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Gene Section
Review

CHST11 (carbohydrate (chondroitin 4) sulfotransferase 11)

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Abstract

Review on CHST11, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: C4ST, C4ST-1, C4ST1, HSA269537

HGNC (Hugo): CHST11

Location: 12q23.3

Local order: Centromere - NFYB - TXNRD1 - **CHST11** - SLC41A2 - ALDH1L2.

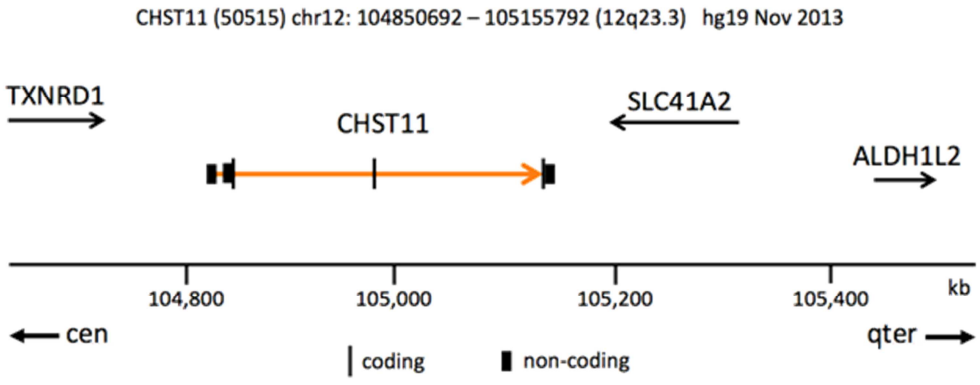
DNA/RNA

Description

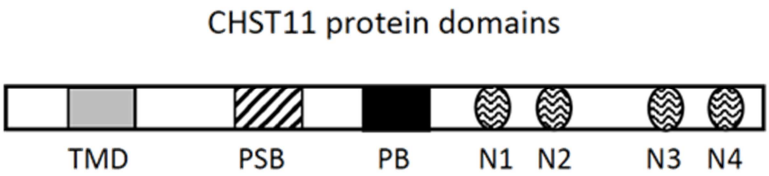
The CHST11 gene spans 305 kb on chromosome 12q23.3.

Transcription

The CHST11 gene contains one 5' non-coding exon and three coding exons and is transcribed into a 5.7 kb mRNA.
Transcription of CHST11 has been shown to be positively regulated by signaling through transforming growth factor-beta (TGFβ) pathways (Klüppel et al., 2002).



Genomic organization of the CHST11 locus on chromosome 12q23.3, encompassing nucleotides 104850692 to 105155792. Orientation (5' to 3') of CHST11, and neighbouring genes TXNRD1, SCL41A2, and ALDH1L2 are indicated by arrowheads. cen: centromere; qter: telomere of q-arm. Adapted from USCS Genome Browser, hg19 (November 2013).



Schematic illustration of the protein structure of CHST11 with known motifs indicated. CHST11 contains a transmembrane domain (TMD) for anchorage in the Golgi membrane (encoded by exon III), and a large luminal catalytic domain harboring a sulfotransferase domain, which contains a 5'-phosphosulfate site (PSB), a 3' phosphate binding site (PB), as well as four C-terminal N-glycosylation sites (N1-N4) (all encoded by exon IV).

Using a bioinformatical approach, conserved long-range cis-regulatory modules were identified in the CHST11 locus.
Luciferase reporter assays identified a functional CHST11 promoter, as well as a number of cis-regulatory modules able to positively and negatively regulate CHST11 expression in a TGFβ-dependent as well as -independent manner (Willis et al., 2009).

Protein

Description

The CHST11 protein contains 352 amino acids, and has an approximate molecular mass of 43 kDa. CHST11 is a single pass type II membrane-bound protein (Klüppel, 2010).
CHST11 protein contains a transmembrane domain (TMD) for anchorage in the Golgi mebrane, a 5' phosposulfate binding site (PSB), a 3' phosphate binding site (PB), required for binding of the phosphate donor PAPS and transfer of sulfate groups, and four N-linked glycosylation sites (N1 to N4) in the C-terminal end of the protein.

Expression

CHST11 has a highly specific temporal and spatial expression pattern during mouse embryogenesis, and has been detected in notocord, heart valves and myocardium, apical ectodermal ridge during limb generation, neural tube, hair follicles, kidney, and proliferating chondrocytes in the cartilage growth plate during skeletal development (Klüppel et al., 2002; Klüppel et al., 2005).
In adult tissues, CHST11 has been reported to be widely expressed, including in spleen, thymus, bone marrow, peripheral blood leukocytes, lymph node, heart, brain, lung and placenta (Habuchi and Miyashita, 1982; Hiraoka et al., 2000; Okuda et al., 2000; Yamauchi et al., 2000).

Localisation

CHST11 is a single pass type II membrane-bound protein localized to the Golgi (Klüppel, 2010). However, CHST11 was initially identified as a protein secreted from chondrocytes and chondrosarcoma cells (Habuchi et al., 1991; Yamauchi et al., 1999).

Function

Role in carbohydrate metabolism:
CHST11 catalyzes the transfer of sulfate from the universal intracellular sulfate donor PAPS (3'-Phosphoadenosine 5'-phosphosulfate) to the C4 position of the glycosaminoglycan chondroitin, generating chondroitin-4-sulfate (C4S) and adenosine 3',5'-bisphosphate (Habuchi, 2000; Klüppel, 2010). Through a subsequent CHST11-independent enzymatic sulfation reaction, C4S can be transformed into the double-sulfated chondroitin sulfate-E (CS-E) (Habuchi, 2000; Klüppel, 2010). Different chondroitin sulfation forms have been shown to have distinct biological functions. CHST11 has also been shown to positively regulate chondroitin sulfate chain elongation (Anggraeni et al., 2011). N-glycosylation of CHST11 is required for its enzymatic function and heat stability (Yusa et al., 2005).
Role in cartilage development and osteoarthritis (OA):
Mouse CHST11 has been shown to be required for cartilage growth plate morphogenesis (Klüppel et al., 2005). Loss of CHST11 caused chondrodysplasia with severely shortened long bones, caused by shortened and thickened cartilage growth plates with disorganized and hypo-cellular cartilage growth plates with fibrillated ECM and an overall loss of chondroitin sulfate. Increased apoptosis of mutant chondrocytes was observed, and TGFbeta and BMP signaling was disturbed in mutant growth plates (Klüppel et al., 2005). Many of these cartilage deficiencies are characteristic of the degenerative alterations observed in OA, a degenerative disease characterized by loss of matrix GAGs and cartilage integrity. Increased CHST11 expression has been observed in OA (Zeggini et al., 2012). Combined, these data suggest a requirement for tightly controlled regulation of CHST11 expression in the development and maintenance of healthy cartilage.
Role in HSV infection:
Herpes simplex virus (HSV) envelope glycoproteins utilize cell-surface GAGs to efficiently bind to and infect host cells. The gC HSV envelope protein has been suggested to bind cell-surface CS-E-proteoglycans with high affinity,

and treatment with exogenous CS-E could potently inhibit HSV infectivity, thus identifying CS-E chains of cell-surface proteoglycans as key receptors for HSV entry into a host cell. Deficiency in CHST11 expression leads to drastically reduced susceptibility to HSV infection in L-cell fibroblasts, presumably through the absence of CHST11-mediated CS-E synthesis (Uyama et al., 2006).

Role in malaria:

Malaria is caused by the parasites of the species Plasmodium, and is transmitted through infected mosquitos. High affinity adherence of P. falciparum-infected erythrocytes to endothelial cells is mediated by the CHST11 product C4S on endothelial cell-surface proteoglycans (Rogerson et al., 1995; Cooke et al., 1996; Pouvelle et al., 1997; Beeson et al., 1998).

Role in Costello syndrome:

Costello syndrome is a pediatric genetic disorder linked to oncogenic germline mutations in the HRAS gene (Gripp, 2005; Quezada and Gripp, 2007; Rauen, 2007; Gripp and Lin, 2012). The disease is characterized by multiple developmental abnormalities as well as predisposition to malignancies (White et al., 2005; Quezada and Gripp, 2007; Rauen et al., 2008). Reduction in CHST11 mRNA and protein expression, as well as loss of C4S has been identified in primary fibroblasts derived from Costello syndrome patients (Hinek et al., 2005; Klüppel et al., 2012). Oncogenic HRAS in normal fibroblasts can repress CHST11 expression, while interference with oncogenic HRAS signaling in these cells elevated CHST11 expression, thus identifying CHST11 as a negatively regulated target gene of HRAS signaling (Klüppel et al., 2012). Forced expression of CHST11 in Costello fibroblasts rescued the proliferation and elastogenesis defects associated with oncogenic HRAS signaling in these cells (Klüppel et al., 2012). These results indicate that reduced CHST11 expression and a subsequent chondroitin sulfation imbalance mediate the effects of oncogenic HRAS signaling in the pathogenesis of Costello syndrome.

Role in cancer:

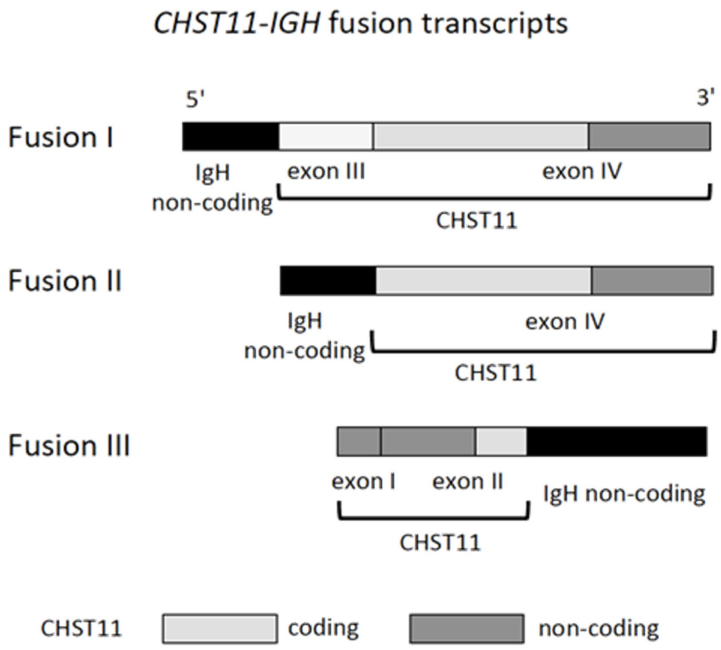
Changes in CS levels and chondroitin sulfation balance have been described during tumor progression (Ricciardelli et al., 1997; Suwiwat et al., 2004; Theocharis et al., 2006; Sakko et al., 2008; Teng et al., 2008; Svensson et al., 2011; Vallen et al., 2012). Experimental elimination of chondroitin sulfate in orthotopic breast cancer mouse models lead to increased metastasis, demonstrating a critical role of chondroitin epitopes in tumor progression in vivo (Prinz et al., 2011). The CHST11 gene was highly expressed in aggressive breast cancer cells, but significantly less so in less aggressive breast cancer cell lines (Cooney et al., 2011). Moreover, a positive correlation was observed between the expression levels of CHST11 and P-selectin-mediated adherence of breast cancer cells to endothelial cells (Cooney et al., 2011). Increased expression of the CHST11 gene has been observed in multiple myeloma (Bret et al., 2009). One case report of a patient with B-cell chronic lymphocytic leukemia (B-CLL), a chromosomal translocation with breakpoints in the IGH locus on chromosome 14, and the CHST11 locus on chromosome 12 [t(12;14)(q23;q32)] was identified. The translocation breakpoint mapped to intron 2 of the CHST11 locus, and resulted in the expression of two truncated forms of CHST11 (Schmidt et al., 2004).

Role in Wnt-β-catenin signaling:

Studies were performed in mutant sog9 L-cell fibroblasts, which lack the expression of both EXT1 (Extosis-1, required for heparan sulfate biosynthesis) and CHST11 genes (Nadanaka et al., 2008). Mutant cells had a significant decrease in Wnt3a-stimulated β-catenin accumulation, which could be rescued by stably expressing CHST11, but not EXT-1 (Nadanaka et al., 2008). In addition, this study showed that the specific chondroitin sulfate form CS-E, but not the other chondroitin sulfate forms, was able to bind Wnt3a ligand with high affinity. Addition of CS-E to normal L-cells reduced β-catenin levels, much like what was seen in the sog9 mutant L-cells lacking CHST11 expression (Nadanaka et al., 2008).

Together, this data suggested that the CHST11, through its ability to produce CS-E containing proteoglycans, might play a role in the Wnt/β-catenin signaling pathway.

The investigators of this study suggested a model in which CHST11 expression increases the level of CS-E containing proteoglycans, which can then bind Wnt3a, and facilitate the binding of Wnt ligands to its receptor complex, thus increasing the efficiency of ligand-receptor interactions. In a follow-up study, Nadanaka et al. (2011) show that L-cells stably expressing the Wnt3a ligand had a reduction in CHST11 gene expression, and subsequently a change in sulfation balance with a higher concentration of chondroitin sulfate products with low affinity for Wnt3a ligand binding (Nadanaka et al., 2011). This allows the Wnt3a ligand to freely diffuse across L-cell fibroblast cultures. Forced expression of CHST11 was suggested to inhibit the diffusion of Wnt3a ligand in L-cell fibroblast cultures, because of the increase in production of CS-E containing proteoglycans (Nadanaka et al., 2011). These and previous studies suggested that CHST11 expression is able to inhibit Wnt3a diffusion and sustained signaling, but CHST11 gene expression is negatively regulated by active Wnt/β-catenin signaling (Nadanaka et al., 2011).



CHST11-IgH fusion transcripts generated by a chromosomal translocation t(12;14)(q23;q32) in a patient with B-cell chronic lymphocytic leukemia. Fusions I and II retain 3' parts of the CHST11 coding sequence, including the sulfotransferase domain in exon IV. Fusion III retains the 5' part of the CHST11 transcript, including non-coding exons I and exon II, which encodes the transmembrane domain. Thus, fusions I and II are predicted to lack transmembrane domains, but retain sulfotransferase activity, whereas fusion III contains the CHST11 transmembrane domain, but lacks the sulfotransferase domain. The IgH components in all fusion transcripts are mainly non-coding sequences; the largest reading frame in the IgH-derived sequences are 36 bp in length (Schmidt et al., 2004). Figure adapted and modified from Schmidt et al., 2004.

We reported the identification of the CHST11 product CS-E as an inhibitor of specific molecular and biological outcomes of Wnt3a signaling in NIH3T3 fibroblasts (Willis and Klüppel, 2012). CS-E could decrease Wnt3a signaling through negative regulation of LRP6 receptor activation. However, this inhibitory effect of CS-E only affected Wnt3a-mediated induction, but not repression, of target gene expression (Willis and Klüppel, 2012). We went on to identify a critical Wnt3a signaling threshold that differentially affects target gene induction versus repression. This Wnt3a signaling threshold also differentially controlled the effects on proliferation and serum starvation-induced apoptosis (Willis and Klüppel, 2012). These data established the feasibility to manipulate the chondroitin sulfate biosynthesis machinery, in particular CHST11, to selectively inhibit Wnt/β-catenin transcriptional programs and biological outcomes through the exploitation of intrinsic signaling thresholds (Willis and Klüppel, 2012).

Homology

Homologous genes: CHST12, CHST13.

Mutations

Note

A chromosomal translocation t(12;14)(q23;q32) has been described in one patient with B-cell chronic lymphocytic leukemia (B-CLL) (Schmidt et al., 2004). Breakpoints of this have been mapped to the IGH locus on chromosome 14, and the CHST11 locus on chromosome 12 [t(12;14)(q23;q32)] (Schmidt et al., 2004). The translocation breakpoint mapped to intron 2 of the CHST11 locus, and resulted in the expression of three CHST11-IgH fusion transcripts (Schmidt et al., 2004).

It was not determined whether these fusion transcripts lead to the expression of truncated CHST11 proteins, or whether the expression of the observed fusion transcripts might have any functional consequences on chondroitin sulfate biosynthesis and/or disease development or severity.

Somatic

This is a somatic mutation in B-CLL cells (Schmidt et al., 2004).

Implicated in

B-cell chronic lymphocytic leukemia (B-CLL)

Cytogenetics

Translocation t(12;14)(q23;q32).

Hybrid/Mutated gene

This translocation generates a IGH-CHST11 hybrid gene, with breakpoints in the IGH locus on chromosome 14, and the CHST11 locus on chromosome 12. A functional role of this hybrid

gene in tumor progression has not been elucidated (Schmidt et al., 2004).

Multiple myeloma

Note

Microarray analysis identified increased expression of a number genes involved in glycosaminoglycan biosynthesis, including CHST11 (Bret et al., 2009). The authors hypothesized that heparan sulphate and chondroitin sulphate side chains of the proteoglycan syndecan-1 play critical roles in mediating the biological changes from memory B cells to malignant plasma cells (Bret et al., 2009).

Breast cancer

Note

The CHST11 gene is highly expressed in aggressive breast cancer cells, but significantly less so in less aggressive breast cancer cell lines (Cooney et al., 2011). Moreover, a positive correlation was observed between the expression levels of CHST11 and P-selectin-mediated adherence of breast cancer cells to endothelial cells (Cooney et al., 2011).

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