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# Gene Section
**Review**

# FAT1 (FAT tumor suppressor homolog 1 (Drosophila))

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## Identity

**Other names:** CDHF7; CDHR8; FAT; ME5; hFat1

**HGNC (Hugo):** FAT1

**Location:** 4q35.2

**Note**

FAT1 is an ortholog of the Drosophila tumor suppressor gene 'fat'. In Drosophila, it is essential for controlling cell proliferation during development. The gene product is a member of the cadherin superfamily, characterized by the presence of cadherin-type repeats. In addition to containing 34 tandem cadherin-type repeats, the gene product has five epidermal growth factor (EGF)-like repeats and one laminin A-G domain. This gene is expressed at high levels in a number of fetal epithelia. Its product probably functions as an adhesion molecule and/or signaling receptor, and is likely to be important in developmental processes and cell-cell communication.

## DNA/RNA

### Description

FAT1 gene is located on the chromosome 4q35.2 (Accession: NC_000004.11). The total length of the gene is 136050 bases (187509746 bp to 187630981 bp from pter) of reverse strand. There are 27 exons.
An alternate assembly suggested to be starting from 187745931 bp to 187881981 bp from pter.

### Transcription

The length of the transcript is 14773 bps made from 27 exons (Accession: NM_005245.3).

### Pseudogene

FAT tumor suppressor homolog 1 (Drosophila) pseudogene 1 (FAT1P1).
Other name: dJ697P8.1; sequence accession ID: AL050403; location chromosome: 20p12.2.

## Protein

**Note**

Known protein coding gene.
Protein names
Recommended name: protocadherin Fat 1.
Alternative names: Cadherin-related tumor suppressor homolog, Protein fat homolog, Cadherin family member 7.

### Description

4588 aa (Accession: NP_005236.2).

### Expression

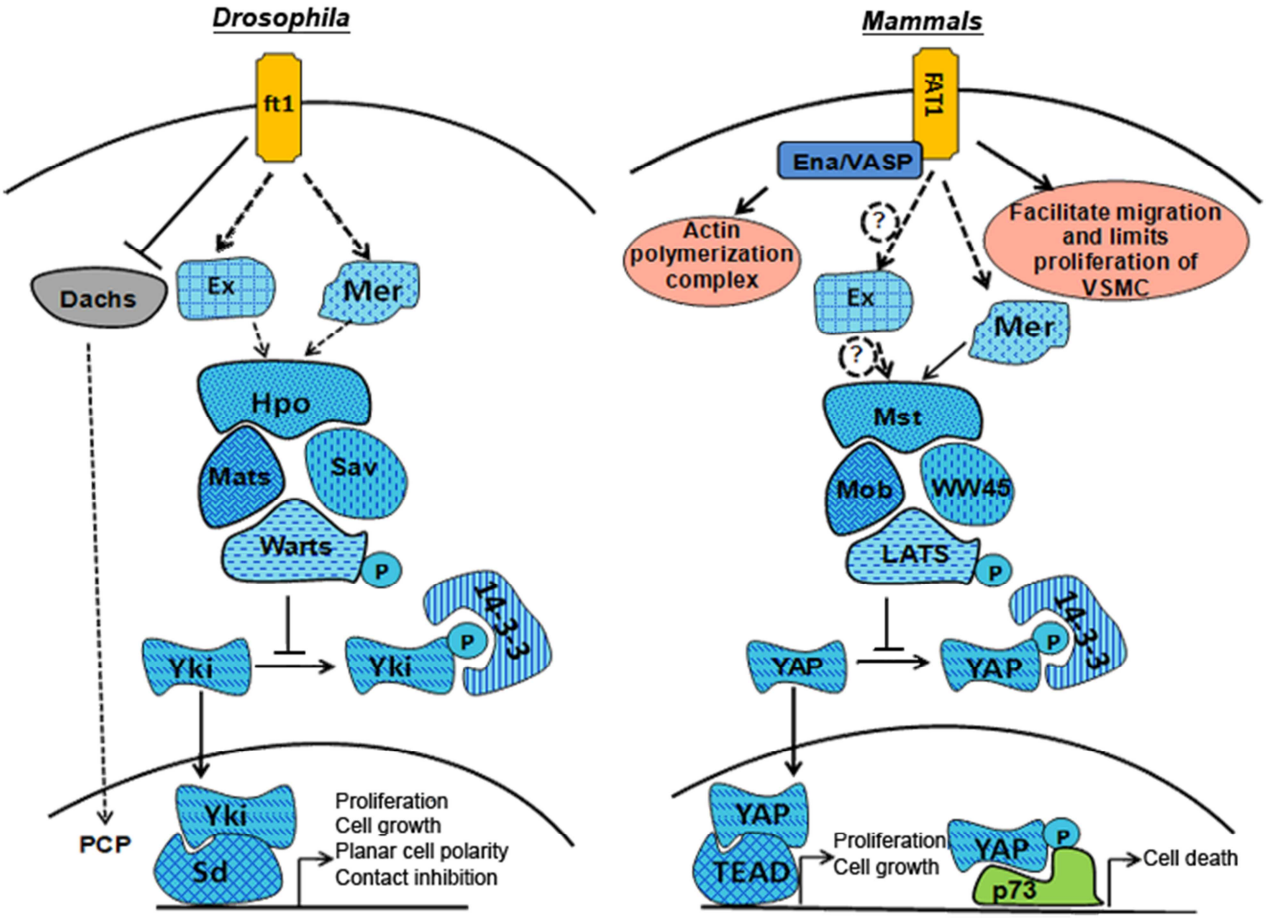
Expressed in epithelial, endothelial and smooth muscle cells.

### Localisation

Cell membrane; single-pass type I membrane protein.

### Function

Could function as a cell-adhesion molecule, cell signalling molecule, and have a role in cell migration.
Fat in Drosophila acts via SWH signalling pathway as tumour suppressor gene. Homolog of SWH pathway molecules are present in human, so there is a possibility of acting FAT1 as an upstream regulator of SWH pathway in human.




**Salvador-Warts-Hippo pathway.** Mammalian hippo signaling pathway shows homology with Drosophila pathway proteins (depicted in similar color and shape).
In Drosophila fat (ft) interacts with core kinase cascade via Expanded (Ex). The core kinase cascade includes kinase Hippo (hpo), adaptor proteins mats and Salvador (Sav) and kinase Warts. The core kinase cascade inhibits phosphorylation of transcriptional co-activator Yorkie (Yki) causing its translocation to nucleus where it binds to transcriptional activator Scalloped (Sd) and modulates gene expression.
In mammals, whether FAT1 is involved in hippo pathway regulation is not clear. The effector molecule, phospho-YAP, is reported to interact with p73 in the nucleus and promotes cell death. There is no p73 homolog known to be reported in Drosophila. YAP is also found to interact with other transcription factors and modulate gene expression, thus, the outcome of hippo pathway is context dependent.

| Organism | Gene | Locus | Description | Similarity to human FAT1 |
|---|---|---|---|---|
| **Dog** (Canis familiaris) | FAT1 | Chr. 16 | FAT tumor suppressor homolog 1 (Drosophila) | 86.95(n), 91.17(a) |
| **Pig** (Sus scrofa) | FAT1 | Chr. 17 | FAT tumor suppressor homolog 1 (Drosophila) | 86(n), 90(a) |
| **Cow** (Bos Taurus) | FAT1 | Chr. 27 | FAT tumor suppressor homolog 1 (Drosophila) | 84.18(n) 89.93(a) |
| **Rat** (Rattus norvegicus) | Fat1 | Chr. 16q11 | FAT tumor suppressor homolog 1 (Drosophila) | 82.93(n) 88.16(a) |
| **Mouse** (Mus musculus) | Fat1 | Chr. 8 (25.00 cM) | FAT tumor suppressor homolog 1 (Drosophila) | 82.51(n) 88.14(a) |
| **Chicken** (Gallus gallus) | FAT | Chr. 4 | FAT tumor suppressor homolog 1 (Drosophila) | 76.35(n) 81.43(a) |
| **Zebrafish** | fat1 | Chr. 1 | FAT tumor suppressor | 64.68(n) 64.82(a) |

| | | | | |
|---|---|---|---|---|
| (Danio rerio) | | | homolog 1 | |
| **Fruit fly** (Drosophila melanogaster) | ft and fat2 | Chr. 2L (ft) Chr. 3L (fat2) | fat and fat2 | ft - 42.8(n) 42(a), fat2 - 47.99(n) 39.02(a) |
| **Worm** (Caenorhabditis elegans) | cdh-4 | Chr. III | Cadherin family | 44.19(n) 30.89(a) |
| **African malaria mosquito** (Anopheles gambiae) | AgaP_AGAP011526 | Chr. 3L | AGAP011526-PA | 48.06(n) 39.5(a) |

**Table. Orthologs for FAT1 gene from other species.**

In human, FAT1 expression is highest at the embryonic stages and diminishes later in adult life. In human fetal tissues, high levels of FAT1 transcripts were found in kidney, lungs, and eye epithelia, and the expression was found to be down regulated in the corresponding adult tissues, indicating the role of FAT1 in organ development. FAT1 also has a role in cell migration (Moeller et al., 2004; Tanoue and Takeichi, 2004) and found to be up-regulated in migrating cells, also crucial for efficient wound healing (Braun et al., 2007).

In Drosophila, fat is an upstream regulator of the Salvador-Wart-Hippo (SWH) signaling pathway (Cho et al., 2006; Bennett and Harvey, 2006). The signalling molecules of SWH pathway are conserved in mammals (figure below) but the role of FAT1 as an apical regulator of SWH pathway in human has not yet been established.

### Homology

Paralogs for FAT1 gene: FAT2, FAT3, FAT4. See table above.

## Mutations

**Note**

No known mutations. Single nucleotide polymorphism (SNPs): gene: FAT1 (ENSG00000083857).

## Implicated in

### Various cancers

**Note**

FAT1, a member of the cadherin gene family, is homologue of Drosophila tumour suppressor gene fat. In Drosophila, fat gene is important in controlling cell proliferation during development and any defect in the expression of fat would lead to tumor development (Bryant et al., 1988). Dunne et al. (1995) have identified the human homologue and studied the tissue distribution of FAT transcripts in adult and fetal tissues.

Loss of heterozygosity and altered expression of FAT1 has been found in human glial tumors (Chosdol et al., 2009). Homozygous deletion of FAT1 gene was detected in oral cancer (Nakaya et al., 2007). Kwaepila et al. (2006) found higher FAT1 expression in more malignant form of breast cancer tissues by immunohistochemistry (IHC). There are studies showing LOH and/or deletion of the chromosome 4q34-35 region (which harbors FAT gene) in many tumors including gliomas. LOH was found in grade IV gliomas using microsatellite markers (Hu et al., 2002), though the gene itself has not been implicated. Other tumors like small cell lung carcinoma (Cho et al., 2002), hepatocellular carcinoma (Zhang et al., 2005; Chang et al., 2002) and cervical carcinoma (Backsch et al., 2005) etc showed alterations/LOH in the chromosomal 4q34-q35 locus and significant association of 4q34-q35 region with increased risk of progression of these tumors was suggested. Since the FAT gene is located in this region it may have an important role to play in the development and progression of these tumors.

### Astrocytic tumour

**Note**

Loss of heterozygosity and altered expression of FAT1 in astrocytic tumors (Chosdol et al., 2009).

### Breast cancer

**Note**

Increased FAT1 expression contributes to loss of duct formation, and increased cell migration and invasion in breast cancer (Kwaepila et al., 2006).

### Oral cancer

**Note**

Homozygous deletion of FAT in the cell lines and in primary oral cancers was studied. Homozygous deletion hot spots were observed in exon 1 (9/20, 45%) and exon 4 (7/20, 35%). The methylation status of the FAT CpG island in squamous cell carcinomas correlated negatively with its expression. Mutations in FAT is suggested as an important factor in the development of oral cancer. Moreover, loss of gene expression was identified in other types of squamous cell carcinoma (Nakaya et al., 2007).

### Psychiatric disorders

**Note**

Bipolar disorder: a positional cloning strategy, combined with association analysis have provided

evidence that a cadherin gene, FAT, confers susceptibility to bipolar disorder (Blair et al., 2006).

### *Cell migration*

**Note**

FAT1 is known to play role in cell migration. FAT1 knockdown decreases cell migration in vascular smooth muscle cells (Hou et al., 2006; Hou and Sibinga, 2009). FAT1 plays an integrative role in regulating cell migration by participating in Ena/VASP-dependent regulation of cytoskeletal dynamics (Moeller et al., 2004).

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