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Gene Section
Mini Review

CCRK (cell cycle related kinase)

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Identity

Other names: CDCH; p42; P42; EC 2.7.11.22; PNQALRE

HGNC (Hugo): CCRK

Location: 9q22.1

Local order: 235kb telomeric to cathepsin L1 (CTSL1).

DNA/RNA

Description

Human CCRK gene spans around 8.3kb of genomic DNA on the chromosome 9q22.2 in telomere-to-centromere orientation. This gene locates within the locus tag RP11-350E12.2. A block of hypermethylated CpGs has been identified in the CCRK promoter and is associated with its high expression in adult human brain cortex (Farcas et al., 2009).

Transcription

Four alternative spliced transcript variants of CCRK gene are known. The generic variant 3 (GenBank#: NM_001039803) consists of 8 exons, with the start codon on exon 1 and stop codon on exon 8. Both transcript variant 1 (GenBank#: NM_178432) and variant 2 (GenBank#: NM_012119) have had their exon 5 deleted. Variant 1 also differs from the other variants by an additional 39nt on exon 2. The cardiac splice variant (GenBank#: AY904367) lacks both the exons 5 and 6, and has truncated 5'- and 3'-untranslated regions.

Pseudogene

No pseudogenes for CCRK are known.

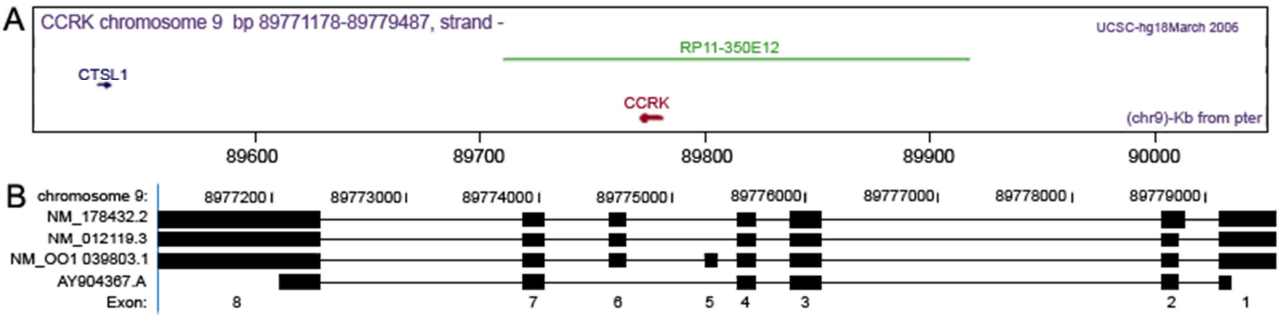
Protein

Note

There has been controversy over whether CCRK functions as a second cyclin-dependent kinase (CDK)-activating kinase (CAK) (i.e., in addition to CDK7). Inconsistent with other studies, Wohlbold and colleagues (2006) reported that monomeric CCRK has no intrinsic CAK activity.

Description

The open reading frame encodes a 346-amino acid



(A) Chromosomal location of human CCRK gene. (B) Genomic organization of four CCRK transcript variants.

protein, with molecular weight of 42kDa. CCRK protein has a protein kinase domain extending from residues 4-288, in which typical ATP-binding region and serine/threonine kinase active site can be identified. Its interacting proteins include CDK2, cyclin H and casein kinase 2.

Expression

In human tissues, the 2.2kb CCRK transcript is expressed predominantly in the brain and kidney, and to lesser extent in the liver, heart and placenta. The cardiac CCRK isoform is detectable only in heart, liver and kidney. CCRK is also widely expressed in cell lines originating from glioblastoma (U87, U118, U138, U373 and SW1088), cervical adenocarcinoma (HeLa), colorectal carcinoma (HCT116), osteogenic sarcoma (U2OS), breast adenocarcinoma (MCF-7), ovarian carcinoma (UACC-1598, UACC-326, OVCAR-3, HO-8910 and TOV-21G), lung fibroblast (WI-38), myoblast (C2C12), and lymphocyte (GM08336).

Localisation

Mainly in nucleus and perinuclear region. Relative low expression in cytoplasm.

Function

CCRK is an important regulator of G1- to S-phase transition in cell cycle and is indispensable for cell growth. It possesses CDK-activating kinase activity that is essential for the phosphorylation of CDK2 at Thr160 (Liu et al., 2004) and male germ cell-associated kinase-related kinase (MRK) at Thr157 in mammalian cells (Fu et al., 2006). CCRK also acts as a negative regulator of apoptosis and may confer cells with drug resistance (MacKeigan et al., 2005). Moreover, CCRK splice variant expressing in the heart has been shown to promote cardiac cell growth and survival (Qiu et al., 2008).

Homology

CCRK belongs to the CDK family. Among the other 10 CDK members, human CCRK shares the highest sequence identity (43%) with a well known CAK, CDK7. Orthologs of CCRK are found in orangutans, Old World monkeys, bovine, dog, boar, mouse, rat, fishes, frog, budding yeast and fission yeast.

Implicated in

Colorectal carcinoma

Note

Knockdown of CCRK inhibits HCT116 cell proliferation (Wohlbold et al., 2006). A small molecule kinase inhibitor (RGB-286147) that targets CCRK has been shown to promote HCT116 cell death in the absence of cell cycle progression (Caligiuri et al., 2005).

Glioblastoma multiforme

Note

In 14 of 19 (74%) human high-grade glioblastoma multiforme patient samples, CCRK mRNA expression levels are more than 1.5-fold higher than those of 3 normal brain tissue samples. By contrast, only 2 of 7 (29%) low-grade glioma samples have elevated CCRK expression. Knockdown of CCRK suppresses glioma tumor growth in mouse xenograft model. CCRK knockdown also inhibits glioblastoma cell proliferation via G1/S-phase arrest and reduction of CDK2 phosphorylation in vitro. Overexpression of CCRK induces malignant transformation of non-tumorigenic glioblastoma cells (U138) both in vitro and in vivo (Ng et al., 2007).

Ovarian carcinoma

Note

By CCRK immunohistochemical staining of CCRK in ovarian tissue microarray, CCRK is overexpressed in 65/122 (53%) invasive ovarian carcinoma patient samples, as compared with 22 normal ovarian surface epithelium samples. In 12 pairs of primary ovarian carcinoma and adjacent normal tissue specimens, CCRK expression is elevated in 6 (67%) ovarian carcinoma samples. Ectopic expression of CCRK promotes tumor growth in vivo and ovarian carcinoma cell proliferation in vitro via upregulation of cyclin D1 (Wu et al., 2009).

Prognosis

CCRK expression is positively correlated with ascending histological grade and advanced clinicopathologic features. It is also an independent biomarker for shortened survival time of patients with ovarian carcinoma.

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