Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Review

AFDN (afadin, adherens junction formation factor)

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Abstract

Afadin, the protein coded by AFDN (6q27), also known as AF6 or MLLT4, is a cytoskeletal and junction-associated protein that links nectins, transmembrane proteins, to the F-actin (actin cytoskeleton) in a type of cell-cell junctions: the adherens junctions (AJs). Afadin plays an important role in AJs integrity and apical-basal polarity. There is growing evidence of it's role in carcinogenesis.

Keywords
Afadin; AFDN; AF6; MLLT4; Cytoskeleton; Cell-cell junctions; Adherens junctions; Apical-basal polarity; Epithelial-mesenchymal transition; Tight junctions; Mitotic spindle orientation; Migration; Nectin; Actin; Acute myeloid leukemia; Breast cancer; Colon cancer; Pancreatic cancer; Endometrial cancer; Gastric cancer; Osteosarcoma; Neurone synapse.

Identity

HGNC (Hugo): AFDN

Location: 6q27

Other names: MLLT4, AF6

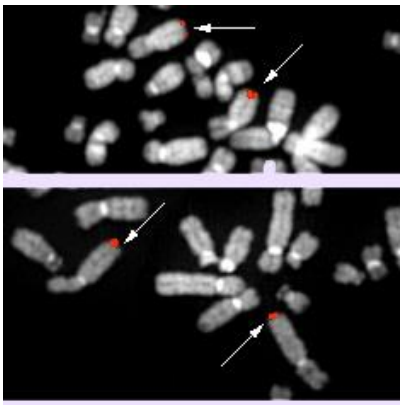


Figure 1 Localization of AFDN (also called AF6 or MLLT4) - Courtesy Mariano Rocchi.

DNA/RNA

Description

The AFDN gene, located on 6q27, has a genomic size of 145,030 bases and encodes for several transcripts on the position chr6:167826991-167972020 in the + strand.

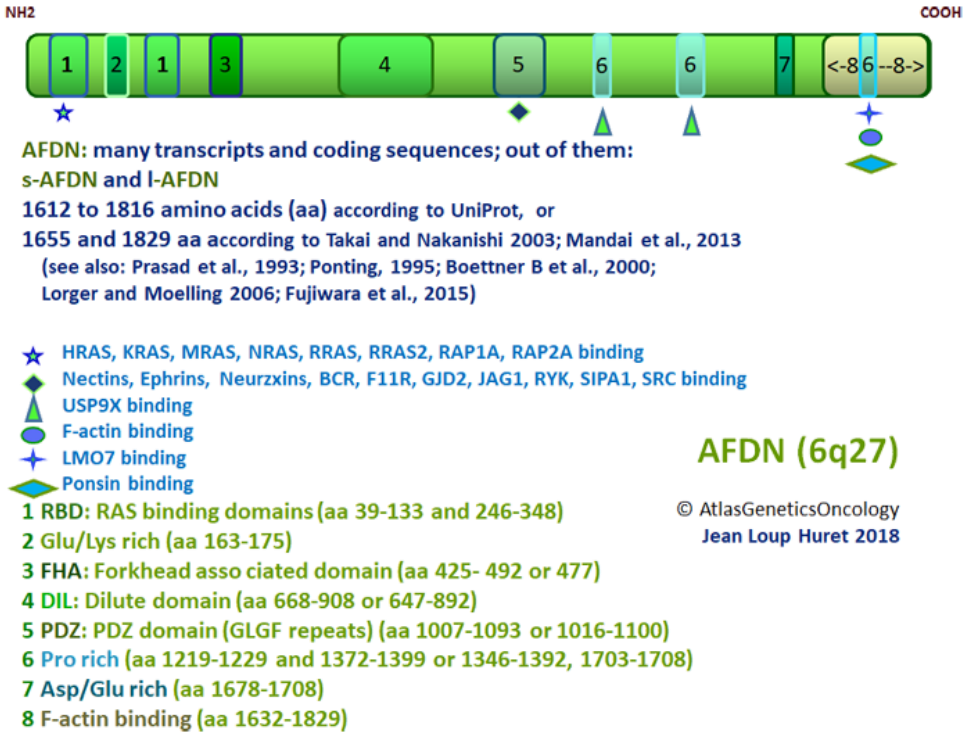


Figure 2 Afadin protein

Transcription

According to RefSeq, there are 3 transcripts (see below) and an anti-sens (NR_027906)
AFDN at chr6:167826991-167972020 - (NM_001207008) afadin isoform 1: 7,459 bp
AFDN at chr6:167826991-167965113 - (NM_001040000) afadin isoform 2: 7,629 bp
AFDN at chr6:167827635-167972020 - (NM_001291964) afadin isoform 4: 7,750 bp
PSEUDOGENE

Protein

Description

The AFDN gene codes for the afadin protein.
From N-term to C-term, afadin possess two Ras-association (RA) domains, a forkhead-associated (FHA) domain, a DIL domain (responsible for actin stress fiber formation (Saito et al., 2015)), a PDZ domain (responsible for binding the cytoplasmic C-terminus of nectins; where TJP1 (ZO-1) also binds (Kuriyama et al., 1996)), three proline-rich (PR) domains, one of which interacts with USP9X (FAM): (aa 1130-1612) (Hock et al., 199; Taya et al., 1998), and an F-actin-binding domain (see Figure 2).
PDZ domain (PDZ): GLGF (glycine-leucine-glycine-phenylalanine):
IITVT**L**KKQN**G**M**GL**SIVAAK**G**A**G**QDK**LG**IYV KSVVK**GG**AADVD**G**R**L**AA**G**DQ**LL**SVD**G**RS**L** V**GL**SQERAAE**L**MTRTSSVVT**L**EVAKQ**G** (Prasad et al., 1993).

Phosphorylation sites: KE**R**Q**R**LF**S**QG (aa 1792-1801 according to UniProt). There is an AKT phosphorylation site at Ser1718 in l-Afadin (large variant, see below). Phosphorylation of l-Afadin by AKT at Ser1718 promotes nuclear localization, which enhances migration and perturbs cell to cell adhesion (Ellol et al. 2014).
Afadin has many splice variants, in particular two of them: the larger l-afadin and the smaller s-afadin. s-Afadin lacks the F-actin-binding domain and the third proline-rich domain. These variants are made of 1612 to 1816 amino acids (aa) according to UniProt, or 1655 and 1829 aa according to others (see Figure 2).
l-Afadin links nectins to actin filaments (F-actin). Through its PDZ domain, l-Afadin binds to the nectin conserved motif of four amino acid residues (Glu/Ala-X-Tyr-Val) (except for nectin-4), and F-actin through its F-actin-binding domain. Afadin binds nectins (NECTIN1, NECTIN2, NECTIN3, NECTIN4), but not nectin-like molecules (Necls: CADM1, CADM2, CADM3, CADM4, PVR) (Review in Ogita and Takai, 2006).
Afadin forms homodimer.
The 3 main isoforms produced by alternative splicing are:
Canonic sequence (Isoform 4, identifier: P55196-4). 1,824 amino acids; 206,804 Da.
s-afadin (Isoform 1, identifier: P55196-2); 1,612 aa; 182,000 Da. Compared to the canonical sequence, are missing aa: 139, 393-407, 1605-1628, 1629-1824.

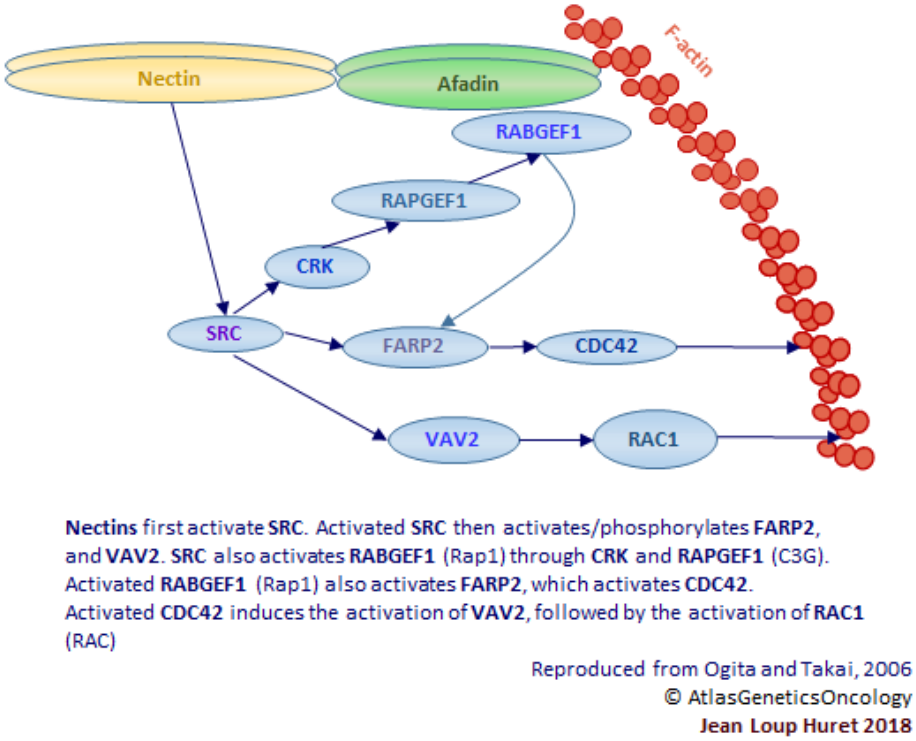


Figure 3 Nectin/Afadin: nectin activations.

l-afadin (Isoform 2, identifier: P55196-1); 1,816 aa; 205,605 Da. Compared to the canonical sequence, are missing aa: 139, 393-407, 1048-1048, 1747-1824.

Expression

L-afadin is widely expressed in epithelial cells, while s-afadin expression is restricted to the brain (Buchert et al., 2007)

Localisation

Afadin is mainly located at the cell junctions named adherens junctions. s-afadin is able to localize both to the plasma membrane or to the nucleus while l-afadin was said to be unable to localize to the nucleus (Buchert et al., 2007).

Function

Epithelial cells contain three types of cell-cell junction: tight junctions, localized in the apex of the cells, adherens junctions (AJs), and desmosomes.

Adherens junctions: two types of cell adhesion molecules (CAMs), cadherins and nectins, interact with actin filaments (F-actin). They interact through their cytoplasmic domain to form adherens junctions.

Cadherins and nectins: In epithelial cells, β-catenin (CTNNB1) directly binds to cadherins and links it to the actin cytoskeleton through &alpha-catenin (CTNNA1, CTNNA2, CTNNA3), while nectins are linked to the actin cytoskeleton through afadin (Tachibana et al., 2000; Ogita and Takai, 2006) (see Figure 4).

Nectins first activate SRC. Activated SRC then activates/phosphorylates FARP2, and VAV2. SRC also activates RABGEF1 (also known as Rap1) through CRK and RAPGEF1 (C3G).

Activated RABGEF1 (Rap1) also activates FARP2, which activates CDC42 40012. Activated CDC42 induces the activation of VAV2, followed by the activation of RAC1 (RAC) (see Figure 3).

Activated RABGEF1 (Rap1) is essential for down-regulation of Rho signaling and actin stress fiber dissolution (Birukova et al., 2013).

Some of the downstream effectors for VAV2 and RAC1 are actin filaments (F-actin)-binding proteins.

Nectins associate with cadherins through the interaction of afadin with alpha-catenin and: a ponsin (SORBS1) - vinculin (VCL) unit, an SSX2IP (ADIP) - a-actinin (ACTN1, ACTN2 and ACTN3) unit, and a LMO7 - a-actinin unit (see Figure 4). RABGEF1 (Rap1) activates afadin to interacts with CTNND1 (p120 catenin) and strengthens its binding to E-cadherin (CDH1), which results in reduced E-cadherin endocytosis (Bégay-Müller et al., 2002; Kooistra et al. 2007; Sakisaka et al., 2007 ; Birukova et al., 2013; Takeichi 2014)

Tight junctions/role of ZO-1 Afadin also associates transiently with tight junction protein TJP1 (ZO-1). ZO-1 is a member of F-actin-binding ZO proteins, which bind CAMs of tight junctions (TJs) such as claudins, occludin (OCLN), and junctional adhesion molecules (JAMs) and link them to the actin cytoskeleton (Sakisaka et al., 2007) (see Figure 4). Occludin, EPHA2, a transmembrane tyrosine kinase

receptor, and afadin also cooperate in tight junction organization (Perez White et al., 2017). Afadin is therefore a peripheral component of tight junctions in epithelial cells. The binding of claudins to tight junction proteins (or zonula occludens ZOs) and afadin and other proteins constitutes a step in cellular signal transduction (Zhang et al., 2018).

Apico-basal polarization/role of Par-3: PARD3 (Par-3), Par-6 and atypical protein kinase C (PRKCI) are required for apico-basal polarization of epithelial cells. Nectin-1 and nectin-3, but not nectin-2, bind the PDZ domain of Par-3 (Rakotomamonjy et al., 2017)

1- Par-3 regulates association of afadin with trans-interacting nectin and the formation of AJs;

2- Par-3 regulates E-cadherin-induced activation of Rac and formation of AJs;

3- Par-3 and afadin cooperatively regulate nectin-induced formation of TJs (Sakisaka et al 2007)

Migration Afadin is localized at cell-cell contact sites in mesangial cells. Afadin forms a complex with CTNNB1 (β-catenin) in cultured mesangial cells and Afadin regulates migratory polarity (Tsurumi et al., 2016). Afadin is required for the maintenance of the radial glial scaffold for neuronal migration during cortical development (Yamamoto et al., 2015b).

Mitotic spindle orientation Afadin is required for mitotic spindle orientation and correct epithelial morphogenesis (Carminati et al., 2016). Afadin orients the mitotic spindle and is required for lumen continuity in developing renal tubules by orienting the mitotic spindle during cell division (Gao et al., 2017). Afadin controls cell polarization and mitotic spindle orientation in developing cortical radial glia (Rakotomamonjy et al., 2017).

Actin polymerization/profilin profilin plays an important role in actin polymerization. Profilin 1 and Profilin 2 (PFN1 and PFN2) are afadin-binding protein (Boettner B et al., 2000)

MAPK cascade Afadin interacts with HRAS, KRAS, and NRAS GTPases and the Ras-related RAP1A leading to MAPK activation (Yamamoto et al., 1997). MRAS, whose GTP/GDP cycle is sensitive to the Ras GEFs, SOS1 42355, and RASGRF1 43453 (GRF1) and to RASA1 (p120 RASGAP) interacts with Afadin (Quilliam et al. 1999). RRAS, RRAS2 also interact with Afadin (Linnemann et al., 1999). Afadin also acts downstream of EGFR-Ras and provides a link from EGFR to cytoskeletal elements in the cell motility process (Gaengel and Mlodzik 2003).

Ubiquitination Afadin is a substrate of the USP9X deubiquitinating enzyme. USP9X can release ubiquitin from Afadin (Taya et al., 1998).

Ephrin receptors Eph receptor tyrosine kinases are membrane-bound proteins implicated in cell migration and intercellular communication during embryonic development, regulating cell pattern formation during organogenesis. EPHA7, EPHB2, EPHB3, and EPHB6 interact with Afadin. Afadin is phosphorylated specifically by EPHB3 and EPHB2 (Hock et al., 1998)

Homology

Homologs of the AFDN gene: The AFDN gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, C.elegans, and frog (Orthologs from Annotation Pipeline: 201 organisms have orthologs with human gene AFDN).

Implicated in

Top note

AFDN is implicated in a few translocations and/or fusion genes, in particular in the t(6;11) seen in leukemia (see Figure 5).

Down regulation of afadin appears to drive to carcinogenesis in a number of cancer types.

t(6;11)(q27;q23)/AML --> KMT2A/AFDN

Disease

Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) of children and adults. Translocation t(6;11) represent about 5% of acute leukemia with 11q23/KMT2A rearrangement and is more frequent in AML than in ALL (Prasad et al., 1993; review in Huret 2018).

Prognosis

The prognosis is poor.

Cytogenetics

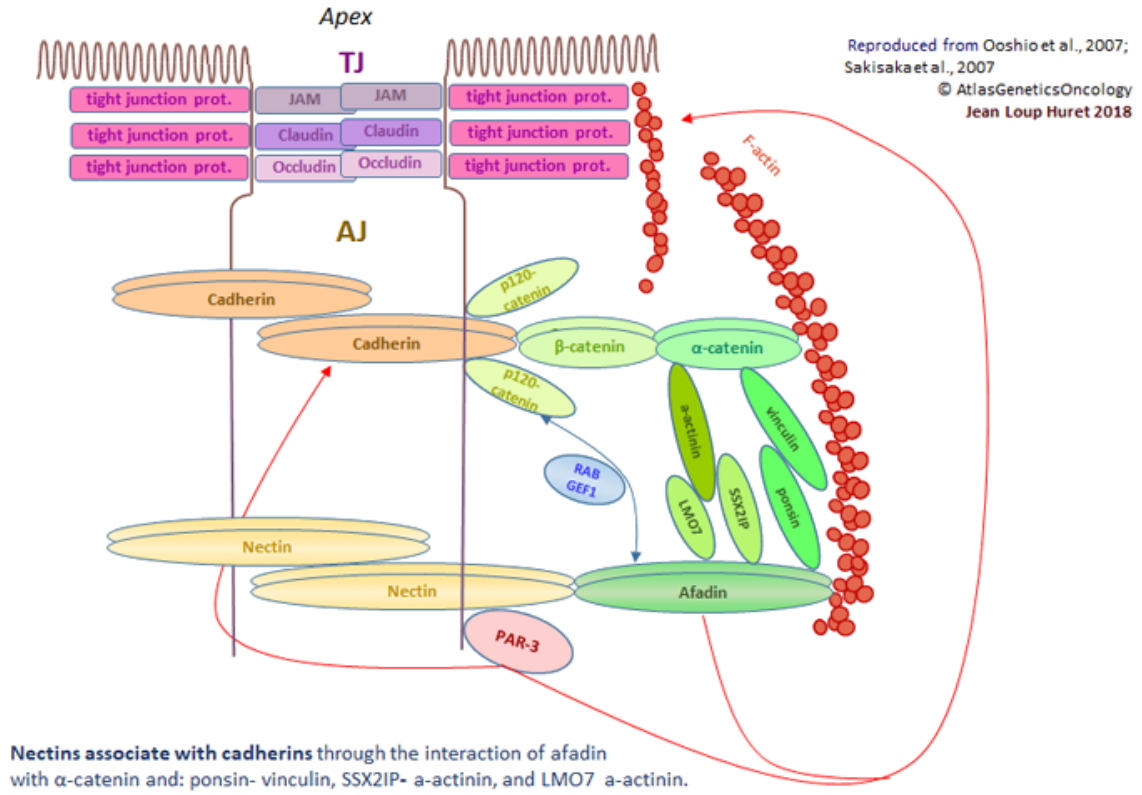
may be overlooked; The t(6;11) is the sole abnormality in most cases, but may be accompanied with, +8, +19 and+21.

Hybrid/Mutated gene

5' KMT2A- 3' AFDN

Abnormal protein

NH2-term KMT2A (with the AT hook and DNA binding motifs) is fused to most of AFDN. KMT2A/AFDN, through constitutive self-association and in cooperation with the histone-methyltransferase DOT1L, activates aberrant gene expression (Deshpande et al., 2013). KMT2A/AFDN directly upregulates BHLHE41 (SHARP1) by DOT1L. SHARP1 binds to transcriptionally active chromatin. Suppression of SHARP1 induces robust apoptosis. The circadian clock transcription factor SHARP1 as an oncogenic target in KMT2A/AFDN cells (Numata et al., 2018).



Nectins associate with cadherins through the interaction of afadin with α-catenin and: ponsin- vinculin, SSX2IP- a-actinin, and LMO7 a-actinin.
RABGEF1 (Rap1) activates afadin to interacts with CTNND1 (p120 catenin) and strengthens its binding to E-cadherin
Tight junctions (TJ) and adherens junctions (AJ)
Claudins, occludin, and junctional adhesion molecules (JAMs) bind tight junctions proteins (TJP), which link them to the actin cytoskeleton. Afadin associates transiently with TJP1 (ZO-1).
Par-3, Par-6 and atypical protein kinase C (aPKC) are required for **apico-basal polarization** of epithelial cells.
Nectins bind Par-3. Par-3 regulates association of afadin with nectin and the formation of Ajs, regulates E-cadherin-induced activation of Rac and formation of AJs; Par-3 and afadin cooperatively regulate nectin-induced formation of TJs

Figure 4 Afadin in adherens junctions (**AJ**) and tight junctions (**TJ**)

AFDN is expressed in the cytoplasm of normal cells and controls RAS levels. By contrast, in KMT2A/AFDN localize in the nucleus, leading to aberrant activation of RAS and of its downstream targets (Joh et al. 1997).

Breast carcinoma

In breast cancer, loss of afadin protein expression induces cell migration and cell invasion (Yamamoto et al., 2015a), and is associated with adverse prognosis (Letessier et al., 2007; Fournier et al., 2011). Afadin loss of expression (in 15% of breast carcinoma) is also associated with an increased risk of metastatic relapse (Fournier et al., 2011).
The nuclear localization of L-Afadin, regulated by phosphorylation at Ser1718 by the Akt pathway, is clinically relevant for breast cancer progression (Ellol et al. 2014).
The fusion gene AFDN/ KCNAB1 has been found in breast adenocarcinoma (Yoshihara et al., 2015).
The fusion gene AFDN/ HMGCLL1 has also been found in breast adenocarcinoma (Hu et al. 2018).

Uterus cancer

Afadin expression was significantly associated with myometrial invasion and high histological grade in uterine corpus endometrial carcinoma (Yamamoto et al., 2015a).
The fusion gene ATG5/AFDN has been found in uterine carcinosarcoma (Hu et al. 2018).

Ovarian serous cystadenocarcinoma

The fusion gene AFDN/ UNC93A has been found in ovarian serous cystadenocarcinoma (Yoshihara et al., 2015).

Prostate adenocarcinoma

The fusion gene AFDN/ EXOC6B has been found in prostate adenocarcinoma (Yoshihara et al., 2015).
The fusion gene AFDN/ SYK has also been found in prostate adenocarcinoma (Hu et al. 2018).

Clear cell renal cell carcinoma

The fusion gene AFDN/ TTLL2 has been found in clear cell renal cell carcinoma (Hu et al. 2018).

Colon cancer

Lower expression of CFTR and/or afadin is correlated with a poor prognosis in colon cancer (Sun et al., 2014). Loss of afadin induces cell migration and cell invasion (Yamamoto et al., 2015a).

Pancreatic cancer.

Afadin is expressed at low levels in pancreatic cancer. Depletion of Afadin promotes proliferation through upregulation of the expression of SNAIL proteins, and this requires the nuclear localization of afadin (Xu et al., 2015).

Gastric cancer

Helicobacter pylori disrupts cell-cell junctions through down regulation of afadin and induces epithelial to mesenchymal transition (EMT) of gastric cells, leading to the acquisition of an aggressive phenotype, which can contribute to gastric carcinogenesis (Marques et al., 2018).
AFDN antisense RNA 1 (AFDN-AS1) is significantly downregulated in gastric cancer and a predictor of a poor prognosis (Lai et al., 2017).

Low grade glioma

The fusion gene AFDN/ SASH1 has been found in low grade glioma (Yoshihara et al., 2015).

Osteosarcoma

High expression of CLDN2 (claudin2) induces high expression of afadin, which results in silencing of the MAPK signaling pathway and inhibits the metastasis phenotype in osteosarcoma cells (Zhang et al., 2018).

Lung squamous cell carcinoma

The fusion gene AFDN/ GMDS has been found in squamous cell carcinoma of the lung (Hu et al. 2018).

Neurone synapse and nucleus

Afadin signaling at synapses contributes to activity-dependent spine morphogenic activity. Following stimulation by 17β-estradiol, afadin locates to both synapses and the nucleus. Accumulation of afadin in the nucleus induces phosphorylation of kinases MAPK3 / MAPK1 (pERK1/2), phosphorylation of RPS6KA1 (p90RSK) that can directly phosphorylate histone H3 at serine 10 (H3S10p.). This in turn contributes to long term alterations in synapse structure (VanLeeuwen et al., 2014; Sellers et al., 2018).

Breakpoints

See Figure 5.

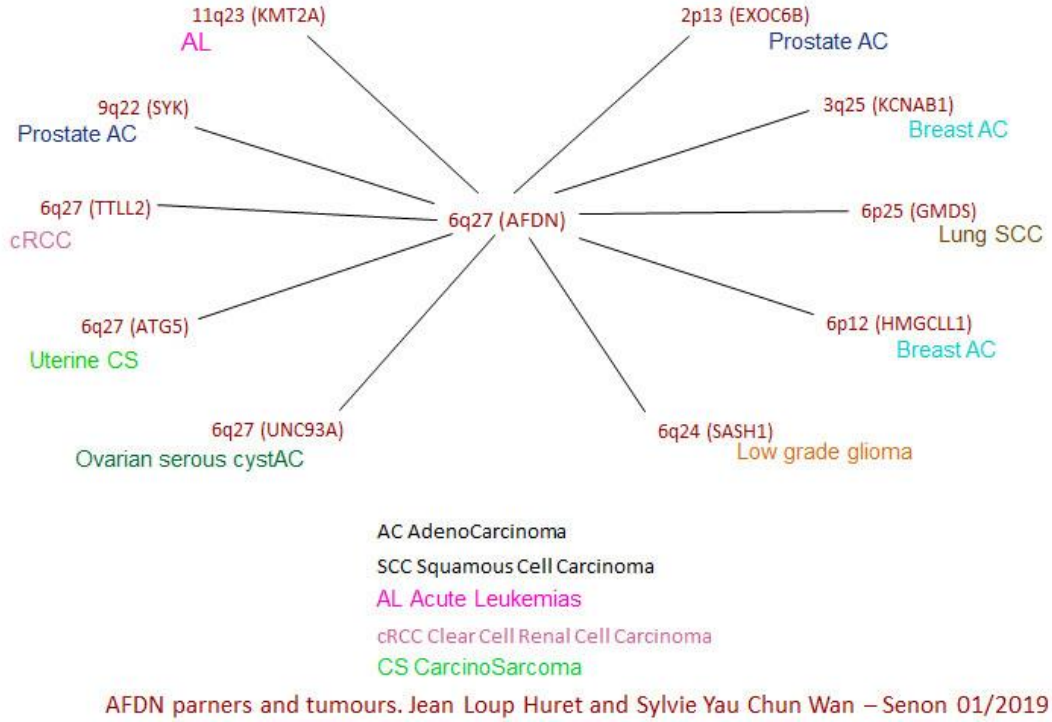


Figure 5 ADFN fusion partners.

To be noted

TARGET THERAPY
Targeting the DVL2 - FOXE1 -Snail signalling axis may thus represent a promising therapeutic strategy (Xu et al., 2015)
Exposure of KMT2A/AFDN -rearranged AML blasts to tipifarnib, a RAS inhibitor, leads to cell autophagy and apoptosis, thus supporting RAS targeting as a novel potential therapy (Manara et al. 2014).

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