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Gene Section
Review

GPC5 (glypican 5)

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Identity

HGNC (Hugo): GPC5

Location: 13q31.3

Local order: Centromere - MIR17HG - GPC5 - GPC6 - DCT - TGDS - GPR180 - SOX21 - telomere.

DNA/RNA

Note

The gene spans 1.47 Mb of DNA, comprising 8 exons.

Transcription

2.904 kb mRNA. 1718 bp open reading frame.

Protein

Description

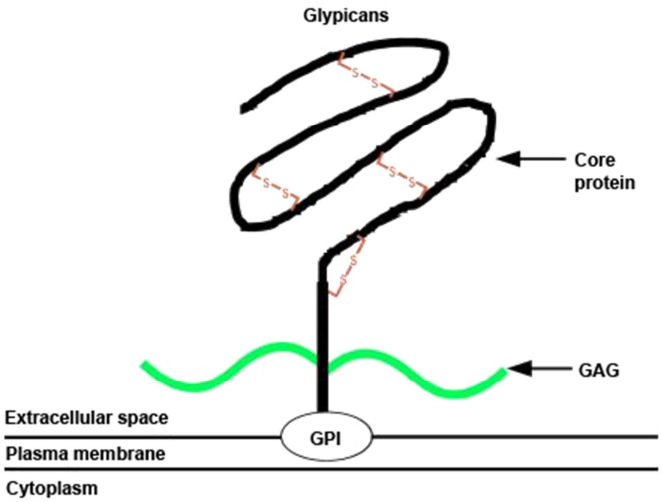
572 amino acids; 64 kDa protein (core protein). GPC5 is a heparan sulfate proteoglycan (HSPG), that is bound to the cell surface by a glycosyl-phosphatidylinositol (GPI) anchor.

Expression

GPC5 is expressed mainly in fetal tissues, including brain, lung and liver. In the adult, expression is primarily in brain tissue.

Localisation

Attached to the cell membrane by a GPI anchor.



Schematic of glypican protein structure at the cell surface. The protein is held in the plasma membrane by a GPI anchor at the carboxyl terminus. Numerous glycosoaminoglycan (GAG) attachment sites close to the membrane surface allow heparin and chondroitin sulphate chains to be attached to the core protein (shown in green). The amino terminal end of the protein is a globular structure held together by a conserved set of cysteine residues forming disulphide bridges. (Picture reproduced from Filmus and Selleck, 2001).

Function

The precise functions of GPC5 have yet to be fully established. HSPGs are common constituents of cell surfaces and the extracellular matrix (ECM), with essential functions in cell growth and development (Burgess and Macaig, 1989; Andres et al., 1992). Glypicans appear to be expressed predominantly during development, with expression levels changing in a stage- and tissue-specific manner, suggesting their involvement in morphogenesis (Sing and Filmus, 2002). As they can bind numerous ligands and be associated with a variety of receptors, they act as co-receptors for a number of heparin-binding growth factors, modulating their activity. The heparan sulfate modifications of glypicans can mediate interactions with growth factors or ECM proteins, but ligands and ECM proteins can also bind through motifs in the core proteins (Mythreye and Blobe, 2009). Glypicans can be secreted from the cell surface, such soluble forms can also bind growth factors. Evidence to date suggests that glypicans can regulate Wnt, hedgehog, fibroblast growth factor and bone morphogenetic protein pathways. The effect on these pathways may be stimulatory or inhibitory depending on cellular context (Gallet et al., 2008; Capurro et al., 2008; Kreuger et al., 2004; Yan and Lin, 2007; Grisaru et al., 2001; Yan et al., 2010).

GPC5 expression has been shown in the developing central nervous system, limbs and kidneys of mice, and its expression in mammalian fetal tissues suggests roles in growth and differentiation during development (Veugelers et al., 1997; Saunders et al., 1997; Luxardi et al., 2007). Its almost exclusive expression in adult brain tissue suggests a possible role in controlling neurotropic factors and maintaining neural function.

Homology

GPC5 is a member of the glypican family of HSPGs, of which six members (GPC1, GPC2, GPC3, GPC4, GPC5, GPC6) have been identified in mammals. GPC3 is the most homologous member to GPC5 in humans. There is approximately 20-60% sequence homology between family members, including conservation of a pattern of 14 cysteine residues. Homolog glypican-like genes are also present in Drosophila (dally and dally-like).

Implicated in

Tumourigenesis

Note

Amplification of 13q31-32 has been shown in poor prognosis liposarcomas, breast cancers and neurologic tumours (Reardon et al., 2000; Ojopi et al., 2001; Ullmann et al., 2001; Schmidt et al., 2005). Amplification of 13q31-32 has also been shown in approximately 20% of alveolar rhabdomyosarcoma, as well as gain of GPC5 copies in both alveolar and embryonal rhabdomyosarcoma (Gordon et al., 2000). GPC5 is overexpressed in the majority of rhabdomyosarcomas compared with normal skeletal muscle and has been shown to modulate responses to FGF2 in rhabdomyosarcoma cells (Williamson et al., 2007). GPC5 may also potentiate hedgehog signalling in these cells as it can bind to both Hedgehog and the Patched receptor (Li et al., 2010a). A recent genome wide association study has linked polymorphisms in GPC5 to risk of lung cancer in never-smokers (Li et al., 2010b). The high-risk allele was coincident with lower expression of GPC5, suggesting that the role of GPC5 is likely to be tumour type-specific in an analogous manner to GPC3, the closest family member to GPC5.

Developmental disorders

Note

Studies on the role of GPC5 in disease are still relatively limited. In humans, deletions of the 13q31-32 region are associated with the 13q deletion syndrome, a developmental disorder with a wide phenotypic spectrum including mental and growth retardation, congenital defects and craniofacial dysmorphy, and GPC5 is suggested as a candidate gene for digital malformations in this syndrome (Quelin et al., 2009). Correspondingly, GPC5 is also a candidate gene for postaxial polydactyly type A2, which is associated with duplication of 13q31-32 (van der Zwaag et al., 2010).

Multiple sclerosis

Note

Several genome wide association studies have identified GPC5 as having a potential role in Multiple Sclerosis (MS) (Baranzini et al., 2009; Lorentzen et al., 2010). Several different GPC5 polymorphisms were also highlighted in an independent study designed to determine which genes are associated with efficacy of interferon beta therapy in MS (Byun et al., 2008), this finding has subsequently been confirmed in a separate study (Cenit et al., 2009). HSPGs are found in dense networks in active MS plaques, where they may sequester pro-inflammatory cytokines.

References

Burgess WH, Maciag T. The heparin-binding (fibroblast) growth factor family of proteins. Annu Rev Biochem. 1989;58:575-606

Andres JL, DeFalcis D, Noda M, Massagué J. Binding of two growth factor families to separate domains of the proteoglycan betaglycan. J Biol Chem. 1992 Mar 25;267(9):5927-30

Saunders S, Paine-Saunders S, Lander AD. Expression of the cell surface proteoglycan glypican-5 is developmentally regulated in kidney, limb, and brain. Dev Biol. 1997 Oct 1;190(1):78-93

Veugelers M, Vermeesch J, Reekmans G, Steinfeld R, Marynen P, David G. Characterization of glypican-5 and chromosomal localization of human GPC5, a new member of the glypican gene family. Genomics. 1997 Feb 15;40(1):24-30

Gordon AT, Brinkschmidt C, Anderson J, Coleman N, Dockhorn-Dworniczak B, Pritchard-Jones K, Shipley J. A novel and consistent amplicon at 13q31 associated with alveolar rhabdomyosarcoma. Genes Chromosomes Cancer. 2000 Jun;28(2):220-6

Reardon DA, Jenkins JJ, Sublett JE, Burger PC, Kun LK. Multiple genomic alterations including N-myc amplification in a primary large cell medulloblastoma. Pediatr Neurosurg. 2000 Apr;32(4):187-91

Filmus J, Selleck SB. Glypicans: proteoglycans with a surprise. J Clin Invest. 2001 Aug;108(4):497-501

Grisaru S, Cano-Gauci D, Tee J, Filmus J, Rosenblum ND. Glypican-3 modulates BMP- and FGF-mediated effects during renal branching morphogenesis. Dev Biol. 2001 Mar 1;231(1):31-46

Ojopi EP, Rogatto SR, Caldeira JR, Barbiéri-Neto J, Squire JA. Comparative genomic hybridization detects novel amplifications in fibroadenomas of the breast. Genes Chromosomes Cancer. 2001 Jan;30(1):25-31

Ullmann R, Petzmann S, Sharma A, Cagle PT, Popper HH. Chromosomal aberrations in a series of large-cell neuroendocrine carcinomas: unexpected divergence from small-cell carcinoma of the lung. Hum Pathol. 2001 Oct;32(10):1059-63

Song HH, Filmus J. The role of glypicans in mammalian development. Biochim Biophys Acta. 2002 Dec 19;1573(3):241-6

Kreuger J, Perez L, Giraldez AJ, Cohen SM. Opposing activities of Dally-like glypican at high and low levels of Wingless morphogen activity. Dev Cell. 2004 Oct;7(4):503-12

Schmidt H, Bartel F, Kappler M, Würl P, Lange H, Bache M, Holzhausen HJ, Taubert H. Gains of 13q are correlated with a poor prognosis in liposarcoma. Mod Pathol. 2005 May;18(5):638-44

Luxardi G, Galli A, Forlani S, Lawson K, Maina F, Dono R. Glypicans are differentially expressed during patterning and neurogenesis of early mouse brain. Biochem Biophys Res Commun. 2007 Jan 5;352(1):55-60

Williamson D, Selfe J, Gordon T, Lu YJ, Pritchard-Jones K, Murai K, Jones P, Workman P, Shipley J. Role for amplification and expression of glypican-5 in rhabdomyosarcoma. Cancer Res. 2007 Jan 1;67(1):57-65

Yan D, Lin X. Drosophila glypican Dally-like acts in FGF-receiving cells to modulate FGF signaling during tracheal morphogenesis. Dev Biol. 2007 Dec 1;312(1):203-16

Byun E, Caillier SJ, Montalban X, Villoslada P, Fernández O, Brassat D, Comabella M, Wang J, Barcellos LF, Baranzini SE, Oksenberg JR. Genome-wide pharmacogenomic analysis of the response to interferon beta therapy in multiple sclerosis. Arch Neurol. 2008 Mar;65(3):337-44

Capurro MI, Xu P, Shi W, Li F, Jia A, Filmus J. Glypican-3 inhibits Hedgehog signaling during development by competing with patched for Hedgehog binding. Dev Cell. 2008 May;14(5):700-11

Gallet A, Staccini-Lavenant L, Thérond PP. Cellular trafficking of the glypican Dally-like is required for full-strength Hedgehog signaling and wingless transcytosis. Dev Cell. 2008 May;14(5):712-25

Baranzini SE, Wang J, Gibson RA, Galwey N, Naegelin Y, Barkhof F, Radue EW, Lindberg RL, Uitdehaag BM, Johnson MR, Angelakopoulou A, Hall L, Richardson JC, Prinjha RK, Gass A, Geurts JJ, Kragt J, Sombekke M, Vrenken H, Qualley P, Lincoln RR, Gomez R, Caillier SJ, George MF, Mousavi H, Guerrero R, Okuda DT, Cree BA, Green AJ, Waubant E, Goodin DS, Pelletier D, Matthews PM, Hauser SL, Kappos L, Polman CH, Oksenberg JR. Genome-wide association analysis of susceptibility and clinical phenotype in multiple sclerosis. Hum Mol Genet. 2009 Feb 15;18(4):767-78

Cénit MD, Blanco-Kelly F, de las Heras V, Bartolomé M, de la Concha EG, Urcelay E, Arroyo R, Martínez A. Glypican 5 is an interferon-beta response gene: a replication study. Mult Scler. 2009 Aug;15(8):913-7

Mythreye K, Blobe GC. Proteoglycan signaling co-receptors: roles in cell adhesion, migration and invasion. Cell Signal. 2009 Nov;21(11):1548-58

Quélin C, Bendavid C, Dubourg C, de la Rochebrochard C, Lucas J, Henry C, Jaillard S, Loget P, Loeuillet L, Lacombe D, Rival JM, David V, Odent S, Pasquier L. Twelve new patients with 13q deletion syndrome: genotype-phenotype analyses in progress. Eur J Med Genet. 2009 Jan-Feb;52(1):41-6

Li FE, Shi W, Capurro M, Filmus J.. Glypican-5 stimulates rhabdomyosarcoma cell proliferation by activating hedgehog signaling. Proceedings of the 101st Annual Meeting of the American Association for Cancer Research; 2010 Apr 17-21; Washington, DC. Philadelphia (PA): AACR; 2010a. Abstract no. 3191.

Li Y, Sheu CC, Ye Y, de Andrade M, Wang L, Chang SC, Aubry MC, Aakre JA, Allen MS, Chen F, Cunningham JM, Deschamps C, Jiang R, Lin J, Marks RS, Pankratz VS, Su L, Li Y, Sun Z, Tang H, Vasmatzis G, Harris CC, Spitz MR, Jen J, Wang R, Zhang ZF, Christiani DC, Wu X, Yang P.. Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. Lancet Oncol. 2010b Apr;11(4):321-30. Epub 2010 Mar 19.

Lorentzen AR, Melum E, Ellinghaus E, Smestad C, Mero IL, Aarseth JH, Myhr KM, Celius EG, Lie BA, Karlsen TH, Franke A, Harbo HF.. Association to the Glypican-5 gene in multiple sclerosis. J Neuroimmunol. 2010 Sep 14;226(1-2):194-7. Epub 2010 Aug 6.

van der Zwaag PA, Dijkhuizen T, Gerssen-Schoorl KB, Colijn AW, Broens PM, Flapper BC, van Ravenswaaij-Arts CM.. An interstitial duplication of chromosome 13q31.3q32.1 further delineates the critical region for postaxial polydactyly type A2. Eur J Med Genet. 2010 Jan-Feb;53(1):45-9. Epub 2009 Nov 23.

Yan D, Wu Y, Yang Y, Belenkaya TY, Tang X, Lin X.. The cell-surface proteins Dally-like and Ihog differentially regulate Hedgehog signaling strength and range during development. Development. 2010 Jun;137(12):2033-44.

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