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Gene Section
Mini Review

MCPH1 (microcephalin 1)

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Identity

Other names: BRIT1; MCT

HGNC (Hugo): MCPH1

Location: 8p23.1

Local order: According to NCBI Map Viewer, genes flanking MCPH1 in telomere to centromere direction on 8p23.1 are: ANGPT2 (angiopoietin 2); MCPH1 (also BRIT1); AGPAT5 (1-acylglycerol-3-phosphate O-acyltransferase 5 (lysophosphatidic acid acyltransferase, epsilon)); XKR5 (XK, Kell blood group complex subunit-related family, member 5); DEFB1 (defensin, beta 1); DEFA6 (defensin, alpha 6, Paneth cell-specific).

Note

MCPH1 is one of DNA damage response proteins that interact with other DNA damage and repair proteins and signal transducers, form a DNA damage response protein complex which can be seen through immunofluorescent microscopy, and participate into DNA repair, cell cycle checkpoint control, and eventually maintain genomic integrity. The aberrant expression of MCPH1 is observed in ovarian cancer and breast cancer tissues and cell lines. Thus, functional impairment of MCPH1 may significantly contribute to tumour susceptibility and/or tumour development. In addition, indivi-duals who harbor a germline mutation of MCPH1 gene may be highly susceptible to an autosomal recessive neurological disorder, called primary microcephaly.

DNA/RNA

Description

According to Entrez-Gene, MCPH1 gene maps to NC_000008.9 in the region between 6251529 and 6493434 on the plus strand and spans across 241.9 kilo bases. According to GenBank, MCPH1 has 14 exons, the sizes being 90, 92, 119, 88, 115, 144, 90, 1155, 110, 38, 163, 78, 238, and 5512 bp.

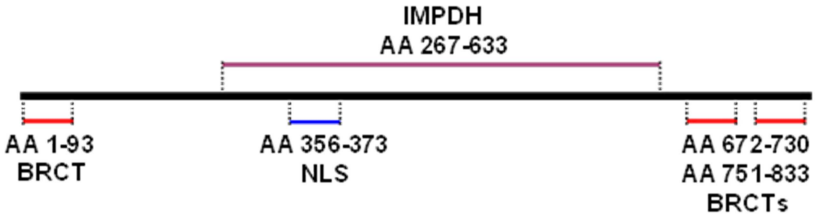
Transcription

8032 bp mRNA (NM_024596.2), 2508 bp open reading frame.

Protein

Note

MCPH1 has three BRCA1 carboxyl-terminal (BRCT) domains, so it is regarded as a protein family member involved in DNA damage repair and checkpoint control.



The protein of MCPH1 contains three BRCT domains, the nuclear localization signal motif and the large middle IMPDH domain. (AA, amino acids).

Description

MCPH1 protein contains 835 amino acids with about 110 kDa of the molecular weight. According to MotifScan prediction, MCPH1 has three BRCT domains, one nuclear localization signal motif and the large central IMPDH domain as depicted in the diagram above. The BRCT domains of MCPH1, one in N-terminus (N-BRCT), the other two tandemly arranged in C-terminus (C-BRCTs), specifically bind to the phosphorylated proteins commonly involved in DNA damage response pathways. The N-BRCT is required for centrosomal localization in irradiated cells, and also essential to rescue the premature chromosome condensation in MCPH1-deficient cells. C-BRCTs direct self-oligo-merization of MCPH1, and are necessary for ionizing radiation-induced foci formation. The function of IMPDH domain predicted by MotifScan is not clear yet. However, the region (residues 376-485) in the central IMPDH domain (or middle domain), binding with Condension II, participates in homologous recombination.

Expression

MCPH1 is ubiquitously expressed in human with the higher levels observed in the brain, testes, pancreas and liver. It is a putative tumor suppressor and the aberrant expression of MCPH1 is correlated with ovarian and breast cancer. This reduced expression of MCPH1 may have been caused by gene deletion detected by high-density array comparative genomic hybridization (CGH).

Localisation

Mainly localized in nucleus.

Function

MCPH1 function in DNA damage response: MCPH1 can modulate activities of two distinct DNA damage repair networks, the ATM (ataxia telangiectaisia mutated) pathway and the ATR (ATM and Rad3-related) pathway. Upon exposure to DNA damaging reagents, MCPH1 co-localizes with numerous proteins associated with these two signaling pathways including gamma-H2AX, MDC1, 53BP1, NBS1, p-ATM, ATR, p-RAD17 and p-RPA34. In the absence of MCPH1, all of these proteins with the exception of gamma-H2AX, fail to localize to sites of DNA damage. The depletion of MCPH1 inhibits the recruitment of phosphorylated ATM to double-stranded DNA break ends, and subsequently impair t phosphory-lation of multiple down-stream members of the ATM pathway. MCPH1 deficiency also abolishes the UV-induced phosphorylation of RPA34 and reduces the levels of phosphorylated RAD17, suggesting the roles of MCPH1 in the ATR path-way. Rad51, a homolog of the bacterial RecA, is a central executioner in homologous recombination (HR), catalyzing the invasion of the single stranded DNA in a homologous duplex and facilitating the homology search during the establishment of joint molecules. Lack of MCPH1 can alleviate localization of RAD51 onto the DNA break sites. So MCPH1 is strongly implicated in HR.

Role of BRIT1 in cell cycle control: MCPH1 has been demonstrated to regulate the expression of BRCA1 and Chk1 and required for activation of intra-S and G2/M cell cycle checkpoint after cellular exposure to ionizing radiation. In the absence of MCPH1, BRCA1 and ChK1 expression is significantly reduced and NBS1 fails to be phosphorylated, leading to loss of intra-S and G2/M checkpoint control. Cells derived from a micro-cephaly patient (MCPH1 defective) maintain a persistent level of CDC25A and reduced level of Cdk1-cyclin B complex, both of which attributes to entry of mitosis. So besides expression control of ChK1 and BRCA1, MCPH1 prevents premature entry into mitosis in an ATR-dependent and ATR-independent manner.

Homology

According to NCBI-HomoloGene:
Chimpanzee (Pan troglodytes): MCPH1 (NP_001009010.1, 835 aa)
Dog (Canis familiaris): MCPH1 (NP_001003366.1, 850 aa)
Rat (Rattus norvegicus): MCPH1 (XP_225006.4, 986 aa)
Mouse (Mus musculus): MCPH1 (NP_775281.2, 822 aa)
Zebrafish (Danio rerio): zgc:136403 (NP_001035453.1, 422 aa)
Drosophila (Drosophila melanogaster): CG30038 (NP_725086.2, 219 aa)

Mutations

Note

Three point mutations in the autosomal recessive mental retardation patients have been described for MCPH1 so far. Two mutations (S25X and 427insA) lead to premature stop condon, and one (T27R) leads to missense mutation in the N-terminal BRCT domain. A non-synonymous SNP (V761A in BRCA1 C-terminus (BRCT) domain) of MCPH1 is significantly associated with cranial volume in Chinese males. In addition, a deletion of approximately 150-200 kb, encompassing the promoter and the first six exons of the MCPH1 gene, was revealed by Array-based homozygosity mapping and high-resolution microarray-based comparative genomic hybridization (array CGH). However, the patients with this deletion just showed borderline of mild microcephaly.

Implicated in

Ovarian cancers

Note

Aberrations of MCPH1 have been identified in various human cancers.

Disease

MCPH1 DNA copy number was substatially decreased in 40% of advanced epithelial ovarian cancer, and its mRNA levels were also dramatically decreased in 63% of ovarian cancer.

Breast cancers

Disease

MCPH1 mRNA and protein levels was aberrantly reduced in several breast cancer cell lines.

Prognosis

Additionally, reduced MCPH1 expression correla-ted with the duration of the relapse-free intervals and with the occurrence of metastasis in breast cancers. BRIT1 deficiency may contribute to development and aggressive nature of breast tumors.

Primary microcephaly

Disease

Primary microcephaly is an autosomal recessive disorder, in which there is a marked reduction in brain size. One form of primary microcephaly, MCPH, is caused by mutation in the gene encoding microcephalin 1 (that is, MCPH1). In these patients, the MCPH1-deficient cells show cellular phenotype of premature chromosome condensation in the early G2 phase of the cell cycle, which, therefore, appears to be a useful diagnostic marker for these individuals. As mentioned above, several mutations of MCPH1 have been observed in these patients, including S25X, 427insA, T27R, V761A and 5'-deletion of a large portion encompassing the promoter region and first six exons, especially the later two showing strong correlation with micro-cephaly.

PCC syndrome

Disease

Premature chromosome condensation (PCC) syndrome is characterized by premature chromosome condensation in the early G2 phase. This disorder is similar to microcephalin 1, and can also be caused by MCPH1 mutations.

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