Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

CHEK2 (CHK2 checkpoint homolog (S. pombe))

Nancy Uhrhammer

Centre Jean-Perrin, BP 392, 63000 Clermont-Ferrand, France (NU)

Published in Atlas Database: May 2004

Online updated version: http://AtlasGeneticsOncology.org/Genes/CHEK2ID312.html
DOI: 10.4267/2042/38092

Identity

Other names: CHK2; CDS1; Rad53

HGNC (Hugo): CHEK2

Location: 22q12.1

DNA/RNA

Description

17 exons spanning 57 kb.

Transcription

Two isoforms are expressed, isoform a (2547nt) includes all 17 exons, while isoform b (2460 nt) does not include exon 12, deleting 87nt (29 codons) from the mRNA. The translation start site is in exon 4.

Protein

Description

61 kDa. Isoform a: 543 amino acids; isoform b: 514 amino acids. Contains FHA and ser/thr kinase domains. Molecular studies of Chk2 typically do not distinguish between the different isoforms.

Expression

All tissues tested.

Localisation

Nuclear.

Function

Chk2 plays a role in the DNA damage signal cascade, especially in response to double-strand breaks. After detection of DNA damage, Chk2 is phosphorylated on Thr-68 by ATM and ATR. Thus activated, Chk2 targets p53 for phosphorylation on Ser20, releasing p53 from its inhibitor MDM2 and allowing transcriptional activation of genes responsible for cell cycle arrest, such as p21waf1/cip1, as well as initiation of apoptosis. In S phase, Chk2 phosphorylates Cdc25A on Ser123, targeting it for degradation and making it unavailable for the activation of cdk2, thus inhibiting the advance of S phase. In G2 phase, Chk2 phosphorylates Ser216 of Cdc25C, blocking entry into mitosis.

Chk2 is also involved in the regulation of BRCA1. Under normal conditions the two proteins are associated; after irradiation Chk2 phosphorylates Ser988 of BRCA1. This step is required for their dissociation, and the liberated BRCA1 participates directly in DNA repair and cell cycle arrest.

Finally, Chk2 can provoke apoptosis independently of p53, for example via phosphorylation of PML.

Homology

26 % identical to the Rad53 S. cereviscea homolog. The FHA and kinase domains are particularly conserved.

Mutations

Germinal

The northern european founder mutation "1100delC" is the most common found in breast cancer families. Other small deletions, stops, and missense mutations in the FHA or kinase domains such as Arg145Trp and Ile157Thr are rare in cancer families but not found in controls. The 1100delC mutation appears to increase the penetrance of mutations in certain other breast cancer genes, notably BRCA2. It should be noted that the publications describing "1100delC" have used the A of the initiation codon as nucleotide 1. This mutation thus corresponds to position 1861 in the complete, isoform a mRNA.

Somatic

Missense mutations in the FHA and kinase domains as well as frameshifts and nonsense mutations have been

found at low frequencies in osteosarcoma and more rarely in carcinomas of the ovary, lung, and vulva. Reduced or missing protein expression has been observed in some cases of non-Hodgkins lymphoma, although neither mutation nor silencing of the gene by methylation was detected.

Implicated in

Li-Fraumeni-like syndrome, somatic osteosarcoma and familial aggregations of breast cancer and colon cancer

Note

The importance of Chk2 mutations in hereditary cancer risk is controversial, as some studies have failed to show an excess of mutations in selected populations, such as male breast cancer and patients with multiple colorectal adenomas developing colon cancer. In addition, some studies of breast cancer families suggest that only the relatively frequent 1100delC mutation is significant.

Prognosis

No known association with the clinical parameters of solid tumors. There is a possible association with more agressive non-Hodgkins lymphomas.

References

Matsuoka S, Huang M, Elledge SJ. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. Science. 1998 Dec 4;282(5395):1893-7

Dasika GK, Lin SC, Zhao S, Sung P, Tomkinson A, Lee EY. DNA damage-induced cell cycle checkpoints and DNA strand break repair in development and tumorigenesis. Oncogene. 1999 Dec 20;18(55):7883-99

Vahteristo P, Tamminen A, Karvinen P, Eerola H, Eklund C, Aaltonen LA, Blomqvist C, Aittomäki K, Nevanlinna H. p53, CHK2, and CHK1 genes in Finnish families with Li-Fraumeni syndrome: further evidence of CHK2 in inherited cancer predisposition. Cancer Res. 2001 Aug 1;61(15):5718-22

Miller CW, Ikezoe T, Krug U, Hofmann WK, Tavor S, Vegesna V, Tsukasaki K, Takeuchi S, Koeffler HP. Mutations of the CHK2 gene are found in some osteosarcomas, but are rare in breast, lung, and ovarian tumors. Genes Chromosomes Cancer. 2002 Jan;33(1):17-21

Lipton L, Fleischmann C, Sieber OM, Thomas HJ, Hodgson SV, Tomlinson IP, Houlston RS. Contribution of the CHEK2 1100delC variant to risk of multiple colorectal adenoma and carcinoma. Cancer Lett. 2003 Oct 28;200(2):149-52

Schutte M, Seal S, Barfoot R, Meijers-Heijboer H, Wasielewski M, Evans DG, Eccles D, Meijers C, Lohman F, Klijn J, van den Ouweland A, Futreal PA, Nathanson KL, Weber BL, Easton DF, Stratton MR, Rahman N. Variants in CHEK2 other than 1100delC do not make a major contribution to breast cancer susceptibility. Am J Hum Genet. 2003 Apr;72(4):1023-8

Syrjäkoski K, Kuukasjärvi T, Auvinen A, Kallioniemi OP. CHEK2 1100delC is not a risk factor for male breast cancer population. Int J Cancer. 2004 Jan 20;108(3):475-6

This article should be referenced as such:

Uhrhammer N. CHEK2 (CHK2 checkpoint homolog (S. pombe)). Atlas Genet Cytogenet Oncol Haematol. 2004; 8(3):202-203.