C>A (Q510K).

Implicated in

Noonan syndrome, Noonan-like/multiple giant cell lesion syndrome and LEOPARD syndrome

Note

Germ-line origin. Gain-of-function mutations. Increased basal protein tyrosine phosphatase activity. Prolonged ligand-dependent activation of the RAS/MAPK cascade.

Disease

Noonan syndrome is a genetically heterogeneous and clinically variable developmental disorder defined by short stature, facial dysmorphism and a wide spectrum of congenital heart defects. The distinctive facial features consist of a broad forehead, hypertelorism, down-slanting palpebral fissures, ptosis, high-arched palate and low-set, posteriorly rotated ears. Cardiovascular abnormalities, primarily pulmonic stenosis and hypertrophic cardiomyopathy, are present in up to 85% of affected individuals. Additional relatively frequent features are multiple skeletal defects, webbed neck, mental retardation, cryptorchidism and bleeding diathesis. Children with Noonan syndrome are predisposed to a spectrum of hematologic abnormalities, including transient monocytosis, thrombocytopenia and rarely juvenile myelomonocytic leukemia and acute leukemia.

Juvenile myelomonocytic leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, chronic myelomonocytic leukemia, melanoma, neuroblastoma, lung adenocarcinoma, colon cancer

Note

Somatic origin.

Prognosis

No data are currently available.

Oncogenesis

Gain-of-function mutations. Increased basal protein tyrosine phosphatase activity. Prolonged ligand-dependent activation of the RAS/MAPK cascade.

References

Ahmad S, Banville D, Zhao Z, Fischer EH, Shen SH. A widely expressed human protein-tyrosine phosphatase containing src homology 2 domains. Proc Natl Acad Sci U S A. 1993 Mar 15;90(6):2197-201

Hof P, Pluskey S, Dhe-Paganon S, Eck MJ, Shoelson SE. Crystal structure of the tyrosine phosphatase SHP-2. Cell. 1998 Feb 20;92(4):441-50

Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet. 2001 Dec;29(4):465-8

Digilio MC, Conti E, Sarkozy A, Mingarelli R, Dottorini T, Marino B, Pizzuti A, Dallapiccola B. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet. 2002 Aug;71(2):389-94

Legius E, Schrander-Stumpel C, Schollen E, Pulles-Heintzberger C, Gewillig M, Fryns JP. PTPN11 mutations in LEOPARD syndrome. J Med Genet. 2002 Aug;39(8):571-4

Tartaglia M, Kalidas K, Shaw A, Song X, Musat DL, van der Burgt I, Brunner HG, Bertola DR, Crosby A, Ion A, Kucherlapati RS, Jeffery S, Patton MA, Gelb BD. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet. 2002 Jun;70(6):1555-63

Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. Trends Biochem Sci. 2003 Jun;28(6):284-93

Tartaglia M, Niemeyer CM, Fragale A, Song X, Buechner J, Jung A, Hählen K, Hasle H, Licht JD, Gelb BD. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat Genet. 2003 Jun;34(2):148-50

Andersen JN, Jansen PG, Echwald SM, Mortensen OH, Fukada T, Del Vecchio R, Tonks NK, Møller NP. A genomic perspective on protein tyrosine phosphatases: gene structure, pseudogenes, and genetic disease linkage. FASEB J. 2004 Jan;18(1):8-30

Araki T, Mohi MG, Ismat FA, Bronson RT, Williams IR, Kutok JL, Yang W, Pao LI, Gilliland DG, Epstein JA, Neel BG. Mouse model of Noonan syndrome reveals cell type- and gene dosage-dependent effects of Ptpn11 mutation. Nat Med. 2004 Aug;10(8):849-57

Bentires-Alj M, Paez JG, David FS, Keilhack H, Halmos B, Naoki K, Maris JM, Richardson A, Bardelli A, Sugarbaker DJ, Richards WG, Du J, Girard L, Minna JD, Loh ML, Fisher DE, Velculescu VE, Vogelstein B, Meyerson M, Sellers WR, Neel BG. Activating mutations of the noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res. 2004 Dec 15;64(24):8816-20

Fragale A, Tartaglia M, Wu J, Gelb BD. Noonan syndrome-associated SHP2/PTPN11 mutants cause EGF-dependent prolonged GAB1 binding and sustained ERK2/MAPK1 activation. Hum Mutat. 2004 Mar;23(3):267-77

Loh ML, Reynolds MG, Vattikuti S, Gerbing RB, Alonzo TA, Carlson E, Cheng JW, Lee CM, Lange BJ, Meshinchi S. PTPN11 mutations in pediatric patients with acute myeloid leukemia: results from the Children's Cancer Group. Leukemia. 2004 Nov;18(11):1831-4

Loh ML, Vattikuti S, Schubbert S, Reynolds MG, Carlson E, Lieuw KH, Cheng JW, Lee CM, Stokoe D, Bonifas JM, Curtiss NP, Gotlib J, Meshinchi S, Le Beau MM, Emanuel PD, Shannon KM. Mutations in PTPN11 implicate the SHP-2 phosphatase in leukemogenesis. Blood. 2004 Mar 15;103(6):2325-31

Tartaglia M, Cordeddu V, Chang H, Shaw A, Kalidas K, Crosby A, Patton MA, Sorcini M, van der Burgt I, Jeffery S, Gelb BD. Paternal germline origin and sex-ratio distortion in transmission of PTPN11 mutations in Noonan syndrome. Am J Hum Genet. 2004 Sep;75(3):492-7

Tartaglia M, Martinelli S, Cazzaniga G, Cordeddu V, Iavarone I, Spinelli M, Palmi C, Carta C, Pession A, Aricò M, Masera G, Basso G, Sorcini M, Gelb BD, Biondi A. Genetic evidence for lineage-related and differentiation stage-related contribution of somatic PTPN11 mutations to leukemogenesis in childhood acute leukemia. Blood. 2004 Jul 15;104(2):307-13

Tartaglia M, Niemeyer CM, Shannon KM, Loh ML. SHP-2 and myeloid malignancies. Curr Opin Hematol. 2004 Jan;11(1):44-50

Zenker M, Buheitel G, Rauch R, Koenig R, Bosse K, Kress W, Tietze HU, Doerr HG, Hofbeck M, Singer H, Reis A, Rauch A. Genotype-phenotype correlations in Noonan syndrome. J Pediatr. 2004 Mar;144(3):368-74

Tartaglia M, Gelb BD. Germ-line and somatic PTPN11 mutations in human disease. Eur J Med Genet. 2005 Apr-Jun;48(2):81-96

This article should be referenced as such:

Tartaglia M, Gelb BD. PTPN11 (Protein tyrosine phosphatase, non-receptor type, 11). Atlas Genet Cytogenet Oncol Haematol. 2005; 9(2):125-128.