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Gene Section
Review

HSPG2 (heparan sulfate proteoglycan 2)

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Identity

Other names: HSPG, PLC, PRCAN, Perlecan, SJA, SJS, SJS1

HGNC (Hugo): HSPG2

Location: 1p36.12

DNA/RNA

Description

The HSPG2 gene consists of 115,014 bases and 97 exons. Evidence suggests that the encoded protein's modular structure is a result of gene duplication and exon shuffling (Cohen et al., 1993). The perlecan gene promoter lacks the TATA and CAAT boxes, but has four GC boxes and three GGGCGG hexanucleotides. The gene also was found to contain multiple start sites (Cohen et al., 1993).

Transcription

The transcribed mRNA is 14,294 bp (Cohen et al., 1993). An alternative transcript for unc-52, the homologous gene to perlecan in C. elegans, has been reported (Spike et al., 2002). In addition, a human alternative transcript was submitted to the NCBI (Accession Q8TEU3_HUMAN) as a sequence for a short version variant, miniperl, encoding a 240 amino acid protein of 25.942 kD. Expression of HSPG2 was found to be induced by TGF-beta via NF-1 (Iozzo et al., 1997), and inhibited by NF-gamma via STAT1 (Sharma and Iozzo, 1998).

Protein

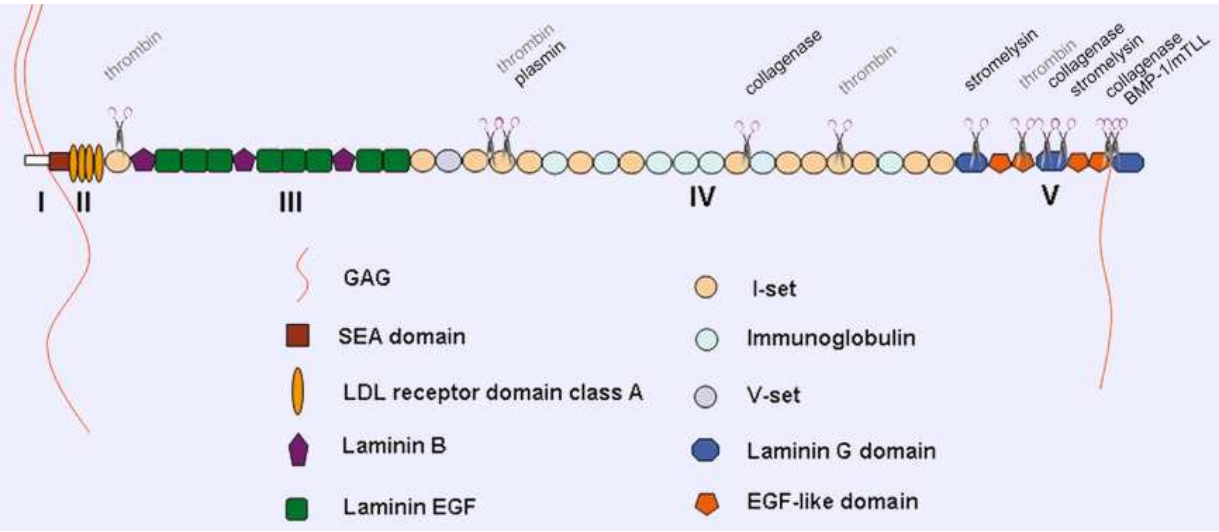

Figure1: Perlecan as a Scaffold: Functional Uncoupling by Proteolysis (from Farach-Carson and Carson, 2007).

Description

4,391 amino acids; 468,825 (core protein) to ~850,000 Da (depends upon amount of glycosaminoglycan (GAG) additions). Perlecan is composed of 5 domains. Following a 21 amino acid signal peptide for ER targeting is the N-terminal domain I, spanning amino acids 22-193 (Murdoch et al., 1992). Domain I contains 3 SGD sequences for attachment of heparan sulfate (HS) and/or chondroitin sulfate (CS) GAGs on serine residues, and a 120 amino acid SEA (Sperm protein, Enterokinase, Agrin) module. The SEA module has no definitive function, but deletion studies in domain I suggest it increases HS chain attachment (Dolan et al., 1997). Domain I of this protein is unique to perlecan, as it shares no significant homology with any other protein (Murdoch et al., 1992). The 210 amino acid domain II (amino acids 194-403) contains 4 cysteine-rich low-density lipoprotein (LDL) receptor-like modules. Adjacent to this is one immunoglobulin G (IgG)-like repeat (residues 404-504). Domain III (1,172 amino acids; residues 505-1676) consists of modules homologous to the short arm laminin alpha-chains including 3 laminin domain IV-like modules and eight laminin epidermal growth factor (EGF)-like repeats. Domain IV is the largest domain (2010 amino acids; residues 1677-3686), containing 21 IgG-like repeats (murine perlecan has only 14 IgG-like repeats, missing IgG repeats 5-12) similar to neural cell adhesion molecules (N-CAM). Domain V (705 amino acids; residues 3687-4391) has 3 modules with sequence homology to the globular domain of laminin alpha-chains and agrin. In addition, this domain contains 4 interspersed EGF-like repeats, and another GAG chain attachment site. Domain V of perlecan also is referred to as endorepellin for its angiostatic properties and was shown to be cleaved from perlecan by BMP-1/mTLL (Mongiat et al., 2003; Gonzalez et al., 2005). Several other cleavage sites are predicted for perlecan including sites for thrombin, plasmin, collagenase, and stromelysin, although some sites may be cryptic (Whitelock et al., 1996; d'Ortho et al., 1997).

Expression

Perlecan is expressed in the basement membranes of pituitary gland, skin, breast, thymus, prostate, colon, liver, pancreas, spleen, heart, and lung. Vascular basement membranes also express perlecan. In the subendothelial region, perlecan is highly expressed in the liver's perisinusoidal space, spleen, lymph nodes, and pituitary gland (Murdoch et al., 1994). In the kidney, perlecan is found in the mesangium, Bowman's capsule, the tubular basement membrane, but is only slightly expressed in the glomerular basement membrane (Groffen et al., 1997). In bone, marrow but not the mineral compartment, is rich in perlecan (Schofield et al., 1999). In human fetal tissue (12-14 week old), pericellular perlecan expression was detected in the rudiment and growth plate chondrocytes, and was found in the perichondrial capillary networks and cartilage canals (Melrose et al., 2004).

Localisation

Perlecan is found in the extracellular matrix (ECM), most commonly in the basement membrane underlying epithelial and endothelial cells. It also is found at high levels in cartilage, bone marrow and in muscle tissue.

Function

Perlecan is a multifunctional protein involved in maintaining the basement membrane, growth factor binding and signaling, cell differentiation, angiogenesis, neuromuscular function and bone development. Perlecan is an important component of the basement membrane. It binds several other basement membrane proteins including aminin 1, fibronectin, nidogen, PRELP, and collagen IV via its core protein or HS chains (Sasaki et al., 1998; Hopf et al., 2001; Kvansakul et al., 2001; Bengtsson et al., 2002).

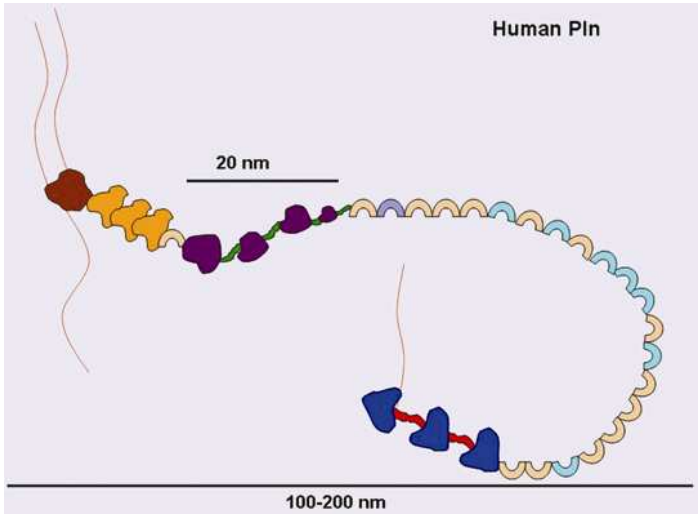

Figure 2: from Farach-Carson and Carson, 2007.

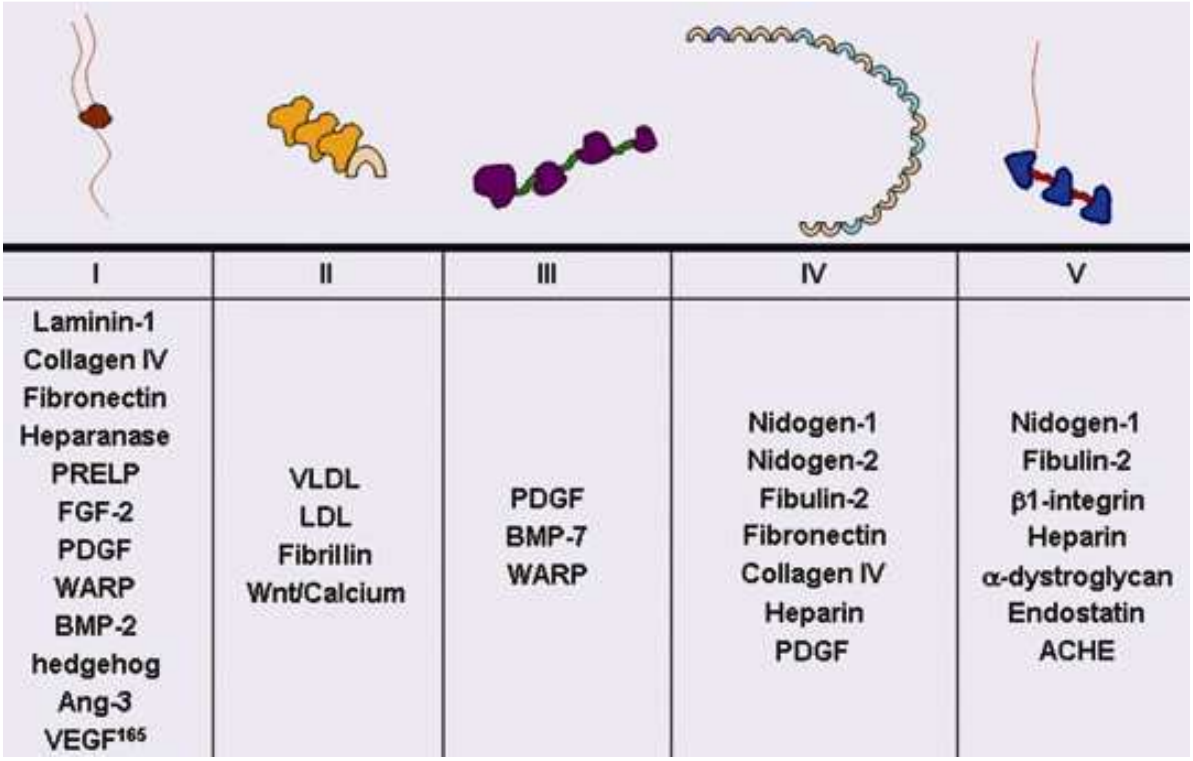

Figure 3: Perlecan as a Scaffold: Domains and interactions (from Farach-Carson and Carson, 2007).

Endorepellin (domain V) also interacts with cell surface integrins (alpha2beta1), forming additional complexes linking the ECM with the cell (Bix et al., 2004). The loss of perlecan and the basement membrane architecture is sometimes indicative of carcinomas, as is the case with invasive breast carcinoma (Nerlich et al., 1997). Perlecan has extensive growth factor regulating functions afforded to its ability to bind, sequester, and activate growth factors and growth factor binding proteins. This function connects perlecan to several actions concerning cell differentiation and proliferation. Perlecan has both pro-angiogenic (whole molecule) and anti-angiogenic (endorepellin) properties, linked to its ability regulate factors such as VEGF and FGF2. Consequently, perlecan has been implicated in supporting tumor angiogenesis in several cancers (reviewed in Bix and Iozzo, 2008). In all, perlecan has been shown to bind many growth factors including BMP-2, CTGF, PDGF, several FGFs, and VEGF and modulate several others (reviewed in Bix and Iozzo, 2008; Melrose et al., 2008). Perlecan has important functions in bone development. Perlecan sustains growth plate chondrocyte organization and hypertrophic chondrocytes, greatly assists endochondral ossification, and maintains cartilage stability in general (Arikawa-Hirasawa et al., 1999; Costell et al., 1999). The complex structure and function of perlecan suggest that it acts as an extracellular matrix scaffold. Based upon rotary shadowing of individual domains and atomic force microscopy, intact perlecan is predicted to span 100-200 nm (Chakravarti et al., 1995; Costell et al., 1996; Brown et al., 1997; Dolan et al., 1997; Hopf et al., 1999; Chen and Hansma, 2000). Given that this matches the dimensions of other scaffolding domains and that perlecan has a modular structure capable of binding many partners at once, perlecan may create stable "signalosomes" by clustering transmembrane proteins and stabilizing their interactions. As a result, perlecan may be essential in directing cell signaling and hence function as an extracellular signaling scaffold (Farach-Carson and Carson, 2007).

Homology

Mouse (~85%), Chicken (67%), Zebrafish (62%), Fruitfly (35%), Worm (35%).

Mutations

Note

Perlecan has 37 reported mutations. Over 34 mutations are attributed to Schwartz-Jampel Syndrome (SJS) and 3 are attributed to dyssegmental dysplasia, Silverman-Handmaker type (DDHS).

Known perlecan mutations

Location	Nucleotide change	amino acid	Predicted effect	perlecan domain	Disease	Reference
Exon 36	4595G>A	C1532Y	Missense (Lost disulfide bond?)	III (L4-3)	SJS	Nicole et al., 2000
Intron 64	8464+4A>G	p.T2773PfsX25	Splicing-->Truncated domain IV	IV (IgG12)	SJS	Nicole et al., 2000
Exon 37	4740G>A		Lost disulfide bond?	III (LE-7)	SJS	Nicole et al., 2000
Intron 56	7374+4 A>G		Splicing: PTC (Exon 57)	IV	SJS	Arikawa-Irasawa et al., 2002
Exon 64	8544 G>A		Splicing: skip exon 64	IV	SJS	Arikawa-Irasawa et al., 2002
Exon 67,Intron 66	deletion cagCTCCAG (n-3 del9)		Splicing: PTC	IV	SJS	Arikawa-Irasawa et al., 2002
Exon 60, 61			Fuse exon 60 and 61,	IV	SJS	Arikawa-Irasawa et al., 2002
Exon 96	7,108 bp deletion (n+21 7108 bp)		Splicing: exon deletion,	V	SJS	Arikawa-Irasawa et al., 2002
Intron 37	c.4741-10T>G		Splicing?	III (LE-7)	SJS	Sturn et al., 2006
Intron 81	c.11208-7G>A		Splicing?	V (LG1)	SJS	Sturn et al., 2006
Intron 6	c.574+481C>T	p.V192AfsX25	Splicing	II (LA1)	SJS	Sturn et al., 2006
Intron 95	c12899+G>A		Splicing?	V (LG3)	SJS	Sturn et al., 2006
Exon 8-Intron 13	c.720_1654del		Deletion	II (LA1-IgG)	SJS	Sturn et al., 2006
Exon 36	c.4432C>T	p.R1478C	Missense	III (L4-3)	SJS	Sturn et al., 2006
Exon 68	c.12191delC	p.P4065RfsX5	Frameshift	V (LG2)	SJS	Sturn et al., 2006
Exon 37	c.4648C>T	p.R1550C	Missense	III (LE-7)	SJS	Sturn et al., 2006
Intron 54	c.7006+1G>A		Splicing?	IV (IgG7)	SJS	Sturn et al., 2006
Exon 80	c.10982G>A	p.R3661Q	Missense	IV (IgG21)	SJS	Sturn et al., 2006
Exon 80	c.10982G>A	p.E3660GfsX114	Splicing	IV (IgG21)	SJS	Sturn et al., 2006
Exon 81	c.11192delG	p.G3731EfsX30	Frameshift	V (LG1)	SJS	Sturn et al., 2006
Exon 36	c.4432C>T	p.R1478C	Missense	III (L4-3)	SJS	Sturn et al., 2006
Exon 75	c.10354C>T	p.R3452X	Nonsense	IV (IgG19)	SJS	Sturn et al., 2006
Exon 36	c.4473_4475del	p.L1491del	Deletion	III (L4-3)	SJS	Sturn et al., 2006
Exon 75	c.10355G>A	p.R3452Q	Missense	IV (IgG19)	SJS	Sturn et al., 2006
Intron 60	c.7874-2A>G	p.H2624_V2625in	Splicing	IV (IgG10)	SJS	Sturn et al., 2006
Intron 60	c.7874-2A>G	p.V2625fs	Splicing	IV (IgG10)	SJS	Sturn et al., 2006
Exon 72	c.9642delC	p.3215KfsX7	Frameshift	IV (IgG17)	SJS	Sturn et al., 2006
Exon 49	c.6179delC	p.P2060LfsX3	Frameshift	IV (IgG5)	SJS	Sturn et al., 2006
Exon 87	c.11792_11793insC	p.L3932AfsX32	Frameshift	V (LG2)	SJS	Sturn et al., 2006
Exon 7	c.665_675del	p.R222QfsX5	Frameshift	II (LA1)	SJS	Sturn et al., 2006
Exon 70	c.9326del	p.H3109PfsX16	Frameshift	IV (IgG15)	SJS	Sturn et al., 2006
Exon 70	c.9326del	p.T3088_H3109d	Splicing	IV (IgG15)	SJS	Sturn et al., 2006
Exon 70	c.9326del	p.D3065_H3109d	Splicing	IV (IgG15)	SJS	Sturn et al., 2006
Exon 24	c.3055C>T	p.P1019L	Missense	III (L4-2)	SJS	Sturn et al., 2006
Exon 34	89 bp duplication btwn 4683-4684		Frameshift, PTC in Exon 36	III	DDSH	Arikawa-Irasawa et al., 2001
Intron 52	G7086+5A		Frameshift, skip exon 52,	IV	DDSH	Arikawa-Irasawa et al., 2001
Exon 73	C10328T		Frameshift, skip exon 73,	IV	DDSH	Arikawa-Irasawa et al., 2001

Abbreviation Code

L4= laminin domain IV like module
SJS= Schwartz-Jampel syndrome
IgG= Immunoglobulin G-like repeat
LE= laminin EGF-like domain
PMC=premature termination codon
LA=LDL receptor
LG=Laminin G like modules
DDSH=Dyssegmental Dysplasia, Silverman-Handmaker type

Implicated in

Prostate Cancer

Note

Perlecan expression was correlated with aggressive prostate tumors (high Gleason score). Primary prostate cancer tumors and metastatic prostate cancer to the lung and liver showed increased perlecan expression, but metastasis to the lymph nodes showed decreased perlecan protein expression. Furthermore, perlecan expression was shown to promote survival of tumors in low androgen and/or low growth factor environments. Perlecan may mediate prostate cancer progression through its regulation of the sonic hedgehog signaling pathway, whose activity has been implicated in prostate cancer (Datta et al., 2006). Targeted reduction of perlecan in prostate cancer xenografts growing in mice reduced tumor growth and vascularization (Savorè et al., 2005).

Disease

Prostate cancer is an adenocarcimona affecting the gland cells of the prostate. It is a slow growing cancer usually affecting older men. The most common site of metastasis of prostate cancer is the bone.

Breast Cancer

Note

Perlecan mRNA expression was shown to be increased in invasive breast carcinomas, yet immunohistochemical analysis showed a lack of perlecan deposition in the carcinoma (Nerlich et al., 1997; Nerlich et al., 1998). This suggests subsequent proteolytic cleavage of perlecan or translational defects in breast cancer. However, in breast cancer stromal cells, high perlecan deposition was also reported (Iozzo et al., 1994).

Disease

Breast cancer refers to the many types of cancer affecting breast tissue including ductal carcinoma and lobular carcinoma. Breast cancers are further defined as in situ or invasive. An especially deadly form is inflammatory breast cancer. The most common target of breast cancer metastasis is the lymphatic system. It is the most common form of cancer for women and the second cause of cancer-related deaths for women.

Prognosis
None.

Melanoma

Note
In metastatic melanoma, perlecan mRNA expression was increased 15 fold over normal tissue, which correlated with enhanced perlecan deposition in the melanoma's pericellular matrix (Cohen et al., 1994). When perlecan expression was blocked with a perlecan antisense cDNA construct in metastatic melanoma cells, the proliferative and invasive properties were reduced. Perlecan serves as a reservoir for growth factors involved in angiogenesis and proliferation (VEGF, bFGF/FGF-2, FGF-7), and is needed for growth factor signaling. bFGF/FGF-2 was shown to be an important autocrine regulator of metastatic melanoma, and perlecan is needed for bFGF to advance melanoma. Without perlecan, growth factor activity is diminished, abrogating tumor progression (Adatia et al., 1997).

Disease
Melanoma is a type of skin cancer originating in the melanocytes.

Prognosis
None.

Colon cancer

Note
When perlecan was blocked by antisense targeting in xenografts with human colon carcinoma cells and tumor allografts, tumor progression and neovascularization were substantially decreased in a mouse model. Perlecan inhibition is thought to suppress FGF-7 binding and receptor activation, thereby blocking tumor growth and angiogenesis (Sharma et al., 1998). As in other cancers, perlecan is a contributing factor in colon cancer progression.

Disease
Colon cancer usually begins as a non-cancerous adenomatous polyp and spreads into the wall of the colon, where it may metastasize through blood vessels or the lymphatic system.

Prognosis
None.

Fibrosarcoma

Note
In contrast to other cancers, when perlecan was suppressed by antisense cDNA in fibrosarcoma cells, the phenotype became more aggressive in that they had increased migration, invasion, and adhesiveness to type IV collagen substrates. Perlecan action in fibrosarcoma is thought to be independent of the bFGF pathway and possibly prevent mesenchymal tumor invasion (Mathiak et al., 1997).

Disease
Fibrosarcoma is a type of malignant tumor originating in the connective tissue, mostly affecting the leg, arm, and jawbone in humans.

Prognosis
None.

Adenoid cystic carcinoma (ACC)

Note
Perlecan expression was increased in ACC cells forming small stromal pseudocysts, but not in advanced flat ACC cells producing large pseudocysts or already attached to peripheral nerves, which have abundant perlecan. This suggests perlecan is needed for initial ACC cell growth (Kimura et al., 2000).

Disease
ACC is a tumor affecting the salivary glands. It is usually slow growing and not as aggressive as other salivary gland cancers.

Prognosis
None.

Intrahepatic cholangiocarcinoma (ICC)

Note
Perlecan is highly expressed in the tumor specific fibromyxoid stroma of ICC. In addition, the ICC cells on the invading fronts expressed higher levels of perlecan than other ICC cells, suggesting that perlecan is an important component of ICC tumor invasiveness (Sabit et al., 2001).

Disease
ICC is a tumor originating in the biliary system (bile ducts) of the liver. It is associated with the hepatitis C virus and chronic cholangitis.

Prognosis
None.

Amyloidosis and related diseases

Note
In a murine model of AA amyloidogenesis perlecan expression increased before the deposits of AA amyloids, indicating that perlecan is required for the earliest stages of amyloid fibrillogenesis (Ailles et al., 1993). Perlecan was shown to accelerate beta-amyloid fibril formation and also stabilize the formed fibrils, demonstrating perlecan's role in beta-amyloidogenesis in Alzheimer's disease (Castillo et al., 1997). In addition, during hemodialysis induced beta2-microglobulin (beta2M) amyloidosis, increased amounts of HSPGs, like perlecan, direct where beta2M deposits will occur and assist fibrillogenesis (Ohashi, 2001).

Disease
Amyloidosis refers to a wide spectrum of diseases where the abnormal deposition of amyloid species

(insoluble proteins in a beta-pleated secondary conformation) occurs in any organ or tissue. Alzheimer's disease is an example of amyloidosis affecting the brain.

Prognosis
None.

Schwartz-Jampel Syndrome (SJS)

Note
Mutations in the perlecan gene were implicated in SJS in 2000 by (Nicole et al., 2000). Two mutations are found in the C-terminal region of domain III, SJS1-H C1532Y and SJS1-B 4740G→A, resulting in lost disulfide bonds. One mutation was found in domain IV, SJS1-A IVS64+4a→g, leaving a truncated protein missing domain IV Ig-like repeats 13-21 and domain V. (Arikawa-Hirasawa et al., 2002) reported additional mutations resulting in early stop codons. (Stum et al., 2006) reported an additional 22 perlecan mutations. In all of these mutational analyses, no evidence of a founder effect existed. The mutated perlecan proteins are secreted in lower amounts or are more susceptible to proteases and have varying degrees of functionality, resulting in the defects characteristic of SJS. However, (Rodgers et al., 2007) using mice with site specific perlecan mutations suggested that it was not the truncated protein or faulty secretion, but a downregulation of perlecan at the transcriptional level. With respect to myotonia, perlecan was shown to localize acetylcholinesterase (AChE) to the neuromuscular junction. With less functional perlecan, AChE is largely absent at the synapse, resulting in a higher concentration of ACh. This aberrantly stimulates the ACh receptor causing muscle contractions associated with myotonia.

Disease
SJS is a rare autosomal recessive disease characterized by skeletal dysplasias and myotonia, a neuromuscular disorder resulting in prolonged muscle contraction. Patients with the disorder have short stature, blepharophimosis (drooping eyelids with reduced size, flat nasal bridge, underdeveloped orbital rim), pursed lips, low-set ears, myopia, and a fixed facial expression. SJS is characterized by several skeletal dysplasias including kyphoscoliosis, platyspondyly (flattened vertebrae), joint contractures, and metaphyseal and epiphyseal dysplasias. Based upon clinical examination, several other disorders including kyphomelic chondrodyplasia, Burton's disease, micromelic chondrodysplasia were suggested by (Spranger et al., 2000) to be reclassified as SJS.

Dyssegmental dysplasia, Silverman-Handmaker type (DDHS)

Note
Functional null mutations of perlecan have been implicated in DDHS. (Arikawa-Hirasawa et al., 2001) reported an 89-bp duplication in exon 34, and a 5' donor site mutation in intron 52 and exon 73, resulting in a truncated perlecan protein core. In contrast to SJS, the truncated perlecan protein is not secreted and deposited, causing a functional null mutation similar to the homozygous perlecan knockout mice. This manifests in more severe defects than SJS, as all DDHS individuals are stillbirths or die shortly thereafter.

Disease
DDSH is a rare autosomal recessive lethal disease characterized by severe skeletal dysplasias, anisospondyly and micromelia. DDSH patients also have a flat face, cleft palate, low joint mobility, micrognathia (undersized jaw), and encephalocoele. The endochondral growth plate has shortening defects, the resting cartilage shows mucoid degeneration, and hypertrophic chondrocytes produce calcospherites that fail to fuse.

Intracranial aneurysms

Note
Two SNPs in the perlecan gene were associated with intracranial aneurysms (Ruigrok et al., 2006). A defect in perlecan is thought to contribute to faulty ECM in the arterial wall, increasing the likelihood of an aneurysm.

Disease
An aneurysm is the dilation of the arterial wall due to defects in the ECM. A dilated blood vessel may rupture resulting in a subarachnoid hemorrhage.

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