

## Gene Section

### Short Communication

# CASC5 (cancer susceptibility candidate 5)

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Published in Atlas Database: June 2012

Online updated version : <http://AtlasGeneticsOncology.org/Genes/AF15q14ID318.html>  
DOI: 10.4267/2042/48462

This article is an update of :  
Takimoto M. CASC5 (Cancer Sensitivity Candidate 5). *Atlas Genet Cytogenet Oncol Haematol* 2007;11(1):8-9.  
Huret JL, Charrin C. AF15q14 (ALL1 fused gene from 15q14). *Atlas Genet Cytogenet Oncol Haematol* 2000;4(2):47.

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## Identity

**Other names:** CT29, KNL1, AF15Q14, D40, PPP1R5, hKNL-1, hSpc105, AF15q14, KIAA1570

**HGNC (Hugo):** CASC5

**Location:** 15q15.1

## DNA/RNA

### Note

Whole genomic size is not determined, but consists of at least 10 exons.

### Transcription

D40/CASC5 mRNA expression is dominant in normal human testis and slight expression are observed in other organs, such as placenta. At least two alternative isoforms of cDNA were identified.

Analysis on cancer cell lines, such as HeLa, gave single band with 8,5 kb. There is another alternative splicing site at the 5' side of this gene that generates a short exon with 78 bp in cDNA.

There are potential other alternative splicing at cancer cell lines.

Northern blotting analysis on testis shows two bands with size of approximately 6 and 8,5 kb which are probably derived from the two isoforms.

## Protein

### Description

Encodes 1833 amino acids and 2342 amino acids.

### Expression

D40/CASC5 protein expressions with molecular weight of approximately 250 kDa and 300 kDa are observed in human testicular germ cells and cancer cell lines.

### Localisation

In germ cell of testis, significant high expressions of D40 protein are observed in nucleus of spermatocytes and pre-acrosome of spermatids. As D40 protein has no hydrophobic signal peptide in its amino terminal, it localizes outer surface of pre-acrosome membrane.

Kinetochores proteins, Knl 1 in *C. elegans*, Spc7 in *Schizosaccharomyces pombe*, Spc105c in *Saccharomyces cerevisiae* and dmSpc105 in *Drosophila* have sequence homology to D40, and it also was shown that D40 is localized in kinetochore in a human cancer cell line.

### Function

D40 is a one of kinetochore protein, constituting KMN (Knl1/Mis12 complex/Ndc80 complex) network. KMN network is the central hub of outer kinetochore, not only connecting mitotic chromosomes and spindles but also coordinating microtubule-binding and spindle assembly checkpoint (SAC) signaling.

There are two microtubule binding activity in KMN network, one in Ndc80/Nurf and the other in D40/Knl1. The N-terminal region of D40 protein binds to protein phosphatase I (PP1) and SAC proteins, Bub1 and BubR1, while the C-terminal half mediates KMN network. D40 binds to Bub1 and BubR1 kinases, through tetratricopeptide repeats (TPRs) of the SAC protein and KI motif of D40. PP1 interacts with RVSF motif of D40 protein, being recruited to kinetochore. PP1 stabilizes microtubule attachments to kinetochores, opposing Aurora B kinase that inactivates microtubule-binding. It is suggested that D40 play a role in SAC silencing through PP1 binding.

The C-terminal region of D40 interacts with Zwint-1 and Mis14 protein. The former mediates the binding

D40 to Ndc80 complex, and the latter is a part of Mis12 complex.

## Implicated in

### ***t(11;15)(q23;q14)/acute non lymphocytic leukemia (ANLL) -->MLL-CASC5***

#### Note

MLL gene and D40 (AF15q14) gene are reported to be translocated each other in three cases of leukemias.

### ***Lung cancer***

#### Note

In primary lung cancer, clinicopathological findings correlate with D40 expression. D40 mRNA expression is more frequent in the tumors with low differentiation than the ones with moderate and high differentiation. Further, the tumors derived from smoker express higher incidence of D40 mRNA than the ones from non-smoker. D40 is a member of cancer/testis gene family.

### ***Spermatogenesis***

#### Note

D40 expressions in testes of the patients with infertility were significantly lower than normal ones. As D40 protein expressions were observed in spermatocytes in seminiferous tube of human testes, D40 may also play a role in cell division as a kinetochore protein in meiotic cells. As D40 protein expressions are also observed in pre-acrosome of spermatids, especially from its early stage, it might be playing some role in acrosome formation.

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*This article should be referenced as such:*

Takimoto M. CASC5 (cancer susceptibility candidate 5). *Atlas Genet Cytogenet Oncol Haematol.* 2013; 17(1):1-2.

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