

## Gene Section

### Review

# CDC25A (cell division cycle 25A)

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## Identity

**Hugo:** CDC25A

**Other names:** CDC25A2

**Location:** 3p21

**Local order:** The gene is located telomeric to CAMP (cathelicidin antimicrobial peptide) and centromeric to LOC729349 (a pseudogene similar to 60S ribosomal protein L17 (L23)). The gene starts at 48,173,672 bp from pter and ends at 48,204,805 bp from pter with a total size of 31,133 bases.

## DNA/RNA

### Description

CDC25A is about 31.13 kb located on the short (p) arm of chromosome 3, in the centromere-to-telomere orientation. The gene has 15 exons and the start codon is located at the end of exon 1 and stop codon in the beginning of exon 15.

### Transcription

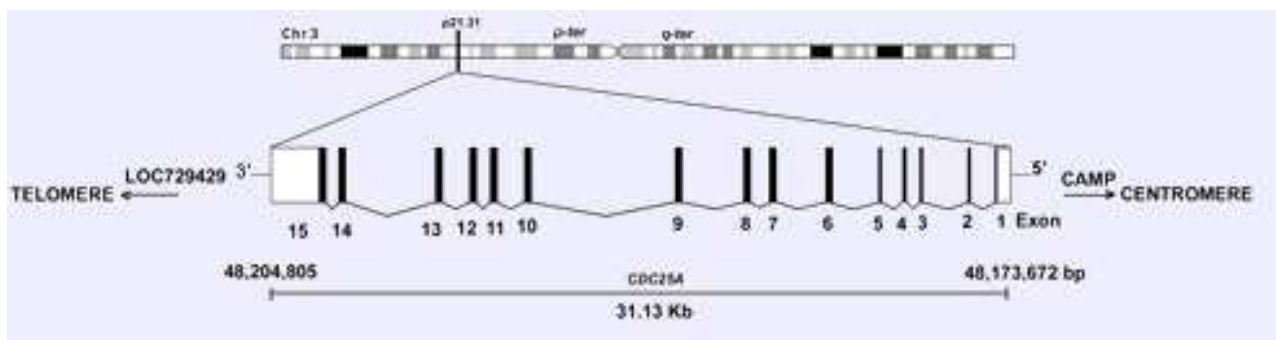
The CDC25A transcript is 3704 bp in length. So far there are two major transcript variant have been

reported, CDC25A1 and A2. The transcript variant CDC25A2, has a deletion of 120 nucleotide (exon 6) resulted in a protein having truncation of 40 amino acid (between amino acid 143-182). However, both the N-terminal and C-terminal end of the protein is the same in both splice variant.

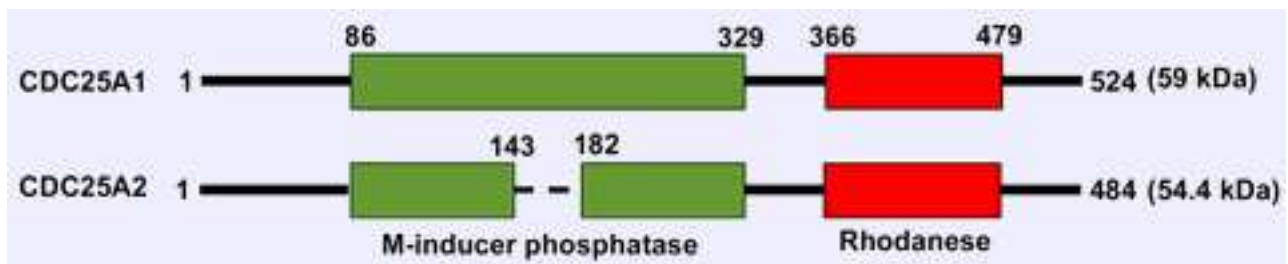
## Protein

### Description

The full length CDC25A protein consists of 524 amino acids with an estimated molecular weight of 59 kDa. The other reported isoform CDC25A2, consists of 484 amino acids with a molecular weight of 54.4 kDa. Both the isoforms have the same N- and C-terminal end, thus expected to have similar catalytic activity. The N-terminal regulatory domain contains several phosphorylation sites and show low sequence homology between CDC25 family members, whereas C-terminal end has conserved Rhodanese homology domain containing the active site cysteine. The catalytic site contain the CX5R motif (C= cysteine; X= any amino acid; R= arginine) common to all protein tyrosine phosphatases.



Genomic organization of human CDC25A gene on chromosome 3 p-ter.



Domains of different isoforms of CDC25A (A1 and A2). The splice variant A2 lacks an in-frame exon (exon 6) encoding 40 amino acids (amino acid 143-182), however, have the same N- and C-termini compared to isoform A1. The approx. molecular weight of each isoform is mentioned in parenthesis.

### Expression

CDC25A is expressed early during embryonic stages and in adults it is expressed in a variety of normal cells and tissues. CDC25A is a highly expressed gene in a variety of human cancers including breast, esophageal, gastric, lung, thyroid, head and neck cancers and also in high grade lymphomas.

### Localisation

CDC25A initially believed to be a nuclear protein. But using fluorescence loss in photobleaching (FLIP) the more dynamic nuclear-cytosolic shuttling of CDC25A localization have been reported. At the very N-terminus end between amino acid 38-59, the nuclear export sequence (NES) is located, whereas between amino acid 272-294, a bipartite nuclear localization signal (NLS) proved to be important for its nuclear localization.

### Function

- It is a member of the M-phase inducer (MPI) phosphatase family protein, which not only regulates mitotic progression by activating mitotic CDKs in a dosage-dependent manner, it is also equally important for G1 to S-phase transition.
- During G1 to S transition, it activates CDK2 by removing two inhibitory phosphates on residues threonine 14 and tyrosine 15. During G2/M transition CDC25A similarly regulates the activity of CDK1 (CDC2).
- It is an important checkpoint protein in response to damage by ionizing radiation (IR), ultraviolet light (UV), replication inhibitor and by various DNA damaging agents. In response to DNA damage, CDC25A undergoes CHK1/CHK2-mediated phosphorylation followed by ubiquitination-dependent degradation leading to growth arrest in a p53-independent manner.
- CDC25A is essential for early embryonic development as Cdc25A-null mice die in utero by embryonic day 7.
- CDC25A is overexpressed in a variety of human cancers including breast, esophageal, gastric, lung, thyroid, head and neck cancers and lymphomas. CDC25A overexpression at least in breast cancer is

mainly due to post-translation stabilization as oppose to gene amplification or transcriptional upregulation.

- CDC25A protein level is important for oncogene-induced transformation and mouse mammary tumor virus (MMTV)-neu/ras induced mammary tumorigenesis.
- During early cell cycle progression glycogen synthase kinase 3-beta (GSK-3beta) can phosphorylate and degrade CDC25A, thus maintain the lower cellular levels of CDC25A. Interestingly, the same report showed that overproduction of CDC25A in human cancers is correlated to the inactivation of GSK-3beta.
- It is an inhibitor of apoptosis by inhibiting apoptosis signal-regulating kinase 1 (ASK1).
- CDC25A plays an important role in spermatogenesis as decreased transcript level of Cdc25A is correlated with spermatogenic failure and failed sperm retrieval in infertile men.

### Homology

CDC25A gene is highly conserved among mammals (99% homology with Chimpanzee; 90% with dog; about 86% with rat and about 85% with mouse). In mammals, CDC25A has two orthologs, CDC25B and CDC25C. Among them, the N-terminal regulatory region show low sequence homology (20-25% identity), however, the C-terminal catalytic region is quite conserved with about 64% homology with CDC25B and about 58% homology to CDC25C.

### Mutations

**Note:** Gene mutation or amplification is not commonly reported for CDC25A. A naturally occurring point mutation (C to A) of mouse Cdc25A gene has been reported where Histidine 128 (CAC) has been converted to Glutamine (CAA). This change caused an increase in CDC25A phosphatase activity and thereby affected erythropoiesis in mice only under certain genetic background.

### Implicated in

**Note:** CDC25A is overexpressed in a variety of human cancers including breast, hepatocellular, ovarian, colorectal, esophageal, head and neck cancer and also in non-Hodgkin lymphoma.

## Breast cancer

**Note:** - In about 47% of early (T1) stage breast cancer patients CDC25A is reported to be overexpressed.

- Although the mechanism of CDC25A upregulation in human patients is not yet clear, however, in some breast cancer cell lines it was reported that CDC25A overexpression is mainly due to increased protein stability as oppose to gene amplification or transcriptional upregulation.

- In mice, overexpression of CDC25A alone in mammary gland using mouse mammary tumor virus (MMTV) promoter, is not sufficient to induce mammary tumorigenesis. However, such mammary specific overexpression of CDC25A does cooperate with HER2/neu-ras signaling to form more aggressive tumors with enhanced genomic instability.

- In contrast, hemizygous loss of Cdc25A in mice protected them significantly from MMTV-neu/ras-induced mammary tumorigenesis, possibly by restricting precancerous cell proliferation and also by enhancing G2-checkpoint response. Thus the protein level of CDC25A is crucial for the initiation and/or progression of breast tumorigenesis in mice.

### Prognosis

Overexpression of CDC25A is correlated with more aggressive breast cancer with poor prognosis.

### Cytogenetics

CDC25A overexpression in MMTV-CDC25A; MMTV-neu double transgenic mice caused faster tumor growth as compared to MMTV-neu single transgenic mice. Importantly, such CDC25A overexpressing tumor cells displayed miscoordination of S phase and mitosis, and had severe genomic instability as evidenced by aneuploidy and deletion of fragile chromosomal regions (e.g., telomeric region of chromosome 4, which is homologous to human chromosome 1p31-36, a hotspot for several human cancers including breast cancer).

## Hepatocellular carcinoma

**Note:** Different CDC25 inhibitor (such as vitamin K analog Cpd 5; phenyl maleimide compound PM-20; 2-Methoxyestadiol, a physiological metabolite of estrogen) are capable of inhibiting the hepatocellular carcinoma growth both in vitro and in vivo.

### Prognosis

CDC25A overexpression is associated with poor prognosis of hepatocellular carcinoma.

## References

Galaktionov K, Beach D. Specific activation of cdc25 tyrosine phosphatases by B-type cyclins: evidence for multiple roles of mitotic cyclins. *Cell* 1991;67(6):1181-1194.

Demetrick D, Beach DH. Chromosome mapping of human CDC25A and CDC25B phosphatases. *Genomics* 1993;18:144-147.

Mailand N, Falck J, Lukas C, Syljuåsen RG, Welcker M, Bartek J, Lukas J. Rapid destruction of human Cdc25A in response to DNA damage. *Science* 2000;288(5470):1425-1429.

Wegener S, Hampe W, Herrmann D, Schaller HC. Alternative splicing in the regulatory region of the human phosphatases CDC25A and CDC25C. *Eur J Cell Biol* 2000;79:810-815.

Bartek J, Lukas J. Mammalian G1- and S-phase checkpoints in response to DNA damage. *Curr Opin Cell Biol* 2001;13(6):738-47. (Review).

Wang Z, Southwick EC, Wang M, Kar S, Rosi KS, Wilcox CS, Lazo JS, Carr BI. Involvement of Cdc25A phosphatase in Hep3B hepatoma cell growth inhibition induced by novel K vitamin analogs. *Cancer Res* 2001;61(19):7211-7216.

Zou X, Tsutsui T, Ray D, Blomquist JF, Ichijo H, Ucker DS, Kiyokawa H. The cell cycle-regulatory CDC25A phosphatase inhibits apoptosis signal-regulating kinase 1. *Mol Cell Biol* 2001;21(14):4818-4828.

Mailand N, Podtelejnikov AV, Groth A, Mann M, Bartek J, Lukas J. Regulation of G(2)/M events by Cdc25A through phosphorylation-dependent modulation of its stability. *EMBO J* 2002;21(21):5911-5920.

Melkun E, Pilione M, Paulson RF. A naturally occurring point substitution in Cdc25A, and not Fv2/Stk, is associated with altered cell-cycle status of early erythroid progenitor cells. *Blood* 2002;100(10):3804-3811.

Löffler H, Syljuåsen RG, Bartkova J, Worm J, Lukas J, Bartek J. Distinct modes of deregulation of the proto-oncogenic Cdc25A phosphatase in human breast cancer cell lines. *Oncogene* 2003;22(50):8063-8071.

Xiao Z, Chen Z, Gunasekera AH, Sowin TJ, Rosenberg SH, Fesik S, Zhang H. Chk1 mediates S and G2 arrests through Cdc25A degradation in response to DNA-damaging agents. *J Biol Chem* 2003;278(24):21767-21773.

Xu X, Yamamoto H, Sakon M, Yasui M, Ngan CY, Fukunaga H, Morita T, Ogawa M, Nagano H, Nakamori S, Sekimoto M, Matsuura N, Monden M. Overexpression of CDC25A phosphatase is associated with hypergrowth activity and poor prognosis of human hepatocellular carcinomas. *Clin Cancer Res* 2003;9(5):1764-1772.

Källström H, Lindqvist A, Pospisil V, Lundgren A, Rosenthal CK. Cdc25A localisation and shuttling: characterisation of sequences mediating nuclear export and import. *Exp Cell Res* 2005;303:89-100.

Kar S, Wang M, Yao W, Michejda CJ, Carr BI. PM-20, a novel inhibitor of Cdc25A, induces extracellular signal-regulated kinase 1/2 phosphorylation and inhibits hepatocellular carcinoma growth in vitro and in vivo. *Mol Cancer Ther* 2006;5(6):1511-1519.

Boutros R, Lobjois V, Ducommun B. CDC25 phosphatases in cancer cells: key players? Good targets?. *Nat Rev* 2007;7:495-507. (Review).

Ray D, Kiyokawa H. CDC25A levels determine the balance of proliferation and checkpoint response. *Cell Cycle* 2007;6(24):3039-3042. (Review).

Ray D, Terao Y, Fuhrken PG, Ma ZQ, DeMayo FJ, Christov K, Heerema NA, Franks R, Tsai SY, Papoutsakis ET, Kiyokawa H. Deregulated CDC25A expression promotes mammary tumorigenesis with genomic instability. *Cancer Res* 2007;67(3):984-991.

Ray D, Terao Y, Nimbalkar D, Hirai H, Osmundson EC, Zou X, Franks R, Christov K, Kiyokawa H. Hemizygous disruption of Cdc25A inhibits cellular transformation and mammary tumorigenesis in mice. *Cancer Res* 2007;67(14):6605-6611.

Kang T, Wei Y, Honaker Y, Yamaguchi H, Appella E, Hung MC, Piwnicka-Worms H. GSK-3 beta targets Cdc25A for ubiquitin-mediated proteolysis, and GSK-3 beta inactivation

correlates with Cdc25A overproduction in human cancers. *Cancer Cell* 2008;13(1):36-47.

Kar S, Wang M, Carr BI. 2-Methoxyestradiol inhibits hepatocellular carcinoma cell growth by inhibiting Cdc25 and inducing cell cycle arrest and apoptosis. *Mol Chemother Pharmacol* 2008 Oct;62(5):831-40.

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*This article should be referenced as such:*

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