

## Gene Section

### Review

# DVL1 (dishevelled, dsh homolog 1 (Droso-phila))

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Published in Atlas Database: June 2011

Online updated version : <http://AtlasGeneticsOncology.org/Genes/DVL1ID463ch1p36.html>

DOI: 10.4267/2042/46080

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## Identity

**Other names:** DVL; DVL1L1; MGC54245

**HGNC (Hugo):** DVL1

**Location:** 1p36.33

## DNA/RNA

### Note

A human DVL1 cDNA was first isolated from a human adult caudate cDNA library by screening with a 200 bp RT-PCR fragment obtained from human fetal brain total RNA that was probed with oligonucleotides corresponding to the mouse Dishevelled homolog (Pizzuti et al., 1996). The cDNA recovered encoded a 670 amino acid protein that was termed DVL-1L.

Around the same time, Semenov and Snyder (1997) cloned and characterized 3 human homologs of the Drosophila Dishevelled gene, one of which encoded DVL1, a 695-amino acid protein (GenBank: AF006011.1).

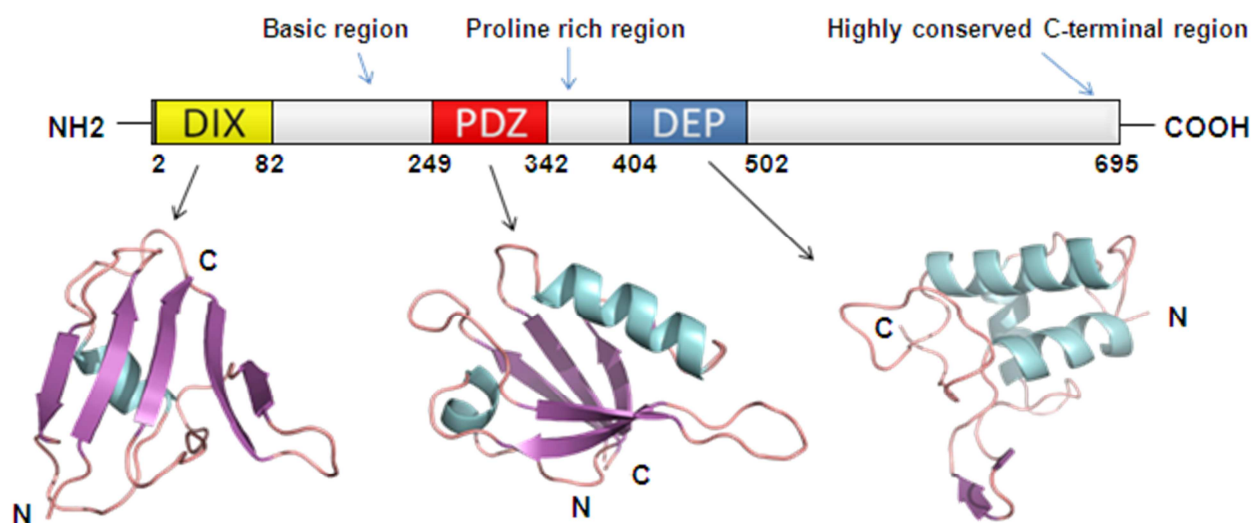
### Description

The DVL1 gene comprises 15 verified exons.

## Protein

### Description

Human DVL1 encodes DVL1 protein, which contains 695 amino acid residues (size 75.2 kDa) (Semenov and Snyder, 1997). DVL1 comprises three domains, DIX (aa 1-82, **DI**shevelled-**aXin**),



**Schematic diagram of DVL1 protein.** Homology model respective structure of DIX, PDZ, or DEP domain in DVL1 protein was generated by using X-ray and NMR structures (for DIX domain, PDB code: 3PZ8; for PDZ domain, PDB codes: 1L06 and 1MC7; for DEP domain, PDB code: 1FSH).

PDZ (aa 249-342, Post Synaptic Density-95, Discs large and Zonula-occludens 1), and DEP (aa 404-502, Dishevelled-EGL-10-Pleckstrin) (Wharton, 2003; Malbon and Wang, 2006; Wallingford and Habas, 2005). In the mouse, the DIX domain of Dvls can associate with the DIX domain of Axin and Dvls (Schwarz-Romond et al., 2007a; Schwarz-Romond et al., 2007b). The PDZ domain of Dvls is the protein-protein interaction module (Wong et al., 2003; Lee and Zheng, 2010) and at least 20 Dvl-binding partners were reported (Wallingford and Habas, 2005). The DEP domain of Dvl proteins has a polybasic stretch region that is responsible for its membrane-targeting activity (Wong et al., 2000; Simons et al., 2009). Furthermore, Dvl proteins have conserved regions harboring positively charged (basic) amino acid residues, proline-rich putative Src-homology 3 (SH3) binding domains (Penton et al., 2002), and highly conserved C-terminal regions (Wallingford and Habas, 2005), but their roles are unknown.

**Structure.** The overall structure of the intact DVL1 protein remains unknown; however, each individual domain in DVL1 has been investigated. The 3D structure of the DIX domain of Dvl-1 has not been reported. The homology model of the DVL1 DIX domain was generated from the 3D structure of the Axin DIX domain (PDB code: 1WSP) and that of a mutant DIX(Y17D) was solved by using X-ray crystallography (PDB code: 3PZ8), which consists of 4 beta-sheets and 1 helix structures (Schwarz-Romond et al., 2007a; Liu et al., 2011). The structure of DVL1's PDZ domain comprises 6 beta-sheets (betaA~betaF) and 2 alpha-helices (alphaA and alphaB) (Wong et al., 2003). The DEP domain of DVL1 consists of a helix bundle with three  $\alpha$ -helices (H1-H3), a beta-hairpin "arm" composed of two beta-strands (B1 and B2) between H1 and H2, and two short beta-strands (B3 and B4) (Wong et al., 2000).

### Expression

DVL1 gene is found in fetal and adult tissues, including brain, lung, kidney, skeletal muscle, and heart; according to Northern blot analysis, the highest mRNA levels are found in adult skeletal muscle, pancreas, and heart muscle (Pizzuti et al., 1996).

### Localisation

Normally present in cytoplasm. After activation of Wnt signaling, the translocation of DVLs is occurred from the cytoplasm to the plasma membrane (Park et al., 2005; Simons et al., 2009) and to the nucleus (Torres and Nelson, 2000; Itoh et al., 2005; Gan et al., 2008).

### Function

Dvl family proteins mediate Wnt signaling pathways: Wnt/beta-catenin, Wnt/JNK (planar cell polarity or convergent extension), and Wnt/Ca<sup>2+</sup> signaling (Klingensmith et al., 1994; Li et al., 1999; Boutros and Mlodzik, 1999; Wallingford et al., 2000; Gao and Chen, 2010). The DIX and PDZ domains are used for

canonical Wnt signaling; the PDZ and DEP domains are used for non-canonical Wnt signaling. After Wnt activates signaling, CK1epsilon, CKII, PKCalpha, or Par-1 kinases hyperphosphorylate Dvl proteins on serine/threonine residues (Yanagawa et al., 1995; Peters et al., 1999; Sakanaka et al., 1999; Kishida et al., 2001; Schulte et al., 2005; Kibardin et al., 2006; Klimowski et al., 2006; Bilic et al., 2007; Zhang et al., 2007; Zeng et al., 2008). DVL1 can interact with a variety of other binding partners including protein phosphatases and kinases (Boutros and Mlodzik, 1999; Williams et al., 2005).

**Binding partners**

- **AXIN** interacts with the DIX domain of DVLs, which leads to the activation of beta-catenin-mediated signaling (Li et al., 1999; Smalley et al., 1999; Cliffe et al., 2003; Kishida et al., 1999; Schwarz-Romond et al., 2007a; Schwarz-Romond et al., 2007b; Fiedler et al., 2011).

- **BP75** (bromodomain-containing M(r) 75000 protein) binds to the DIX domain of mouse Dvl1 in mammalian cells and enhances Wnt signaling by inactivating GSK3beta (Kim et al., 2003).

- **CK1epsilon** (casein kinase Iepsilon) binds to the Dvl proteins and increases the phosphorylation of DVLs in a variety of tissue culture and in vitro assays (Peters et al., 1999; Sakanaka et al., 1999; Kishida et al., 2001). CK1epsilon phosphorylates two highly conserved residues, S139 and S142, of mouse Dvl1 protein, as confirmed by mass spectroscopy. Phosphoserines -139 and -142 are positive regulators of Dvl1-dependent Wnt signal transduction (Klimowski et al., 2006). In *Drosophila*, CK1epsilon phosphorylates the Ser236 residue in Dsh protein as confirmed by mutagenesis analysis (Klein et al., 2006). In *Xenopus*, CK1epsilon activates the Wnt/beta-catenin signaling pathway positively. The interaction between the kinase domain of CK1epsilon and the PDZ domain of *Xenopus* Dishevelled (Xdsh) was identified by a yeast two-hybrid assay (Peters et al., 1999). However, another study suggested that the entire DEP domain, but not the PDZ domain, is necessary for the binding of DVL1 to CK1epsilon in mammalian intact cell assays (Kishida et al., 2001). In *Drosophila*, studies suggested that CK1epsilon facilitates both Wnt/beta-catenin and Wnt/PCP signaling pathways (Strutt et al., 2006; Klein et al., 2006). Consistent with this finding, CK1epsilon activates Dvl proteins via non-canonical Wnt ligands in SN4741 cells, suggesting that CK1epsilon-mediated phosphorylation of Dvl proteins may be a common step in both canonical and non-canonical pathways (Bryja et al., 2007).

- **CKII** (casein kinase II) is a serine/threonine kinase that can phosphorylate and associate with the PDZ domain of *Drosophila* Dsh (or DVLs) (Willert et al., 1997; Lee et al., 1999).

- **Diversin** regulates heart formation and gastrulation movements during development. Diversin's ankyrin repeats are necessary for interaction with the DVL DEP

domain, for activation of the non-canonical Wnt signaling pathway, and for other biological responses (Moeller et al., 2006).

- **Dapper** (Dpr) binds to the PDZ domain of DVL1, which inhibits the Wnt/beta-catenin signaling (Wong et al., 2003). However, another study showed that human DPR1 can bind the DEP domain of DVL1 and inhibit Wnt signaling by promoting DVL1 degradation (Zhang et al., 2006).

- **Daam1**, a Formin-Homology (FH) protein, binds to both DVL and Rho proteins and mediates Wnt-induced Dvl1-Rho complex formation. *Xenopus* Daam1 regulates gastrulation (Habas et al., 2001).

- **EphrinB1** interacts with the PDZ domain of Dishevelled. In *Xenopus* embryos, EphrinB1 plays a role in retinal progenitor cell movement into the eye field through an interaction with DVL (Tanaka et al., 2003; Lee et al., 2006; Lee HS et al., 2009). Phosphorylation of tyrosines 324 and 325 disrupts the EphrinB1/Dsh interaction, thus modulating retinal progenitor movement that is dependent on the planar cell polarity pathway (Lee HS et al., 2009).

- **Frat** protein was originally isolated on the basis of its tumor-promoting activity in human lymphocytes (Jonkers et al., 1997). It also binds to the basic region (aa 220-230) of DVL1 (Li et al., 1999; Hino et al., 2003), an interaction that is enhanced by CK1epsilon, which activates Wnt/beta-catenin signaling (Hino et al., 2003).

- **Frizzled (Fz)** protein, a key component of Wnt signaling, interacts with Dvl proteins (Wong et al., 2003; Shafer et al., 2011). NMR studies showed that a peptide derived from a conserved motif (KTxxxW) located two amino acids C-terminal to the seventh transmembrane domain of Fz directly binds to the PDZ domain of Dvl-1, implying that its interaction is necessary for activating the Wnt/beta-catenin signaling (Wong et al., 2003). Interestingly, Dvl-1 can inhibit PCP signaling by increasing hyperphosphorylation of Fz3 and preventing its internalization (Shafer et al., 2011).

- **Idax** (Inhibition of the Dvl and AXin complex) bound to the PDZ domain of DVL was identified in a rat brain cDNA library that was screened by the yeast two-hybrid method (Hino et al., 2001). Idax interacts with DVL in intact cells also. NMR spectroscopy identified the minimum region in rat Idax protein required for binding to mouse Dvl1 PDZ domain as the internal sequence of the KTxxxI motif (London et al., 2004). Idax suppresses the Wnt3a-dependent accumulation of beta-catenin and activation of Tcf in L cells (Hino et al., 2001). The levels of CXXC4 mRNA, which encodes the protein Idax, in renal cell carcinoma were significantly lower in patients with metastases than in patients without metastases ( $P=0.0016$ ) (Kojima et al., 2009).

- **Naked cuticle** (Nkd) regulates early Wnt activity by

acting as an inducible antagonist. The Nkd EFX domain interacts with the basic/PDZ domain of *Drosophila* Dsh or DVLs in the yeast two-hybrid assay (Wharton et al., 2001).

- **MuSK** kinase domain interacts with Dvl1 DEP domain in a mouse muscle cell line and in HEK293 cells transfected with the mouse constructs, which plays an important role in the agrin- and neuro-induced AChR (acetylcholine receptor) clustering (Luo et al., 2002). In Dvl1 mutant mice AChR clusters had a more disperse distribution at the endplate (Henriquez et al., 2008).

- **PAR-1** is a serine/threonine kinase. In *Drosophila*, Par-1 binds to and phosphorylates Dsh/Dvl protein and promotes Wnt/beta-catenin signaling at the expense of JNK signaling (Sun et al., 2001). Par-1 target sites in Dsh are essential for proper Dsh translocation from the cytoplasmic vesicles to the cell cortex but not for Dsh activity in the canonical Wnt/beta-catenin pathway. Different PAR-1 isoforms mediate two distinct and essential roles in *Xenopus* axial development. PAR-1BY plays an essential role in the PCP branch and mediates Dsh membrane localization while PAR-1A and PAR-BX are essential for canonical Wnt signaling, possibly via targets other than Dishevelled (Ossipova et al., 2005). Mammalian Par-1b promotes cell-cell adhesion and inhibits Dvl-mediated transformation of Madin-Darby canine kidney cells.

- **PIP5K1** (phosphatidylinositol-4-phosphate 5-kinase type I) and DVL co-immunoprecipitate when they are overexpressed in HEK293 cells. The N-terminal half of the PIP5K1beta kinase domain interacts with Dvl1 fragment that contains the DIX and PDZ domains; Wnt3a may regulate this interaction (Pan et al., 2008).

- **Ror2** is a receptor tyrosin kinase (RTK) binds the Dvl C-terminus (Witte et al., 2010).

- **Syndecan-4 (Syn4)** interacts with Dvl protein and also functionally and biochemically with the Wnt receptor Fz7 in *Xenopus* embryos (Muñoz et al., 2006).

- **Transmembrane 88 (TMEM88)**, a two-transmembrane-type protein, interacts with the PDZ domain of Dvl. Using NMR spectroscopy, the interaction between the C-terminal tail of TMEM88 and the PDZ domain of Dvl-1 was confirmed (Lee et al., 2010). In HEK293 cells, TMEM88 attenuated the Wnt/beta-catenin signaling induced by Wnt-1 ligand in a dose-dependent manner, and TMEM88 knockdown by RNAi increased Wnt activity. In *Xenopus*, TMEM88 protein is sublocalized at the cell membrane and inhibits Wnt signaling induced by Xdsh, but not beta-catenin (Lee et al., 2010).

### Homology

Three DVL genes (DVL1, DVL2, and DVL3) have been isolated in mammals and *Xenopus*. Dvl homologs are conserved in *Drosophila* (*dishevelled, dsh*).

## Implicated in

### Breast cancers

#### Note

The DVL1 gene is amplified and DVL1 protein is over-expressed in 13 of 14 primary breast cancers examined. DVL1 protein is prominent in the cytoplasm of cancer cells, but not in normal epithelial cells of the mammary duct or in myoepithelial cells (Nagahata et al., 2003; Schlange et al., 2007). In invasive ductal carcinoma of the breast, immunohistochemical analysis of 96 tumor samples showed that 30% of tumors displayed both nuclear and cytoplasmic staining of DVL protein, while 52% showed nuclear localization. There is a correlation between nuclear localization of DVL and beta-catenin ( $p < 0.01$ , OR=15.8) (Prasad et al., 2007).

### Cervical squamous cell carcinoma

#### Note

Up-regulation and overproduction of DVL1 mRNA were found in these malignant cells (Okino et al., 2003). DVL1 protein was prominent in the cytoplasm of cancer cells whereas it was unreactive in the surrounding normal cervical squamous cells (Okino et al., 2003).

### Prostate cancer

#### Note

Semi-quantitative PCR in 20 primary prostate cancers and assessed the protein expression revealed that DVL1 is significantly overexpressed in prostate cancer (65%). A correlation between DVL1 expression and beta-catenin expression was confirmed (Mizutani et al., 2005).

### Lung cancer

#### Note

RT-PCR of 13 matched normal and invasive squamous cell carcinoma samples revealed that the tumors significantly overexpressed Notch and Wnt pathway family members, including DVL1 ( $P=0.003$ ), LRP8 ( $P=0.008$ ) and NOTCH2 ( $P=0.029$ ) (Garnis et al., 2005). All DVL family members are expressed in non-small cell lung cancer (Wei et al., 2008). The expression levels of DVL1 and DVL3 are significantly higher in nodal metastases than in primary growths, and DVL1 expression is correlated with beta-catenin expression in the metastases (Wei et al., 2008).

### Irritable bowel disease (IBD)-related colon cancer

#### Note

You et al. (2007) found that DVL1 was uniformly expressed in the affected tissues of IBD patients and sporadic colon cancer patients, even though no DVL1 expression was seen in the normal tissues of the same patients. Remarkably, DVL2 and DVL3 were expressed in all normal mucosa samples tested, and

were expressed in sporadic colon cancer but were not expressed in colon cancers arising in patients with IBD (You et al., 2007).

## To be noted

#### Note

**Animal model.** Mice lacking Dvl1 are viable, fertile, and structurally normal; however, they exhibit abnormal social behavior and sensorimotor gating (Lijam et al., 1997). Mutant mice lacking both DVL-1 and DVL-2 have revealed that DVL proteins are required during neural fold closure and cardiac development, but not during early axial patterning (Hamblet et al., 2002; Lijam et al., 1997). Phenotypes of double DVL-1 and DVL-2 mutants display the skeletal defects, organ of corti defects, conotruncal defects, and craniorachishisis; and phenotypes of double DVL-1 and DVL-3 mutants display lethality between E13.5 and E15.5 (Etheridge et al., 2008).

**Pharmaceutical target.** In Wnt/beta-catenin signaling, Wnt ligands bind to the co-receptors of both LRP5/LRP6 and Frizzled (Fz), a 7-membrane domain protein, and activate the phosphoprotein DVL (Wallingford and Habas, 2005). The activated DVL protein relays the Wnt signals to the downstream components. Although the role of DVLs in Wnt signaling is not completely understood, the protein-protein interaction between the membrane-bound Fz receptor and the DVL PDZ domain in the cytoplasm plays a role in transducing the Wnt signals downstream (Umbhauer et al., 2000; Wong et al., 2003; Bilic et al., 2007). In *Xenopus*, peptides bound to the DVL PDZ domain attenuate Wnt-induced signaling at the DVL level (Wong et al., 2003). In addition, in several cancer models, peptides and small molecules bound to the DVL PDZ domain inhibit the Wnt signaling induced by Wnt ligands (Wang et al., 2008; Shan et al., 2005; Zhang et al., 2009; Shan and Zheng, 2009; Grandy et al., 2009; Lee et al., 2009a; Lee et al., 2009b). Interestingly, sulindac, a non-steroidal anti-inflammatory drug with chemoprotective effects for several cancer types, interacts with DVL in this fashion (Lee et al., 2009b). Thus, developing inhibitors of the DVL PDZ domain is very attractive because these inhibitors could be used as tools to dissect molecular mechanisms and as potential pharmaceutical agents (Wang et al., 2008).

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- Lee HJ, Zheng JJ. DVL1 (dishevelled, dsh homolog 1 (Drosophila)). *Atlas Genet Cytogenet Oncol Haematol*. 2011; 15(12):998-1004.
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