Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

MCM5 (minichromosome maintenance complex component 5)

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Published in Atlas Database: July 2011

Online updated version : http://AtlasGeneticsOncology.org/Genes/MCM5ID41321ch22q12.html
DOI: 10.4267/2042/46072

Identity

Other names: CDC46; MGC5315; P1-CDC46

HGNC (Hugo): MCM5

Location: 22q12.3

Local order: Telomere to centromere.

DNA/RNA

Description

Spanning 24,4 kb of genomic DNA, the MCM5 gene consists of 17 exons and 16 intervening introns.

Transcription

The unique transcript of the MCM5 gene is 2546 nt. The human MCM5 gene was shown to be expressed widely in many normal tissues, but its mRNA levels vary a lot. The highest levels of MCM5 mRNA transcripts were detected in A-431 epidermoid carcinoma cells, U-2 OS osteosarcoma cells, and U-251 MG astrocytoma cells. Expression of all human genes of the MCM family is induced by growth stimulation and their mRNA levels peak at G1/S transition. The growth-regulated expression of MCM5 is primarily regulated by members of the E2F family through binding to multiple E2F sites of the MCM5 gene promoter.

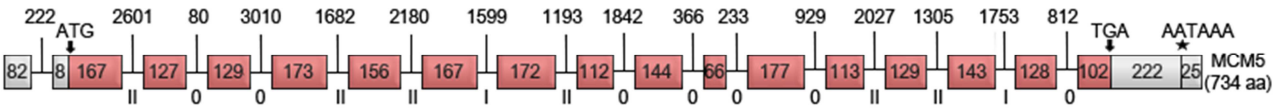

Figure 1. Schematic representation of the MCM5 gene. Exons are shown as boxes and introns as connecting lines. The coding sequence is highlighted as red, while 5' and 3' untranslated regions (UTRs) are shown in white. The numbers inside boxes indicate exon lengths and the vertical connecting lines show the intron lengths. The arrows show the position of the start codon (ATG) and stop codon (TGA), and the asterisk shows the position of the polyadenylation signal (AATAAA). Roman numerals indicate intron phases. The intron phase refers to the location of the intron within the codon; I denotes that the intron occurs after the first nucleotide of the codon, II denotes that the intron occurs after the second nucleotide, and 0 means that the intron occurs between distinct codons.

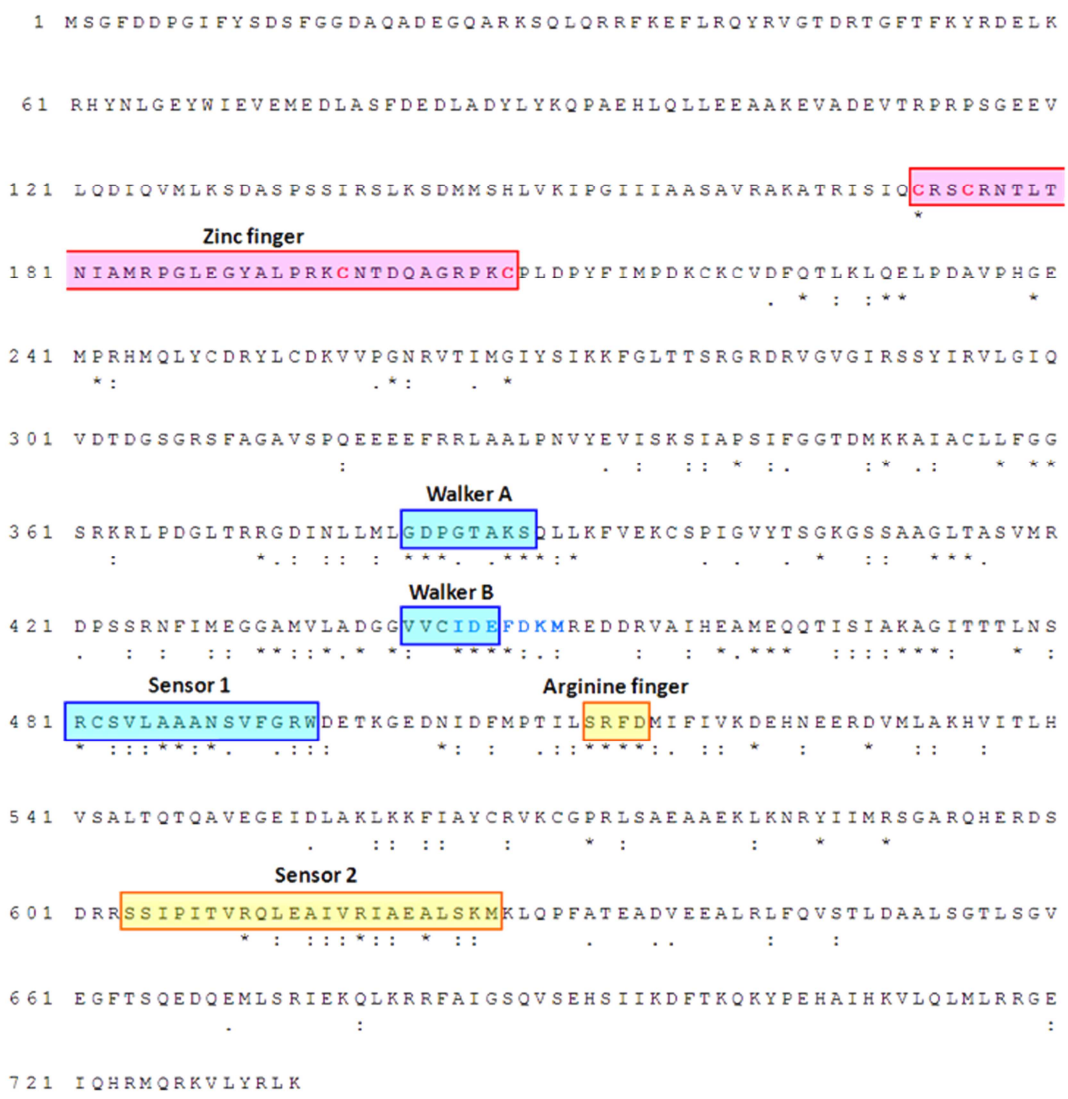

Figure 2. Amino acid sequence and structural motifs of the MCM5 protein. The asterisks (*) indicate amino acid residues being fully conserved in the human MCM protein family, the colons (:) indicate residues with strongly similar properties among all members of the human MCM family, and periods (.) indicate residues with weakly similar properties among all members of the same family. Light blue denotes the cis-acting ATPase elements (Walker A motif, Walker B motif and sensor 1), while yellow highlights the trans-acting ATPase elements (arginine finger and sensor 2). When combined in the heterohexameric MCM complex, the cis and trans motifs of adjacent subunits act together as an ATPase domain. Moreover, the sequence IDEFDKM (shown in dark blue color) is characteristic of most MCM family members. The MCM5 protein also contains a zinc finger (highlighted in pink), comprising four cysteine residues (shown in red color). This zinc finger is considered to play a role in the assembly of the MCM complex and its ATPase activity.

Pseudogene

Not identified so far.

Protein

Description

The MCM5 protein is composed of 734 amino acid residues, with a calculated molecular mass of 82,3 kDa and a basal isoelectric point of 8,64. MCM5 is a member of the MCM family, a distinct subgroup of the AAA+ family, which consists of ATPases associated with various cellular activities. The MCM5 protein is one the six subunits composing the minichromosome maintenance (MCM) complex. The structural characteristic of MCM5 is an MCM box consisting of approximately 200 amino acids. This includes a Walker A motif containing the P-loop (phosphate-binding loop) of the active site and the invariant lysine residue found in all ATP-binding proteins, a hydrophobic Walker B element that is responsible for ATP hydrolysis, and an arginine finger. The Walker B motif is part of the sequence IDEFDKM, which is conserved in all MCM proteins and defines the MCM family.

MCM proteins form ATPase active sites at clefts between two subdomains: one containing a series of loops connecting adjacent parallel beta-strands (P-loop) and a second positioned C-terminal to the P-loop domain, called the lid. Both subdomains contain conserved active-site motifs: the P-loop contains motifs

involved in binding ATP (Walker A motif) and orienting the nucleophilic water molecule (Walker B motif and sensor 1), while the lid domain contains motifs that contact the gamma-phosphate of ATP (arginine finger and sensor 2). Therefore, ATPase active sites of the heterohexameric MCM complex are formed at dimer interfaces, with one subunit contributing the P-loop (cis motifs), while the adjacent subunit contributes the lid (trans motifs). The MCM5 also possesses a zinc finger, located prior to the MCM box. This zinc finger is considered to play a role in the assembly of the MCM complex and its ATPase activity.

Expression

MCM5 is upregulated in the transition from the G0 to G1/S phase of the cell cycle. This protein is mainly expressed in bone marrow hematopoietic cells, lymphocytes in tonsil, and trophoblastic cells in placenta. This DNA replication licensing factor is also expressed in a few other cell types, including colorectal glandular cells, epidermal cells of the skin and bronchus, urothelial cells of the urinary bladder, decidual cells of placenta, and glandular cells of the pre-menopause uterus, though at lower intensity. Recently, it was shown that MCM5 is downregulated in neuroblastoma cells by miR-885-5p, which binds to the 3'-UTR of the MCM5 mRNA.

Localisation

The MCM5 protein is localized to the nucleus.

Function

MCM5 is a member of the MCM family of chromatin-binding proteins, implicated in the initiation of DNA replication. This protein can interact with at least two other members of this family, namely MCM2 and MCM3. MCM5 participates in the formation of the heterohexameric MCM complex, which is loaded onto the chromatin at origins of DNA replication with the aid of the multimeric CDC6-CDT1-ORC-DNA, thus forming together the pre-replication complex (pre-RC). Except for being responsible for the initiation of replication, the proteins composing the MCM complex serve as DNA helicases that unwind the DNA double helix at the replication forks. Moreover, MCM5 may actively participate in cell cycle regulation. Finally, the MCM complex is responsible for genome stability, as it limits the replication to once per cell cycle.

MCM5, MCM3 and MCM2 constitute the peripheral subunits of the complex that negatively regulate the active MCM core subunits (MCM4, MCM6 and MCM7). It has been proposed that MCM2 and MCM5 form a gate in the MCM toroid. When the conformation is in a closed status, the dimer MCM2-MCM5 binds ATP; on the other hand, when the gate is open, the active site of the dimer is empty since no nucleotide is bound, and therefore no helicase activity is observed.

Further studies suggest that the very existence of the gate, its topology, its conformation and the complex discontinuity that the MCM2/5 dimer causes, is capable of regulating the helicase activity of the MCM complex and/or is essential for the initial loading of the complex onto the origins of replication.

MCM5 was shown to interact with CDC45, a key molecule that regulates the stages of initiation and elongation in the eukaryotic DNA replication. Interestingly, the heterodimer MCM3-MCM5 can also interact with the transcription factor STAT1a (STAT1 alpha isoform), thus implying a possible role of MCM5 in transcription regulation. Increased levels of MCM5 are associated with activation of transcription. Another recent study showed that the MCM complex is co-localized with RNA polymerase II (RNA Pol II) on chromatin of genes being constitutively transcribed, and that MCM5 is required for transcription elongation of RNA Pol II. In fact, the integrity of the MCM heterohexameric complex and the DNA helicase domain of MCM5 are essential for the process of transcription. Additionally, human minichromosome maintenance proteins including MCM5 can bind to and interact with histones, such as H3 and H4.

Homology

Human MCM5 shares 96% amino acid identity and 99% similarity with the mouse and rat Mcm5 protein. Moreover, it shows 35% identity and 53% similarity with the human MCM4 protein ("minichromosome maintenance complex component 4", also known as "CDC21 homolog"), and to quite the same extent with other minichromosome maintenance complex components, including MCM2, MCM3, MCM6, MCM7 isoforms 1 and 2, MCM8 isoforms 1 and 2, and MCM9 isoform 1. Moreover, MCM5 is structurally very similar to the CDC46 protein from Saccharomyces cerevisiae, a protein involved in the initiation of DNA replication.

Mutations

Note

A mutation in a conserved residue (P -->L) enables MCM5 to bypass CDC7 phosphorylation, which is otherwise essential for the DNA replication to ensue, while the same mutation in other subunits of the MCM complex does not have any effect. It has been suggested that the MCM5 protein bearing this mutation obtains an altered conformation that allows it to promote the unwinding of the double helix without the necessity of phosphorylation of the other subunits of the MCM complex. Furthermore, MCM5 was shown to directly interact with the hypoxia-inducible factor-1 alpha subunit (HIF1A), along with other MCM proteins, in order to inhibit the alterations occurring in gene expression by the basic helix-loop-helix transcription factor HIF1 under hypoxic conditions.

Implicated in

Urothelial carcinoma, ovarian adenocarcinoma, cervical cancer

Prognosis

MCM5 protein overexpression was significantly associated with advanced histopathological stage, low grade of differentiation and poor prognosis in muscle-invasive urothelial carcinoma. MCM5 protein expression was also found to be significantly higher in ovarian adenocarcinomas compared to tumors of low malignant potential. In ovarian adenocarcinoma, MCM5 upregulation was significantly associated with advanced tumor histopathological stage, low grade of differentiation, and presence of bulky residual disease, therefore constituting an unfavorable prognostic biomarker. MCM5 expression showed also a linear correlation with the grade of cervical dysplasia, being independent of HPV infection.

Gastric adenocarcinoma, esophageal cancer, biliary cancer

Prognosis

Elevated expression of the MCM5 protein is significantly associated with advanced tumor size, presence of lymph node metastases, advanced tumor histopathological stage, and poor prognosis in gastric adenocarcinoma. Interestingly, MCM5 overexpression was significantly associated with lymph node positivity and advanced histopathological stage in diffuse-type gastric adenocarcinoma, while it predicted poor prognosis in intestinal-type gastric adenocarcinoma. Furthermore, MCM5 protein expression levels in gastric aspirates were shown to possess high predictive value for esophageal cancer. MCM5 protein expression was also significantly higher in malignant biliary tissues, compared to benign ones.

Laryngeal squamous cell carcinoma

Prognosis

MCM5-positive cells were present in cytological preparations from laryngeal squamous cell carcinoma, but not in those presenting atypical hyperplasia or inflammation in non-neoplastic tissues, supporting the notion that liquid-based cytology enhanced by immunohistochemistry for MCM5 can distinguish between patients requiring further investigation and those who could be followed up without resort to biopsy.

Anaplastic thyroid cancer

Prognosis

MCM5 overexpression was noticed in anaplastic thyroid cancer, in contrast with normal thyroid tissue and/or papillary thyroid cancer. MCM5 gene expression was also reported to be up-regulated at the mRNA level in papillary thyroid carcinoma, the follicular variant of papillary thyroid carcinoma, and in follicular thyroid tumors, compared to hyperplastic nodules and follicular adenomas. However, MCM5 mRNA expression was not associated with tumor size, patients' age and gender, tumor histopathological stage, and lymph node metastasis, in malignant thyroid lesions.

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This article should be referenced as such:

Kontos CK, Pavlou MAS, Giaginis C. MCM5 (minichromosome maintenance complex component 5). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(12):1045-1049.