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Gene Section
Review

FBLN1 (fibulin 1)

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Identity

Other names: FBLN, FIBL1

HGNC (Hugo): FBLN1

Location: 22q13.31

Local order: Orientation: plus strand.

Note: Fibulin-1 is an extracellular matrix (ECM) and blood glycoprotein. It is a member of the fibulin glycoprotein family which includes 6 proteins thought to function as bridges in the organization of ECM supramolecular structures (Argraves et al., 1990; Timpl et al., 2003).

DNA/RNA

Description

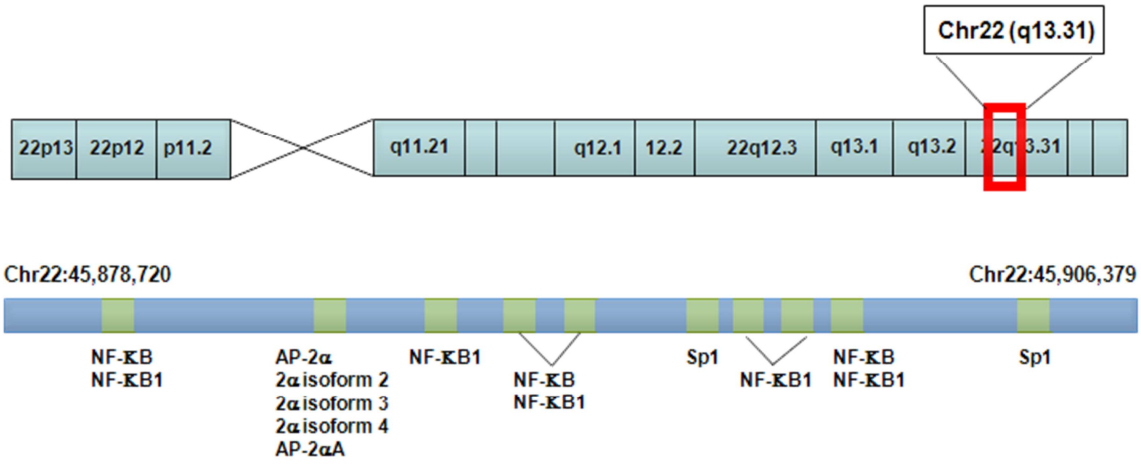
Sequence length: 97, 71 kb, 20 exons, maximum exon length: 818, minimun exon length: 50. Number of SNPs 1038. Four splice variants have been identified which differ in the 3' end and encode different isoforms (A, B, C and D) (Pan et al., 1999).

Variant D: This variant is considered the canonic transcript form: 2947 bp;
- Including exons 18, 19 and 20;
- Lacking exons 15 and 16.

Variant B: 2530 bp;
- Including exon 17;
- Lacking exons, 16, 18, 19 and 20.

Variant A: 2350bp;
- Including exon 15;
- Lackings exons 16 to 20.

Variant C: 2313bp;
- Including exon 16;
- Lacking exons 15 and 17 to 20.



Transcription factor.

Protein

Description

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        10         20         30         40         50         60
MERAAPSRRV PLPLLLLGGL ALLAAGVDAD VLLEACCADG HRMATHQKDC SLPYATESKE
        70         80         90        100        110        120
CRMVQEQCCH SQLEELHCAT GISLANEQDR CATPHGDNAS LEATFVKRCC HCCLLGRAAQ
       130        140        150        160        170        180
AQGQSCEYSL MVGYQCGQVF QACCVKSQET GDLDVGGLQE TDKIIEVEEE QEDPYLNDRC
       190        200        210        220        230        240
RGGGPCKQQC RDTGDEVVCS CFVGYQLLSD GVSCEDVNEC ITGSHSCRLG ESCINTVGSF
       250        260        270        280        290        300
RCQRDSSCGT GYELTEDNSC KDIDECESGI HNCLPDFICQ NTLGSFRCRP KLQCKSGFIQ
       310        320        330        340        350        360
DALGNCIDIN ECLSISAPCP IGHTCINTEG SYTCQKNVPN CGRGYHLNEE GTRCVDVDEC
       370        380        390        400        410        420
APPAEPCGKG HRCVNSPGSF RCECKTGYYF DGISRMCVDV NECQRYPGRL CGHKCENTLG
       430        440        450        460        470        480
SYLCSCSVGF RLSVDGRSCE DINECSSSPC SQECANVYGS YCYCRRGYQ LSDVDGVTCE
       490        500        510        520        530        540
DIDECALPTG GHICSYRCIN IPGSFQCSCP SSGYRLAPNG RNCQDIDECV TGIHNCSINE
       550        560        570        580        590        600
TCFNIQGGFR CLAFECPENY RRSAATLQQE KTDTVRCIKS CRPNDVTCVF DPVHTISHTV
       610        620        630        640        650        660
ISLPTFREFT RPEEIIFLRA ITPPHPASQA NIIFDITEGN LRDSFDIIKR YMDGMTVGVV
       670        680        690        700
RQVRPIVGPF HAVLKLEMNY VVGGVVSHRN VVNVHIFVSE YWF
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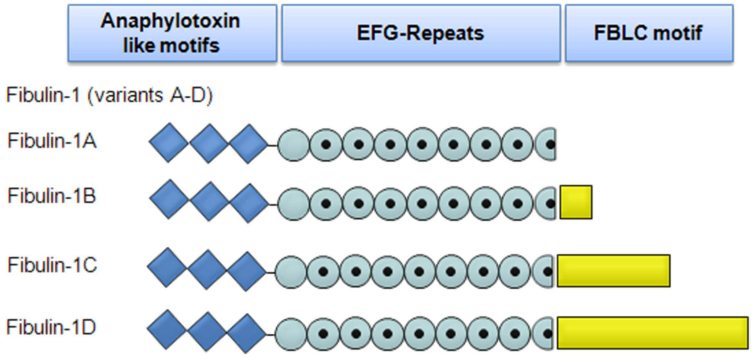
Position	Length	Description
36-76	41	Anaphylatoxin-like 1
77-111	35	Anaphylatoxin-like 2
112-144	33	Anaphylatoxin-like 3
176-215	40	EGF-like 1
216-261	46	EGF-like 2; calcium-binding
262-307	46	EGF-like 3; calcium-binding
308-355	48	EGF-like 4; calcium-binding
356-398	43	EGF-like 5; calcium-binding
399-440	42	EGF-like 6; calcium-binding
441-480	40	EGF-like 7; calcium-binding
481-524	44	EGF-like 8; calcium-binding
525-578	54	EGF-like 9; calcium-binding

Glycosylation	98; 535; 539
Disulfide bond	36↔61; 37↔68; 50↔69; 78↔109; 91↔110; 112↔136; 113↔143; 126↔144; 180↔190; 186↔199; 201↔214; 220↔233; 227↔242; 248↔260; 266↔279; 273↔288; 294↔306; 312↔325; 319↔334; 341↔354; 360↔373; 367↔382; 384↔397; 403↔415; 411↔424; 426↔439; 445↔454; 450↔463; 465↔479; 485↔498; 494↔507; 509↔523; 529↔542; 536↔551; 556↔577

Amino acid modifications (UNIPROT)

Fibulin-1 homomultimerizes and interacts with various ECM components such as fibronectin (FN) (Balbona et al., 1992), laminin subunits alpha-1 and apha-2 (LAMA1 and LAMA2), nidogen (NID), Aggrecan core protein (ACAN), versican core protein (CSPG2) and type IV collagen proteins (Timpl et al., 2003). Fibulin-1 also interacts with amyloid beta A4 (APP) (Ohsawa et al., 2001), insulin-like growth factor-binding protein 9 (NOV) (Perbal et al., 1999), fibrinogen (FGB) (Tran et al., 1995), and human papillomavirus (HPV) type 16, 18, 31 proteins (Du et al., 2002).



Localisation

Secreted, extracellular space, extracellular matrix.

Function

Fibulin-1 is incorporated into FN-containing matrix fibers. It plays a role in cell adhesion and migration along protein fibers within the ECM and is important for certain developmental processes. Fibulin-1 contributes to the supramolecular organization of ECM architecture, in particular to that of the basement membrane. It is implicated in cellular transformation and tumor invasion, and can behave both as an oncosuppressor and oncogene depending on tissue environment. It also plays a role in hemostasis and thrombosis owing to its ability to bind fibrinogen and incorporate into clots and plays a significant role in modulating the neurotrophic activities of APP, particularly soluble APP (Timpl et al., 2003).

Homology

Paralogs: latent-transforming growth factor beta-binding protein 1 (LTBP1), LTBP2, LTBP3, LTBP4, fibrillin-1 (FBN1), FBN2, FBN3, FBLN5, fibulin-2 (FBLN2), epidermal growth factor-like protein 6 (EGFL6), nephronectin (NPNT), EGF-containing fibulin-like extracellular matrix protein 2 (EFEMP2), Von Willebrand factor C (VWCE).

Mutations

Note

- Location: exon 19 (acceptor splice site)
- Substitution: G-A
- Phenotype: Bernard-Soulier syndrome

Implicated in

Various cancers

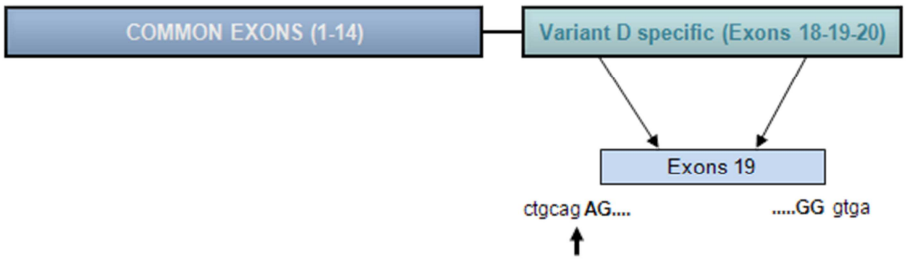
Note

Several studies have reported that fibulin-1 is overexpressed in various human neoplasias and it is implicated in processes such as invasion, motility, and in vivo tumor growth (Qing et al., 1997; Twal et al., 2001; Du et al., 2002; Moll et al., 2002; Greene et al., 2003). Fibulin-1 inhibits in vitro adhesion and motility of various carcinoma cell lines (Twal et al., 2001).

Breast cancer

Prognosis

Fibulin-1 was found aberrantly expressed in ~35% of 528 human primary breast cancers. Its expression is associated with improved survival in patients with lymphoid infiltrate at the tumor site (Pupa et al., 2004), suggesting a possible involvement in triggering a protective antitumor immune response. Fibulin-1 induces specific B- and T-cell-mediated responses in breast cancer patients (Forti et al., 2002; Pupa et al., 2004). Its overexpression can serve as a tool for early detection of breast cancer (Pupa et al., 2002) and acts to promote breast cancer cell survival during doxorubicin treatment (Pupa et al., 2007). In a series of 36 primary breast carcinomas, the expression of mature fibulin-1 polypeptide (100 kDa) did not correlate with estrogen receptor-alpha (ERalpha) or progesterone receptor (PR) levels, whereas a positive correlation was found between fibulin-1 processing (50 kDa fragment) and ERalpha and PR protein levels (Greene et al., 2003).



Ovarian cancer

Disease

The molecular mechanisms involved in ovarian carcinogenesis remain unclear, but growing evidence indicates that estrogens promote progression of ovarian cancer and increase expression levels of some secreted proteins. Differential overexpression of ERalpha versus ERbeta has been demonstrated during ovarian carcinogenesis (Clinton et al., 1996; Moll et al., 2002), suggesting that estrogen-induced proteins, including fibulin-1, may act as ovarian tumor-promoting agents. In ovarian tissues and cancer cell lines, fibulin-1C and -1D are the predominant forms, whereas fibulin-1A and -1B are weakly expressed. An increased fibulin-1C:-1D mRNA ratio in ovarian cancer cells as compared to that in normal ovaries has been observed, suggesting that the C variant is the main one involved in ovarian carcinogenesis. Fibulin-1C overexpression might provide a clue in understanding the putative role of estrogens in ERalpha-promoted ovarian tumor progression (Moll et al., 2002).

Synpolydactyly

Disease

Synpolydactyly is a rare genetic disorder characterized by malformations in the hands and feet, with abnormalities including increased finger and toe numbers and fusion of digits into a single digit. Molecular analysis of the reciprocal chromosomal translocation t(12;22)(p11.2;q13.3) cosegregating with a complex type of synpolydactyly indicated involvement of an alternatively spliced exon of the fibulin-1 gene (FBLN1 located in 22q13.3). Investigation of the possible functional involvement of the fibulin-1 protein in the observed phenotype showed that fibulin-1 is expressed in the ECM in association with the digits in the developing limb (Debeer et al., 2002). Thus, t(12;22) might result in haplo-insufficiency of the fibulin-1D variant, leading to the observed limb malformations.

Bernard-Soulier syndrome

Disease

Bernard-Soulier syndrome is an autosomic-dominant disease that causes alterations of the megakaryocyte/platelet lineage and is characterized by bleeding tendency, giant blood platelets and low platelet counts. An unexpected mutation in the splice acceptor site of fibulin-1 exon 19 was found in affected individuals of the Israeli Fechtner family. In all affected individuals from eight families, expression of fibulin-1 variant D was inhibited by putative antisense RNA (Lanza, 2006), raising the possibility that these autosomal-dominant giant platelet syndromes are associated with aberrant antisense gene regulation of fibulin-1.

Placenta dysplasia

Disease

Placental dysplasia is a rare human placental disorder in which the placenta is enlarged and contains cystic villi and dilated vasculature. A significant correlation was observed between fibulin-1 gene overexpression and murine placental overgrowth (Singh et al., 2006), suggesting that the gene and its product have a functional role in placenta development.

Morphogenesis of neural crest-derived structures

Disease

A significant negative correlation between fibulin-1 gene expression and some morphogenic anomalies of neural crest-derived structures in mice has been reported (Cooley et al., 2008). Such fibulin-1-deficient mice exhibit cardiac ventricular wall thinning and ventricular septal defects, with double outlet right ventricle or overriding aorta, as well as aortic arch arteries anomalies, hypoplasia of the thymus and thyroid, underdeveloped skull bones, malformations of cranial nerves and hemorrhagic blood vessels in the head and neck. The spectrum of malformations is consistent with a role for fibulin-1 in neural crest cell-dependent development of these tissues.

Acute aortic dissection

Disease

Acute aortic dissection (AAD) is a tear in the wall of the aorta that causes blood to flow between the layers of the wall of the aorta and force the layers apart. AAD is a life-threatening condition with high mortality and a mostly unclear pathophysiological mechanism. Downregulation of fibulin-1 noted in AAD compared to control samples might determine a weakening of ECM in the aorta and/or interfere with the transmission of cellular signals causing AAD (Mohamed et al., 2009).

Atherosclerotic lesions

Disease

Fibulin-1 deposits were found in association with fibrinogen in atherosclerotic lesions and in regions containing fresh thrombi. By contrast, fibulin-1 was not detected in sclerotic regions and low levels were associated with smooth muscle cells within and outside lesions (Argraves et al., 2009).

Thrombosis

Disease

Thrombosis, the formation of a blood clot (thrombus) inside a blood vessel, obstructs blood flow through the circulatory system. Analyses of blood plasma revealed an interaction between fibulin-1 and fibrinogen (Tran et al., 1995), pointing to potential new roles for fibulin-1 in hemostasis as well as thrombosis.

Breakpoints

Note

Description: Translocation t(12;22)(p11.2;q13.3).

Phenotype: Synpolydactyly.

Analysis of a Belgian family with a complex type of synpolydactyly (SPD2) and a t(12;22)(p11.2;q13.3) translocation identified the breakpoints located in the intron between the last 2 exons of the fibulin-1D splice variant isoform (exons 19, 20) and the 5' UTR of the C12ORF2 gene. Fibroblasts derived from the patients displayed decreased levels of ECM-related fibulin-1D secreted into the culture medium, whereas levels of the fibulin-1C variant were normal. The findings are consistent with the notion that the t(12;22)(p11.2;q13.3) translocation results in haplo-insufficiency of the fibulin-1D variant, leading to the observed limb malformations. The authors noted that the entire fibulin-1 gene is deleted in the chromosome 22q13.3 deletion syndrome (Debeer et al., 2002).

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