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Gene Section
Mini Review

CDK4 (cyclin-dependent kinase 4)

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Identity

Hugo: CDK4
Other names: CMM3; MGC14458; PSK-J3
Location: 12q14
Local order: Telomeric to the OS9 (amplified in osteosarcoma 9), CENTG1 (centaurin, gamma 1) and TSPAN31 (tetraspanin 31, SAS) genes. Centromeric to the MARCH9 (membrane-associated ring finger (C3HC4) 9), CYP27B1 (cytochrome P450, family 27, subfamily B, polypeptide 1) and METTL1 (methyltransferase like 1) genes. These seven genes are clustered within a genomic region of about 75 kb.

DNA/RNA

Description

CDK4 is a relatively compact gene that spans 4.16 kb of genomic DNA on the long arm of chromosome 12, in the telomere-to-centromere orientation. The gene consists of eight exons of which the first exon is non-coding. The start codon is located in the beginning of exon 2 and the stop codon in the beginning of exon 8.

Transcription

The CDK4 mRNA is 1.44 kb. In the Ensembl database, also a shorter, alternatively spliced transcript (Q96BE9_HUMAN) is listed, but there is no biological evidence for a function of this transcript or the polypeptide it may encode.

Pseudogene

The Ensembl database lists OTTHUMG00000011002 (Vega gene RP11-414B7.1) on chromosome 1 as a processed pseudogene of CDK4.

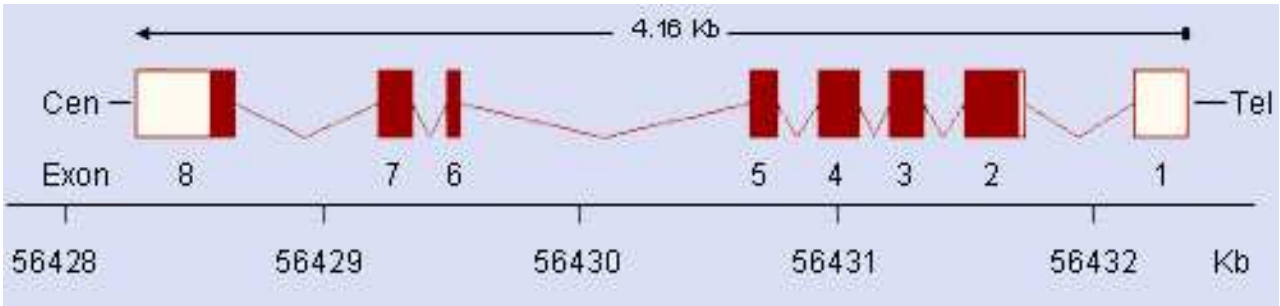
Protein

Description

The open reading frame encodes a 303 amino acid protein with an estimated molecular weight of 33.7 kDa. CDK4 is member of the Ser-Thr protein kinase family and its catalytic domain extends from amino acid 6 to 295.

Expression

CDK4 is expressed in a variety of normal cells and tissues as well as in cancer cells. The protein is often



Genomic organization of the CDK4 gene on chromosome 12.

overexpressed in human tumors (e.g. malignant melanoma, glioma, sarcoma and carcinomas of the breast, colon, lung, ovary and oral cavity).

Localisation

Nuclear or nuclear/cytoplasmic.

Function

CDK4 constitutes the catalytic subunit of a heterodimeric Ser/Thr protein kinase which is involved in controlling progression through the G1 phase of the cell cycle. The activating partner of CDK4 (the regulatory subunit) is one of the D-type cyclins: CCND1, CCND2 or CCND3. Once activated, the CDK4-cyclin D complex phosphorylates members of the retinoblastoma protein family (pRb, p107, p130). The activity of CDK4 is inhibited by the p16 (INK4A) protein, which interferes with the cyclin D-binding region.

Homology

CDK4 belongs to the mammalian Cdk family, which includes about 20 members. The cyclin-binding domain of CDK4 has the amino acid sequence PISTVRE. The overall identity of CDK4 to CDK1 is 42%.

Mutations

Germinal

Germ-line mutations in the CDK4 gene have so far only been found in families with inherited malignant melanoma and multiple atypical nevi. There are six such families reported. The mutations affect the Arg encoded by codon 24, changing it either to Cys (two families) or to His (four families).

Somatic

Amplification of the chromosomal region that includes CDK4 is commonly seen in gliomas and several subgroups of sarcomas, and may also occur in other tumors such a malignant melanomas. Point mutations have only rarely been observed and are of unknown biological significance.

Implicated in

Familial cutaneous malignant melanoma 3 (CMM3)

Sporadic malignant melanoma

Note: Cases with wild-type BRAF and NRAS genes.

Glioma

Disease

Anaplastic astrocytoma and glioblastoma multiforme.

Sarcoma

Disease

In particular liposarcoma, alveolar rhabdomyosarcoma and osteosarcoma.

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