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Gene Section
Review

PPP2R1A (protein phosphatase 2 regulatory subunit A, alpha)

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Abstract

Review on PPP2R1A, with data on DNA, on the protein encoded, and where the gene is implicated.

Identity

Other names: 2AAA, MGC786, PP2A-Aalpha, PP2AAALPHA, PR65A

HGNC (Hugo): PPP2R1A

Location: 19q13.41

Local order: Start at 52693055 and end at 52729678bp. (NCBI 37,August 2010), on the direct strand.

DNA/RNA

Description

PPP2R1A gene is encoded by 15 exons located on chromosome 19q13. The genomic size is 36624 bp.

Transcription

mRNA size: 2509 bp; coding sequence from 296bp-1770 bp.

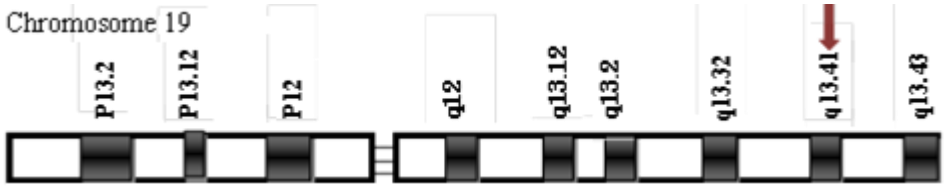
Protein

Note

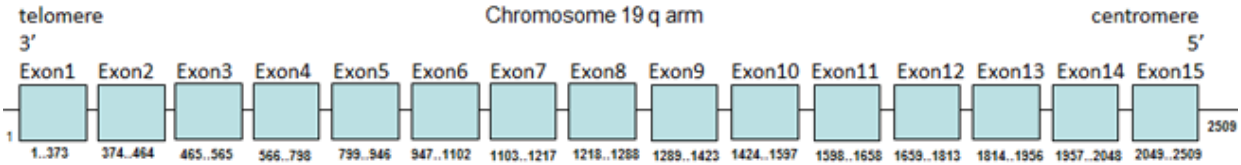
The PPP2R1A cDNA has 1767 bp open reading frame encoding a predicted polypeptide of 589 amino acids with a predicted molecular mass of 65KDa.

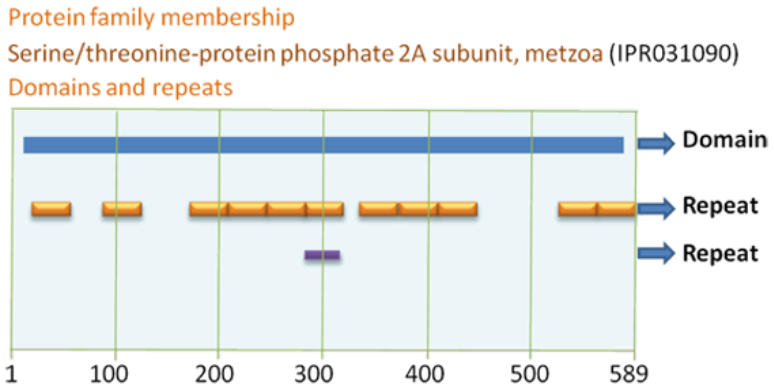
Description

The PR65 subunit of protein phosphatase 2A serves as a scaffolding molecule to coordinate the assembly of the catalytic subunit and a variable regulatory B subunit.
Required for proper chromosome segregation and for centromeric localization of SGOL1 in mitosis.



PPP2R1A gene is located on the long (q) arm of chromosome 19 at position 13.41





Found in a complex with at least ARL2, PPP2CB, PPP2R1A, PPP2R2A, PPP2R5E and TBCD. PP2A consists of a common heterodimeric core enzyme, composed of PPP2CA a 36 kDa catalytic subunit (subunit C) and PPP2R1A a 65 kDa constant regulatory subunit (PR65 or subunit A), that associates with a variety of regulatory subunits. Proteins that associate with the core dimer include three families of regulatory subunits B (the R2/B/PR55/B55, R3/B"/PR72/PR130/PR59 and R5/B'/B56 families), the 48 kDa variable regulatory subunit, viral proteins, and cell signaling molecules. Interacts with IPO9. Interacts with TP53 and SGOL1. Interacts with PLA2G16; this interaction might decrease PP2A activity. Belongs to the phosphatase 2A regulatory subunit A family.

Expression

PPP2R1A is highly expressed from brain (seen 50 times), skin , eye , lung , ovary , uterus , leiomyosarcoma and 129 other tissues.

Localisation

PPP2R1A is located in the cytoplasm, chromosome and centromere in the cell.

Function

PP2A is an important and ubiquitously expressed serine threonine phosphatase family, which plays a critical role in many fundamental cellular processes, such as cell proliferation, signal transduction, DNA repair, and apoptosis. The basis for its multifunctionality rests on the large number of subunits that determine its phosphatase activity, substrate specificity, and subcellular localization. PP2A is a heterotrimer composed of a scaffold subunit (A), a catalytic subunit (C), and one of many regulatory subunits (B). The dimeric form consisting of the scaffold and catalytic subunit also exists as the core-PP2A enzyme. Among these subunits, PP2A-A acts as a structural assembly base to escort the catalytic subunit and to facilitate interaction with the regulatory subunit and other substrates, which is essential for the activity of the holoenzyme. The PP2A scaffold subunit is encoded by two distinct genes, Ppp2r1a and Ppp2r1b, resulting in two isoforms, Aα and A β, which are 87% identical. However, in about 90% of the PP2A assemblies, the core and/or holoenzyme is composed of the A α scaffold subunit and is highly abundant in all tissues. The discovery that Aα is mutated in a variety of human malignancies, including cancer of the breast, lung, skin, and ovaries, provided evidence that PP2A-Aα plays a role in cancer, suggesting its role in tumor suppression. PP2A has been studied in vitro using an exogenous inhibitor, okadaic acid(OA), or RNA interference by others, suggesting its possible role in the regulation of meiosis. Recently, Su et al. found that up-regulation of protein phosphatase 2 catalytic subunit (PPP2CB) is key to the meiotic arrest phenotype, which demonstrated that PP2A might be involved in the regulation of meiosis resumption. Qi et al. and Chambon et al. both found that I2PP2A, the inhibitor of PP2A, was essential for sister chromatid segregation, which also suggested the importance of PP2A in meiosis.

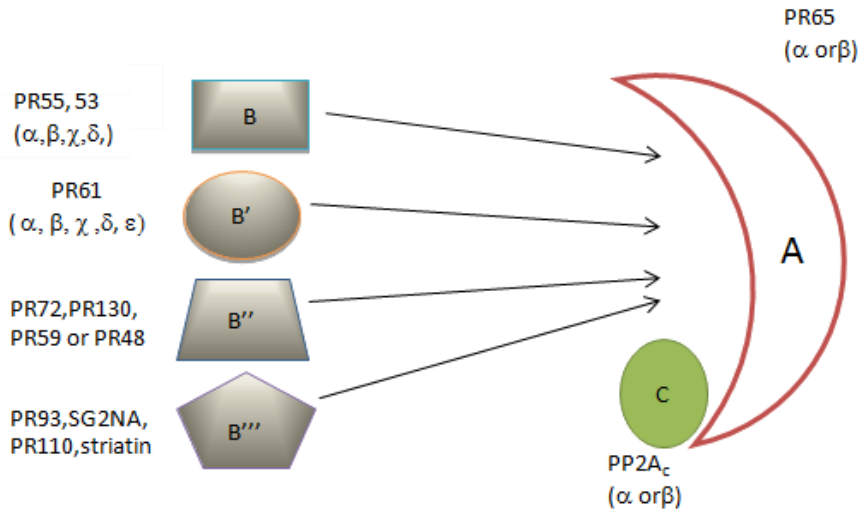
Homology

The PPP2R1A gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, fruit fly, mosquito, C.elegans, S.cerevisiae, K.lactis, E.gossypii, S.pombe, M.oryzae, N.crassa, A.thaliana, and frog.

Mutations

Somatic

Recently, somatic mutations in PPP2R1A have been reported in certain types of ovarian and uterine carcinoma. PPP2R1A mutations were demonstrated in 10 of 110 type I ovarian tumors (9.1%) including low grade serous, low-grade endometrioid, clear-cell, and mucinous carcinomas. Moreover, PPP2R1A mutations were observed in 2 of 30 type I uterine (endometrioid) carcinomas (6.7%) and 5 of 26 type II uterine (serous) carcinomas (19.2%). All mutations were located in the alpha-helix repeats near the interface between the A subunit and the regulatory B subunit of the enzyme complex. All mutations identified were heterozygous missense mutations.



Structure of PP2A: C is the catalytic subunit, A is the second regulatory or structural subunit, and B/B'/B/B''' are the third variable subunits, which are structurally unrelated. In Mammalia, A and C are encoded by two genes (α and β) ; the B/PR55 subunits are encoded by four related genes (α, β, γ, and δ) ; the B'/PR61 family are encoded by five related genes (α, β, γ, δ and ε), some of which give rise to alternatively spliced products ; the B'' family probably contains three related genes, encoding PR48, PR59 and the splice variants PR72 and PR130; SG2NA and striatin comprise the B''' subunit family

Implicated in

Wilms tumorigenesis

Note

PP2A plays a role in the Wnt signaling pathway and has been shown to be present in the multiprotein complex containing the adenomatous polyposis coli (APC) protein, the serine/threonine kinase GSK3B, and AXIN1 (axin) (Fagotto et al., 1999; Hsu et al., 1999; Seeling et al., 1999; Ikeda et al., 2000), suggesting that PP2A has a role in regulating the activity of this complex. Overexpression of the PP2A B56 regulatory subunit has been shown to markedly reduce CTNNB1 levels in mammalian cells (Seeling et al., 1999), which suggests that increased levels of PP2A accelerate the phosphorylation-dependent proteolysis of CTNNB1. Interestingly, CTNNB1 mutations have recently been reported to occur in about 15% of Wilms tumors (Koesters et al., 1999; Maiti et al., 2000), suggesting that the APC/CTNNB1/HNF4A (Tcf)-LEF1 pathway is involved in Wilms tumorigenesis. Since PP2A also plays a role in the Wnt signaling pathway, alterations in one or more of the PP2A subunits could plausibly affect this pathway and contribute to Wilms tumorigenesis.

Mental retardation, autosomal dominant 36 (MRD36)

Note

A form of mental retardation, a disorder characterized by significantly below average general intellectual functioning associate with impairments in adaptive behavior and manifested during the developmental period. The disease is identified 2 different de novo heterozygous missense mutation in the PPP2R1A gene (Hougo et al., 2015). The mutation were found by parent-child trio exome sequencing and confirmed by Sanger sequencing. In vitro functional expression study showed that the patients with MRD36, PPP2R1A mutation affected PP2A holoenzyme formation by variably interfering with interaction of the A-alpha subunit with the C subunit. All mutation resulted in decreased phosphatase activity, consisting with a dominant negative effect.

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