

Gene Section

Review

ITGA6 (integrin, alpha 6)

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Identity

Other names: CD49f, ITGA6B, VLA-6

HGNC (Hugo): ITGA6

Location: 2q31.1

DNA/RNA

Description

ITGA6 (Gene ID: 3655) is located on chromosome 2 at 2q31.1.

Gene ranges from 173292314 to 173371181 on the plus strand with a total length of 78870 bp.

Transcription

The ITGA6 gene has 2 transcript variants encoding two different isoforms.

Transcript variant 1 (NCBI Accession NM_001079818) encodes the longer isoform a (NP_001073286) comprised of 25 exons.

Transcript variant 2 (NCBI Accession NM_000210.2) encodes the shorter isoform b (NP_000201) comprised of 26 exons which has a distinct C-terminus with an alternative coding exon compared to isoform a.

Pseudogene

There are no known pseudogenes.

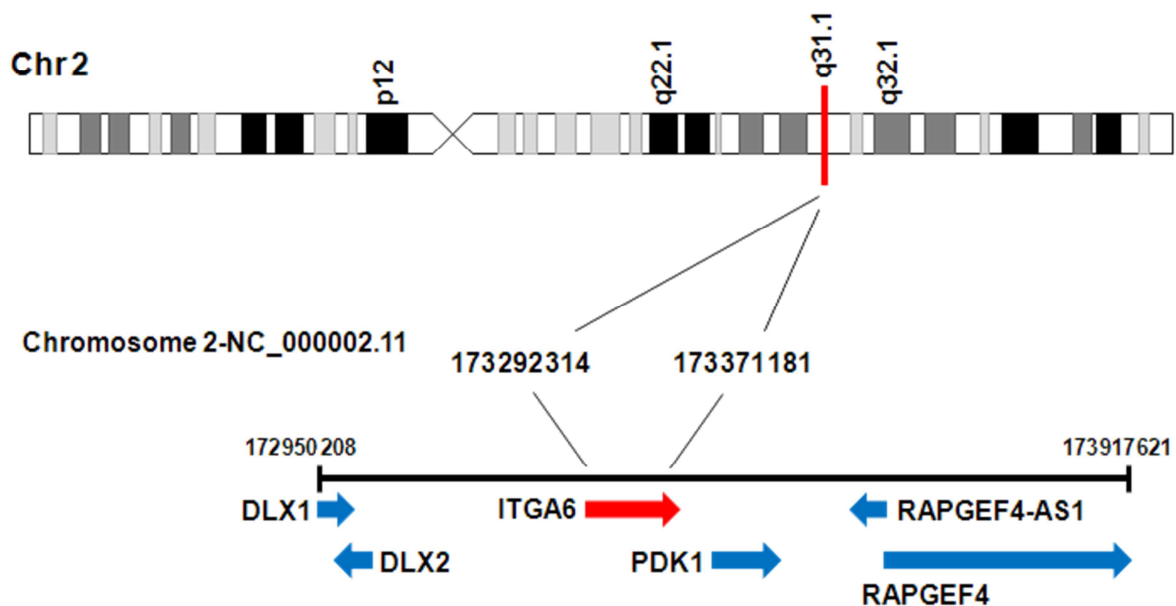
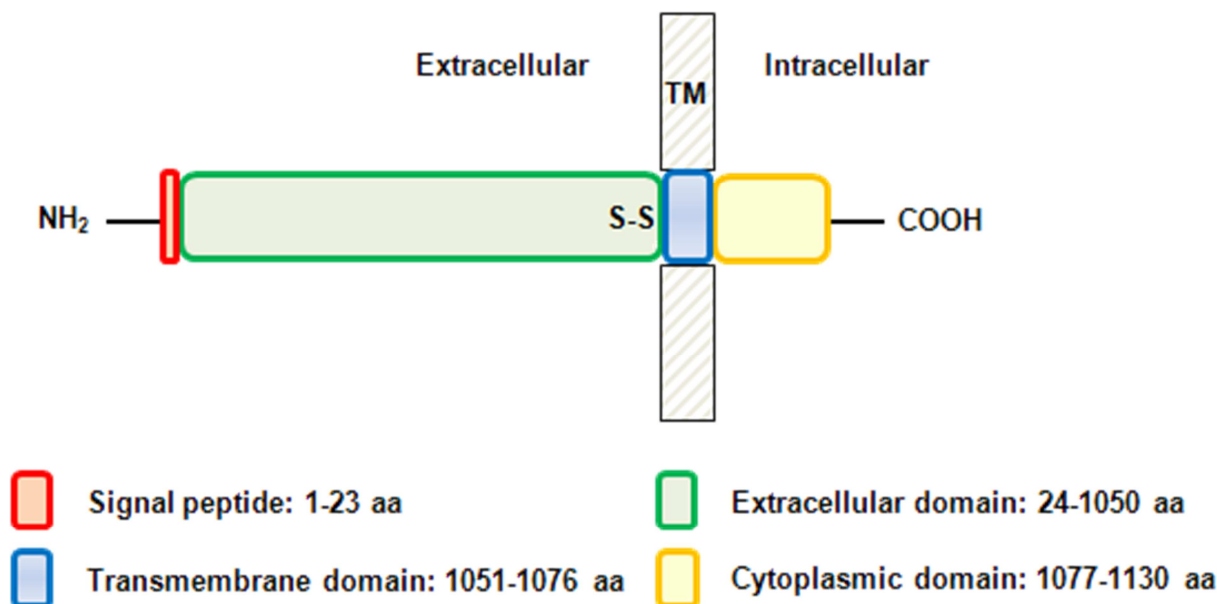


Figure 1. Schematic diagram of ITGA6 location on chromosome 2. Chromosome 2 is represented with banding pattern. ITGA6 is located at 31.1 and ranges from 173292314 to 173371181 on reverse strand. The region surrounding ITGA6 is enlarged. Genes are represented by arrows in the direction of transcription.



Protein

Note

The integrin alpha6 gene encodes for a protein of 10733 amino acid residues (NP_000201), with a molecular mass of 119,467 kDa (P23229; UniProKB). It contains a signal peptide, extracellular domain, transmembrane domain and a cytoplasmic domain.

Description

The integrin alpha 6 subunit consists of a heavy and a light chain linked by a disulfide bond. It forms heterodimers with beta-1 or beta-4 integrin subunits to make $\alpha\beta 1$ integrin or $\alpha\beta 4$ integrin.

Expression

$\alpha\beta 4$ integrin is widely expressed in epithelia and in a few other cell types such as thymocytes, fibroblasts, and Schwann cells. $\alpha\beta 1$ integrin is expressed in platelets, leukocytes and many epithelial cells.

Localisation

Cell surface and hemidesmosome (Sonnenberg et al., 1991; Alt et al., 2001; Geuijen and Sonnenberg, 2002).

Function

Both $\alpha\beta 1$ integrin and $\alpha\beta 4$ integrin are receptors for the laminin family of extracellular matrix proteins. $\alpha\beta 4$ integrin in epithelial cells plays an essential role in strengthening and stabilizing the skin tissue through the formation of hemidesmosome (Dowling et al., 1996; Nievers et al., 1999; Sterk et al., 2000). $\alpha\beta 1$ integrin contributes to the formation of organs and tissues before birth (Georges-Labouesse et al., 1996; Niculescu et al., 2011). In malignant carcinoma cells, both of these integrins serve as signaling receptors that triggers signaling cascades that enhance survival, invasion and metastasis (reviewed in Mercurio et al., 2001).

Homology

Mouse, rat and human homologs of ITGA6 share greater than 90% amino acid identity.

Mutations

Note

A homozygous 1-bp deletion mutation (791delC) have been identified in an infant with epidermolysis bullosa with pyloric atresia and esophageal stenosis (Ruzzi et al., 1997).

Implicated in

Glioblastoma multiforme

Note

Lathia et al identified integrin $\alpha 6$ as a hallmark of glioblastoma stem cells (GSCs) (Lathia et al., 2010). In this study, authors find that integrin $\alpha 6$ is co-expressed with conventional GSC markers such as CD15 and CD133, and localized to the perivascular compartment. However, integrin $\alpha 6$ expression enriches for GSCs lacking CD133 expression. Combining expression of both CD133 and integrin $\alpha 6$ led to higher enrichment of GSCs than CD133 alone did. shRNA mediated knockdown of integrin $\alpha 6$ expression results in a reduction of GSC phenotype such as GSC self renewal and tumor formation. The results suggest that integrin $\alpha 6$ is a promising target for antiglioblastoma therapy.

Disease

Glioblastoma Multiforme (GBM) is the most common and malignant primary brain tumor with poor prognosis (Singh et al., 2004).

Upon diagnosis, 5 year survival rate is less the 3%. GBM is almost incurable because it is cellular heterogeneous and GBM mass invade functional brain area, which makes impossible for the surgeons to totally remove the cancer tissues.

Also, it is resistant to the radiation and other treatments (Stupp et al., 2005). Recently, Integrin $\alpha 6$ garnered a lot of attention as potential candidate for effective glioblastoma therapeutic target due to its high expression in neural stem cells and ability to interact with laminin (Lathia et al., 2010).

Breast cancer

Note

Both $\alpha 6\beta 1$ integrin and $\alpha 6\beta 4$ integrin contribute to survival of breast carcinoma cells under stress conditions (Chung et al., 2002; Chung and Mercurio, 2004) through upregulation of VEGF expression, either at the level of transcription or translation. The $\alpha 6\beta 4$ integrin dependent translation of VEGF derives from the ability of this integrin to stimulate AKT/mTOR pathway (Chung et al., 2002). Under hypoxic condition, the $\alpha 6\beta 1$ integrin is required for transcriptional activation of VEGF via HIF-1 (Chung et al., 2004). $\alpha 6\beta 4$ integrin is implicated in invasion and metastasis of breast carcinoma cells via activation of PI3K/AKT pathway when it is mobilized from hemidesmosome into leading edges (Lipscomb et al., 2005).

Disease

It is the most common cancer among women and the second leading cause of cancer deaths of women in US. Breast cancer is 100 times more common in women than in men. Despite of its mortality, it is mostly curable disease when it is detected at early stages.

Microarray gene expression analysis defines four distinct sub-types of breast cancer, including hormone receptor (HR) positive luminal A and B, human epidermal growth receptor 2 (HER2/neu)-enriched and basal-like breast cancer (BLBC) (Perou et al., 2000). BLBC represent 17% to 37% of all breast cancers and is one of the most aggressive breast cancer sub-types with poor prognosis (Irvin and Carey, 2008). Expression of $\alpha 6\beta 4$ integrin significantly correlates with BLBC (Lu et al., 2008).

Prognosis

High expression of integrin $\alpha 6$ in women with breast cancer significantly correlated with reduced survival times (Friedrich et al., 1995; Chung and Mercurio, 2004).

Co-expression of $\alpha 6\beta 4$ integrin and laminin in breast tumors has been correlated with poor prognosis (Tagliabue et al., 1998).

Co-expression of both $\alpha 6\beta 4$ integrin and Net1 (RhoA-specific guanine nucleotide exchange factor) is correlated with a high risk of distant metastasis in patients with hormone receptor-positive tumors (Gilcrease et al., 2009).

Prostate cancer

Note

Integrin $\alpha 6\beta 1$ contributes to migration and invasion of prostate cancer cells through cell surface

cleavage of integrin $\alpha 6$ in uPA induced manner (Rabinovitz et al., 1995; Demetriou et al., 2004; Pawar., 2007; Ports et al., 2009).

Disease

It is the form of cancer that develops in a gland in the male reproductive system.

While a majority of prostate cancer grow slowly, some cases of aggressive prostate cancer involve metastasis to the bones and lymph nodes.

Prostate cancer usually occurs in older men.

No early symptoms are reported in many cases of prostate cancer, but some patients may experience urinary symptoms and discomfort.

Treatment options include surgery, chemotherapy, cryotherapy, hormonal therapy, and/or radiation.

Epidermolysis bullosa letalis with pyloric atresia (EB-PA)

Note

EB-PA is a rare autosomal recessive genetic disease with a poor prognosis.

It represents frequently lethal, epidermolysis bullosa with variable involvement of skin, nails, mucosa.

EB-PA is caused by defects in ITGA6.

The mutations in the genes encoding two subunit polypeptides of the $\alpha 6\beta 4$ integrin (ITGA 6 and ITGA4) have been reported in the patients with EB-PA (Chung and Uitto, 2010).

Disease

Mucocutaneous fragility, aplasia cutis congenita, and gastrointestinal atresia are common symptoms that affects the pylorus.

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