

## Gene Section

### Review

# CD151 (CD151 molecule (Raph blood group))

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### Identity

**Other names:** CD151 antigen; GP27; MER2; PETA-3; PETA3; PETA3F; RAPH; SFA-1; SFA1; TSPAN24; Tspan-24; Tetraspanin-24

**HGNC (Hugo):** CD151

**Location:** 11p15.5

**Local order:** Telomere--PNPLA2--EFCAB4A--CD151--POLR2L--TSPAN4--Centromere.

### DNA/RNA

#### Note

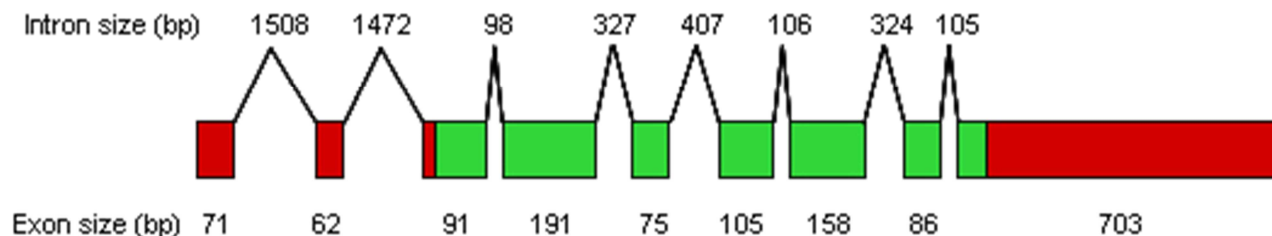
Information sourced from UCSC Genome Database Mar 2006 Assembly (hg18) RefSeq genes and from analysis of mouse gene organisation (Fitter et al., 1998) and human gene structure (Whitlock et al., 2001).

#### Description

5884 bp, 9 exons (7 coding).

#### Transcription

mRNA 1574bp (length may vary for utr alternate splicing).



The red bars indicate utr and green bars indicate coding exons. The size of each intron is indicated at the top and each exon below. An alternate transcript may be generated from splicing out exon 2 in the 5'utr as indicated with the blue lines.

### Pseudogene

None in humans.

### Protein

#### Description

Size: 253 aa, 28247 Da with a mature protein size of 32 kDa; pI: pH 7.44.

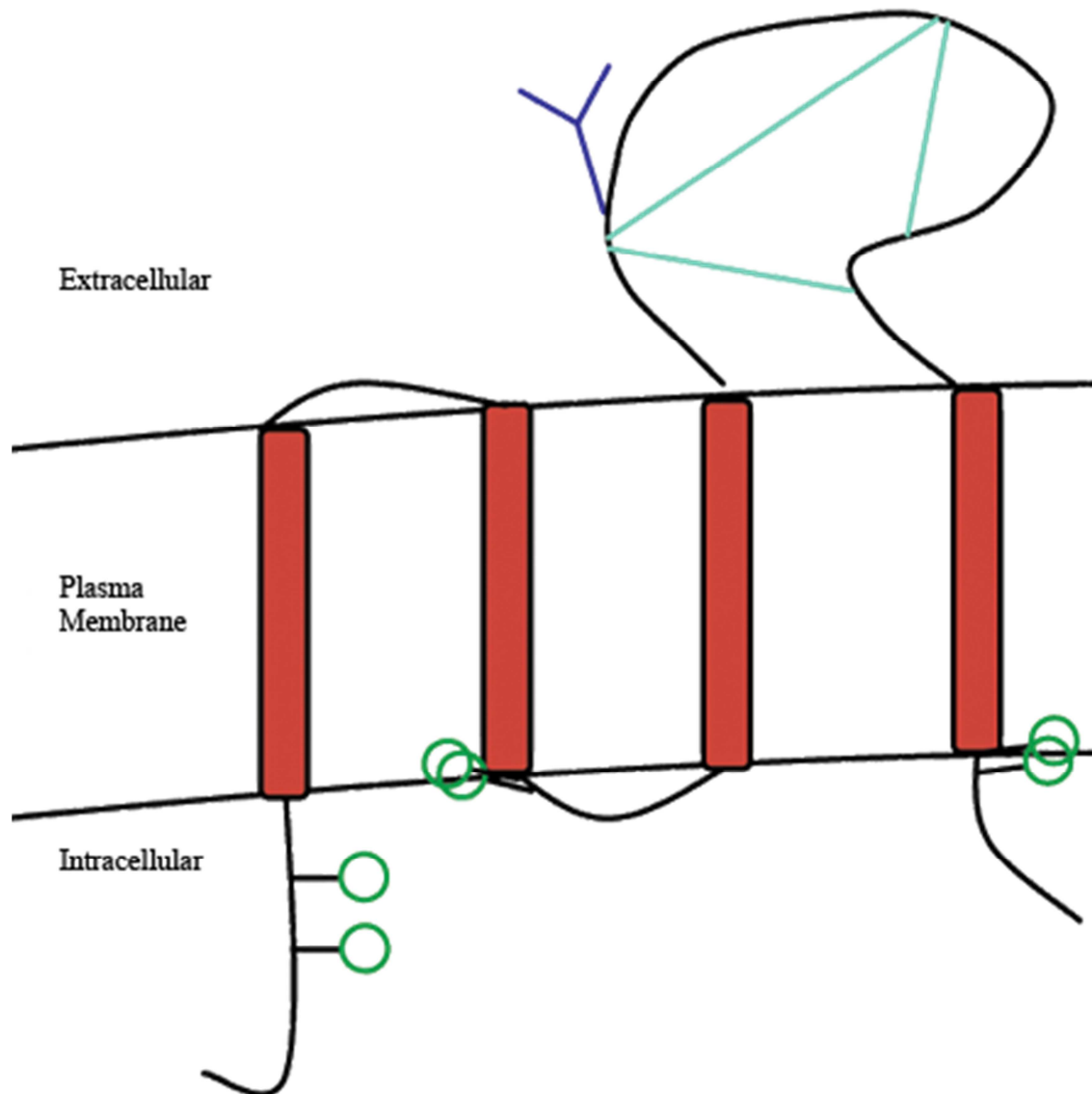
Post-translational modifications include disulphide bridges and an N-linked glycosylation site in the large extracellular loop and 6 palmitoylation sites.

#### Expression

Widely expressed, particularly on epithelial cells, endothelial cells, Schwann cells, muscle cells, megakaryocytes and platelets. Tissues typically display expression restricted to these cell types with lung, kidney, spleen, tonsil and cardiac muscle all having high levels. Low expression detected on fibroblasts, erythrocytes and leukocytes (Sincock et al., 1997).

Highly expressed (mRNA) in: heart, uterus, lung, prostate, liver (adult), spleen, placenta, pancreas.

Low/no expression (mRNA) in: foetal liver, brain, testes, ovaries.



The red bars indicate transmembrane regions as predicted by TMHMM (Krogh et al., 2001), with the green circles palmitoylation sites (Berditchevski et al., 2002). The blue Y indicates an N-linked glycosylation site (Fitter et al., 1995) and the light blue lines indicate approximate sites of potential di-sulphide bridges (Seigneuret et al., 2001).

### Localisation

Plasma membrane, endosomes, endothelial cell junctions and hemidesmosomes in basal epithelial cells (Sincock et al., 1999; Sterk et al., 2000).

### Function

CD151 is a major component of tetraspanin enriched microdomains, which are platforms for assembly of membrane signalling complexes (Hemler et al., 2005; Charrin et al., 2009). CD151 functions in signal transduction through forming direct complexes with integrins particularly  $\alpha 3\beta 1$ ,  $\alpha 6\beta 1$ ,  $\alpha 6\beta 4$  and  $\alpha 11\beta 3$ , thereby influencing a variety of cell functions including motility and adhesion which are outlined further below. CD151 also affects matrix metalloproteinase activity, with overexpression of CD151 in human melanoma cells

resulting in increased expression of MMP9 (Hong et al., 2006). CD151 has been shown to interact with pro-matrix metalloproteinase 7 in osteoarthritic cartilage and regulate its activity (Fujita et al., 2006). In endothelial cells CD151 associates with the matrix metalloproteinase MT1-MMP and regulates its collagenolytic activity (Yañez-Mó et al., 2008).

### Homology

Tetraspanin protein family. This protein family has 33 members in humans and is well conserved throughout vertebrates and also present in invertebrates. Key characteristics include the presence of 4 transmembrane domains with both N- and C-terminals in the cytoplasm, conserved cysteine-containing motifs and disulphide bonds in the large extra cellular loop and charged residues in the transmembrane domains.

## Mutations

### Note

Only 3 mutations have been identified in humans to date, two (G533A and C511T), are predicted not to significantly alter CD151 function and are not associated with disease (Karamatic Crew et al., 2004; Karamatic Crew et al., 2008).

### Germinal

Homozygous 1bp insertion, G383, resulting in a frameshift at Lys127 and a truncated protein at codon 140.

Homozygous G533A substitution resulting in an Arg178His mutation.

Homozygous C511T substitution resulting in an Arg171His mutation.

## Implicated in

### Note

#### In vitro studies

In vitro assays on Cd151-null keratinocytes, showed lack of migration compared to wild-type keratinocytes (Geary et al., 2008). Over-expression and knock-down studies of CD151 in various cell lines generally show that CD151 promotes migration and adhesion, however these findings are influenced by cell type and extracellular matrix components and primarily appear to be modified by the expression of the integrin alpha3beta1 (Berditchevski et al., 2002; Winterwood et al., 2006; Liu et al., 2007; Yang et al., 2008). CD151 is down-regulated by HIF-1alpha in colon cancer cells and is re-expressed upon normal oxygenation. This is proposed to allow detachment from the primary tumour and re-attachment at sites of metastasis (Chien et al., 2008).

#### Oncogenesis

Increased CD151 expression may lead to enhanced tumour progression and metastatic capacity based on enhanced motility, migration and adhesion of CD151 expressing cells. Antibodies to CD151 blocked in vivo metastasis in model systems (Testa et al., 1999; Zijlstra et al., 2008). Xenograft breast cancer models involving silencing of CD151 showed a delay in tumour formation (Yang et al., 2008). CD151 expression is increased in metastasis compared to primary tumour site in colon cancer (Chien et al. 2008).

#### Prostate cancer

##### Note

Immunohistochemical detection of CD151 in a prostate cancer tissue specimens had greater prognostic value than Gleason grading (Ang et al., 2004).

##### Prognosis

High CD151 expression was indicative of poor outcome.

#### Oncogenesis

High CD151 expression indicated poor survival outcome, suggesting a role for CD151 in enhancing tumorigenesis or resistance to treatment. Also refer to 'In vitro studies'.

#### Gingival squamous cell carcinoma

##### Note

Real-time PCR analysis of CD151 gene expression compared to GAPDH was analysed (Hirano et al., 2009). Assessment of protein expression by immunohistochemistry correlated with gene expression however no statistical analyses were performed on protein expression.

##### Prognosis

High CD151 expression was indicative of poor outcome.

#### Oncogenesis

High CD151 expression indicated poor survival outcome, suggesting a role for CD151 in enhancing tumorigenesis or resistance to treatment. Also refer to 'In vitro studies'.

#### Colon cancer

##### Note

Real-time PCR analysis of CD151 gene expression compared to beta-actin was analysed (Hashida et al., 2003). Assessment of protein expression by immunohistochemistry correlated with gene expression however no statistical analyses were performed on protein expression.

##### Prognosis

High CD151 expression was indicative of poor outcome.

#### Oncogenesis

High CD151 expression indicated poor survival outcome, suggesting a role for CD151 in enhancing tumorigenesis or resistance to treatment. Also refer to 'In vitro studies'.

#### Hepatocellular carcinoma

##### Note

Real-time PCR analysis of CD151 gene expression compared to GAPDH was analysed. Assessment of protein expression by immunohistochemistry and immunoblotting generally correlated with gene expression. CD151 expression was increased in hepatocellular carcinomas compared to normal liver tissues (Ke et al., 2009).

Immunohistochemical analysis of tissue microarrays identified a positive correlation between CD151 expression and aggressive histopathological factors such as vascular invasion and poor tumour differentiation. CD151 expression was also indicative of poor outcome (Ke et al., 2009).

**Prognosis**

High CD151 expression was indicative of poor outcome.

**Oncogenesis**

High CD151 expression indicated poor survival outcome, suggesting a role for CD151 in enhancing tumourigenesis or resistance to treatment. Also refer to 'In vitro studies'.

**Non-small cell lung carcinoma****Note**

Real-time PCR analysis of CD151 gene expression compared to beta-actin was analysed (Tokuhara et al., 2001). Assessment of protein expression by immunohistochemistry correlated with gene expression however no statistical analyses were performed on protein expression.

**Prognosis**

High CD151 expression was indicative of poor outcome.

**Oncogenesis**

High CD151 expression indicated poor survival outcome, suggesting a role for CD151 in enhancing tumourigenesis or resistance to treatment. Also refer to 'In vitro studies'.

**Breast cancer****Note**

Immunohistochemical analysis of CD151 expression in a cohort of invasive ductal carcinoma identified a significantly higher risk of death from breast cancer in CD151 positive tumours compared to CD151 negative tumours. CD151 expression was also positively associated with the involvement of regional lymph nodes. No associations between CD151 expression and other clinical factors including estrogen receptor status were found (Sadej et al., 2009).

Immunohistochemical analysis of CD151 in breast tissue Microarrays identified positive correlations between CD151 expression and high tumour grade as well as negativity for the estrogen receptor. No other associations were identified between CD151 expression and clinical factors (Yang et al., 2008). Associations between CD151 expression and outcome were not able to be made due to unavailability of data.

**Prognosis**

High CD151 expression was indicative of poor outcome.

**Oncogenesis**

High CD151 expression indicated poor survival outcome, suggesting a role for CD151 in enhancing tumourigenesis or resistance to treatment. Also refer to 'In vitro studies'.

**Pancreatic cancer****Note**

Immunohistochemical analysis of pancreatic cancer cell lines and pancreatic tumours identified high CD151 expression associated with tumours/cell lines compared to normal tissue. Tumour stroma also expressed CD151 (Geiserich et al., 2005).

**Oncogenesis**

Refer to 'In vitro studies'.

**Neovascularisation/pathologic angiogenesis****Note**

Determined from in vivo studies in Cd151-null mice and in vitro studies of Cd151-null mouse lung endothelial cells (Takeda et al., 2007). Analysis of a rat myocardial ischaemia model also showed that viral delivery of CD151 can promote neovascularisation (Zheng and Liu, 2006).

**Disease**

Cancer, ischaemia

**Oncogenesis**

Lack of Cd151 expression resulted in impaired tumour angiogenesis, suggesting that Cd151 may be involved in promoting tumour angiogenesis.

**Nephropathy****Note**

CD151 is expressed normally in the kidney particularly in the glomerular basement membrane (Sincock et al., 1997).

**Disease**

Nephropathy in humans (Karamatic Crew et al., 2004). Cd151-null mice develop progressive renal failure on the FVB/N strain but not the C57BL/6 strain (Sachs et al., 2006; Baleato et al., 2008).

**Prognosis**

Loss of CD151 activity leads to chronic renal failure.

**Cytogenetics**

Homozygous frameshift mutation causing a premature stop codon (codon 140) due to the insertion of 1bp in exon 5 of CD151 (G383).

**Hybrid/Mutated gene**

Resultant protein lacks the integrin binding domain and causes null expression of the CD151/MER2 antigen (Karamatic Crew et al., 2004).

**Pretibial epidermolysis bullosa****Note**

The Nephropathy described above is attributed to the

same mutation in CD151 and occurs in conjunction with pretibial epidermolysis bullosa and deafness (Karamatic Crew et al., 2004).

Wound repair in wild-type mice is associated with an up-regulation of Cd151 in the migrating epidermis at the wound edge (Cowin et al. 2006).

#### Disease

Pretibial epidermolysis bullosa in humans.

Defective wound repair in Cd151-null mice (Cowin et al. 2006; Geary et al 2008).

#### Cytogenetics

Homozygous frameshift mutation causing a premature stop codon (codon 140) due to the insertion of 1bp in exon 5 of CD151 (G383).

#### Hybrid/Mutated gene

Resultant protein lacks the integrin binding domain and causes null expression of the CD151/MER2 antigen.

#### Deafness

##### Note

This loss of function of CD151 is attributed to the same mutation in CD151 as that described above for nephropathy and pretibial epidermolysis bullosa, with all 3 disorders occurring in the same patients (Karamatic Crew et al., 2004).

#### Prognosis

Progressive deafness occurring by early adulthood.

#### Cytogenetics

Homozygous frameshift mutation causing a premature stop codon (codon 140) due to the insertion of 1bp in exon 5 of CD151 (G383).

#### Hybrid/Mutated gene

Resultant protein lacks the integrin binding domain and causes null expression of the CD151/MER2 antigen.

#### Hemostasis

##### Note

As assessed in Cd151-null mice, loss of Cd151 caused increased bleeding time and decreased clotting ability, suggesting endothelial and/or platelet cell functional defects. Cd151-null mice did not show any overt physiological differences unless challenged (Wright et al., 2004). Further in vitro analysis of Cd151-null platelets showed impaired functions relating to aggregation, spreading and clot retraction (Lau et al., 2004).

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*This article should be referenced as such:*

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