

Gene Section

Mini Review

SHC4 (SHC (Src homology 2 domain containing) family, member 4)

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Identity

Other names: MGC34023; RaLP; SHCD; hShcD

HGNC (Hugo): SHC4

Location: 15q21.1

Note: The mammalian Src homology and collagen (SHC) gene family comprises four distinct loci that encode proteins sharing a unique structural organization. SHC proteins function as phosphotyrosine-binding docking molecule mediating the signaling transduction of cell-membrane receptors, including receptor tyrosine kinases (RTKs). SHC proteins display mutually exclusive tissue localization. SHC1 is ubiquitously expressed except than in the nervous system, while SHC2 and SHC3 are specifically found in the brain. SHC4 is the latest member being identified and its expression is restricted to brain and skeletal muscle

of adult mice, whereas in human it appears primarily expressed in melanoma tissues and cell lines of melanocytic origin.

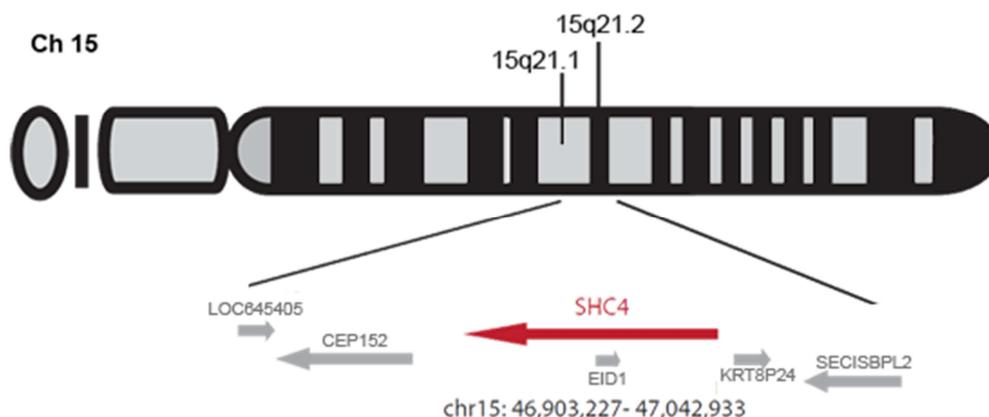
DNA/RNA

Description

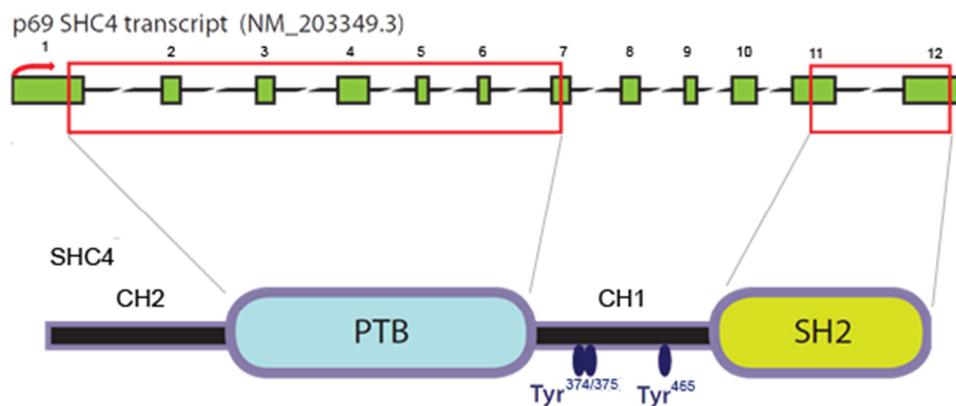
Human SHC4 locus spans 139,707 bases on chromosome 15, starting at position 46,903,227 bp and ending at position 47,042,933 from pter (according to hg18-Mar-2006).

The same locus that codifies for SHC4 transcript also produces the small and unrelated protein EP300 interacting inhibitor of differentiation 1 (EID1) that has been found only in the mammalian genome.

Orthologs of SHC4 are present in other metazoan. The corresponding mouse gene is located on chromosome 2F1.



Genomic position of the human SHC4 locus, situated on the long arm (q21.1-q21.2) of chromosome 15. The DNA sequence containing the SHC4 gene also codifies for the short unrelated transcript EID1.



SHC4 shares the same genomic architecture and protein organization typical of the SHC family. Evolutionarily conserved phosphotyrosine sites in the collagen homology 1 (CH1) region are marked in blue. Green boxes identify exons; bent arrow highlights the first ATG codon.

Transcription

Both human and mouse SHC4 open reading frame consist of twelve exons, producing nucleotide sequences of 1893 nt and 1881 nt respectively that encode for putative polypeptides of 630 amino acids in human and 626 amino acids in mouse. No clear evidence of alternative splicing isoforms of the main mRNA transcript has been found so far.

Pseudogene

None identified.

Protein

Description

The amino-terminal positioning of the phosphotyrosine-binding (PTB) domain and the carboxi-terminal positioning of the Src homology 2 (SH2) domain is a hallmark of the SHC family. These two domains are divided by the CH1 region, which contains three highly conserved tyrosine residues. A second collagen homology (CH2) region is present in the longest isoforms of the Shc family members and in SHC4. The human SHC4 protein consists of 630 amino acids with a total estimated molecular weight of 69 kDa. Although no splicing isoforms are known, it is postulated that two other polypeptides may be produced by the usage of alternate initiator codons, corresponding to predicted products of 59 kDa and 49 kDa.

Expression

Human SHC4 shows a specific expression in advanced-stage melanomas and in no other human normal and tumoral adult tissues. SHC4 protein product is detected in primary cultures and cell lines of metastatic melanoma, while its expression decreases in non-invasive melanoma cell lines and in primary melanocytes. In adult mouse tissues

SHC4 is primarily detected in brain and skeletal muscle.

Localisation

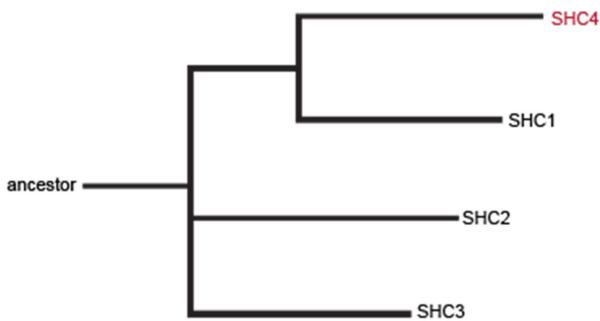
In humans, SHC4 protein is mostly localized in the cytosol of melanocytes and melanoma cells and partly to cell membranes. The murine SHC4 protein was demonstrated to co-localize with muscle-specific kinase (MuSK) at the postsynaptic neuromuscular junction (NMJ).

Function

SHC4 is a substrate of several receptor tyrosine kinases (RTK) and G protein-coupled receptors (GPCR). When ectopically expressed in non-metastatic melanoma cell lines SHC4 becomes phosphorylated upon growth factor stimulation and associates with the growth factor receptor-bound protein 2 (Grb2). Tyrosine-phosphorylated SHC4 induces Ras GTPase and mitogen activated protein kinase (MAPK) activation, resulting in enhanced cell migration. Conversely, silencing of SHC4 expression in metastatic melanoma cells reduces migration without affecting MAPK pathway, suggesting that SHC4 may participate in both Ras - dependent and - independent pathways in human melanoma. SHC4 appears to be important for the regulation of postsynaptic signals of motoneurons through association with MuSK and activation of acetylcholine receptors (AChR), as indicated by biochemical studies of the mouse protein.

Homology

Among all the human paralogous genes, SHC4 shares an overall identity at protein level of 45%, 37% and 41% with SHC1, SHC2, and SHC3 respectively. The highest conservation is detected in the PTB and SH2 regions. Human and murine SHC4 display 75% sequence identity in both the PTB and SH2 domains.



Phylogenetic relationship of SHC proteins based on the comparison of their aminoacidic sequences. SHC4 is most likely derived by gene duplication of the SHC1 locus.

Implicated in

Melanoma

Disease

Melanoma is an extremely aggressive cancer of the skin and of the internal mucosa that is capable of metastasizing in almost every site of the body. Patients with an advanced-stage melanoma are at greater risk of dying of their melanoma.

Prognosis

The more reliable prognostic parameters in melanoma are the Breslow measurement and the Clark level. The Breslow index measures the thickness of the melanoma: the thinner the melanoma, the better the prognosis. In general, melanomas less than 1 millimeter (mm) in depth have a very small chance of spreading and then invading. The Clark level describes how far a melanoma has penetrated into the skin, using a scale of I to V (with higher numbers indicating a deeper melanoma). According to Clark's model, cutaneous melanoma initially develops from an in situ growth to a radial growth phase (RGP) and evolves into the vertical

growth phase (VGP), which is associated to an increased risk of metastatization.

Oncogenesis

The RGP melanoma expands radially into the epidermis and proceeds to the VGP phase invading the dermis, before becoming metastatic. Analysis of a cohort of human melanoma lesions at various stages of the disease revealed that SHC4 expression is found in around 50% of the VGP and metastatic melanomas and not in nevi and RGP melanomas, thus suggesting a putative role for SHC4 as a prognostic marker. When SHC4 is ectopically overexpressed in RGP melanoma cells it can stimulate migration in vitro, without perturbing proliferation. Conversely, SHC4 silencing in metastatic melanoma cell lines inhibits migration and delays tumor formation in vivo, suggesting that SHC4 is important for the invasive potential of melanoma cells.

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