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Gene Section
Review

MTUS1 (mitochondrial tumor suppressor 1)

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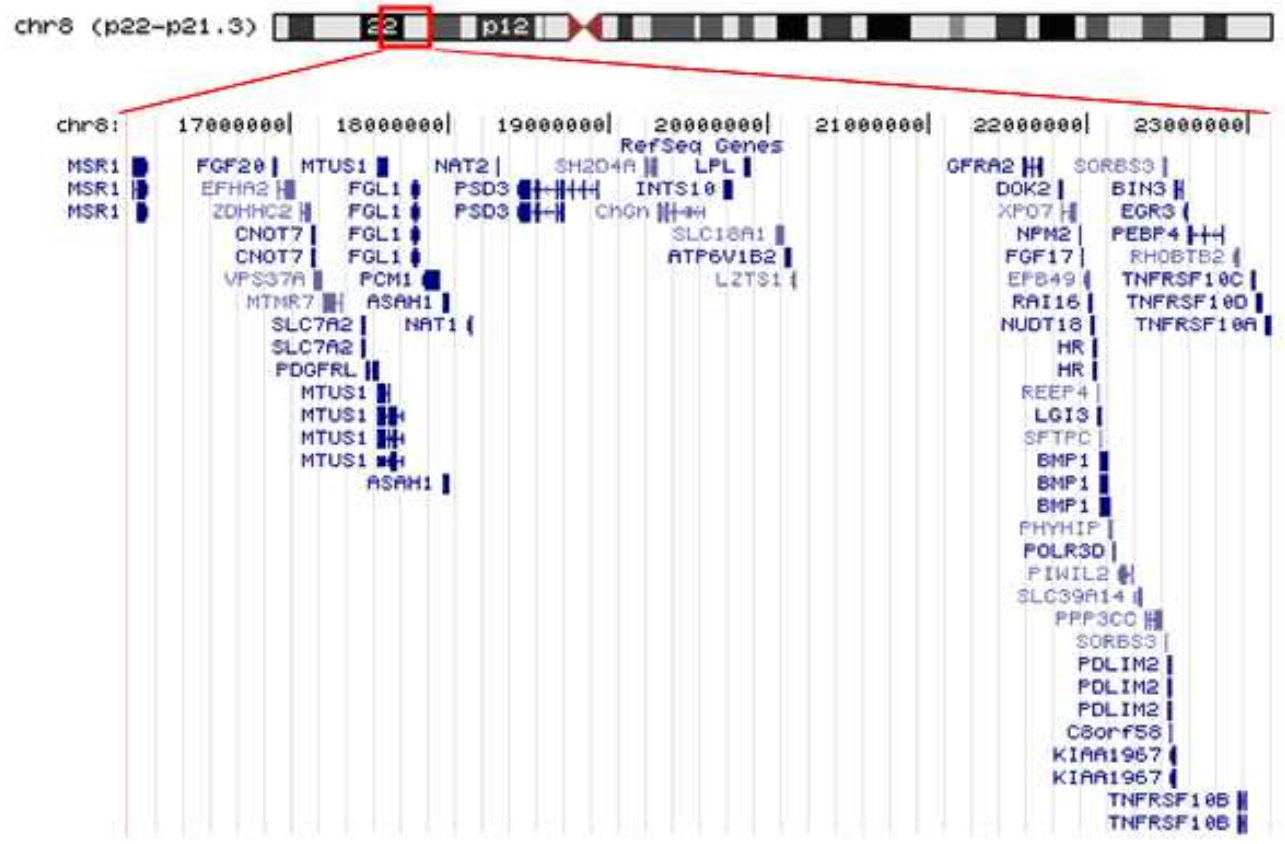
Identity

Other names: MTSG1; ATIP (angiotensin II receptor 2- interacting protein); AGTR2-interacting protein; KIAA1288; MP44; FLJ14295; DKFZp586D1519; DKFZp686F20243

HGNC (Hugo): MTUS1

Location: 8p22

Local order: MTUS1 is located in a frequent LOH region (8p21.3-p22) of approximately 7 Mb in several tumor types.



Genes located in the frequent LOH region at 8p21.3-p22. The frequent LOH region at 8p21.3-p22 was displayed using UCSC Genome Browser. Genes located in this genomic region and their corresponding mRNAs were plotted.

This genomic area is a gene-rich region, which contains 55 known genes. Among those genes, there are several known candidate tumor suppressor genes and cancer related genes, including MTUS1, pericentriolar material-1 (PCM1), leucine zipper putative tumor suppressor-1 (LZTS1), deleted in breast cancer 1 (DBC-1), Rho-related BTB domain-containing protein 2 (RHOBTB2), early growth response 3 (EGR3), tumor necrosis factor receptor superfamily member 10A (TNFRSF10A), and member 10B (TNFRSF10B).

Note

The MTUS1 gene is located on the reverse strand of the human chromosome 8 (8p22). Starts at 17545583, and ends at 17702666 bp from pter.

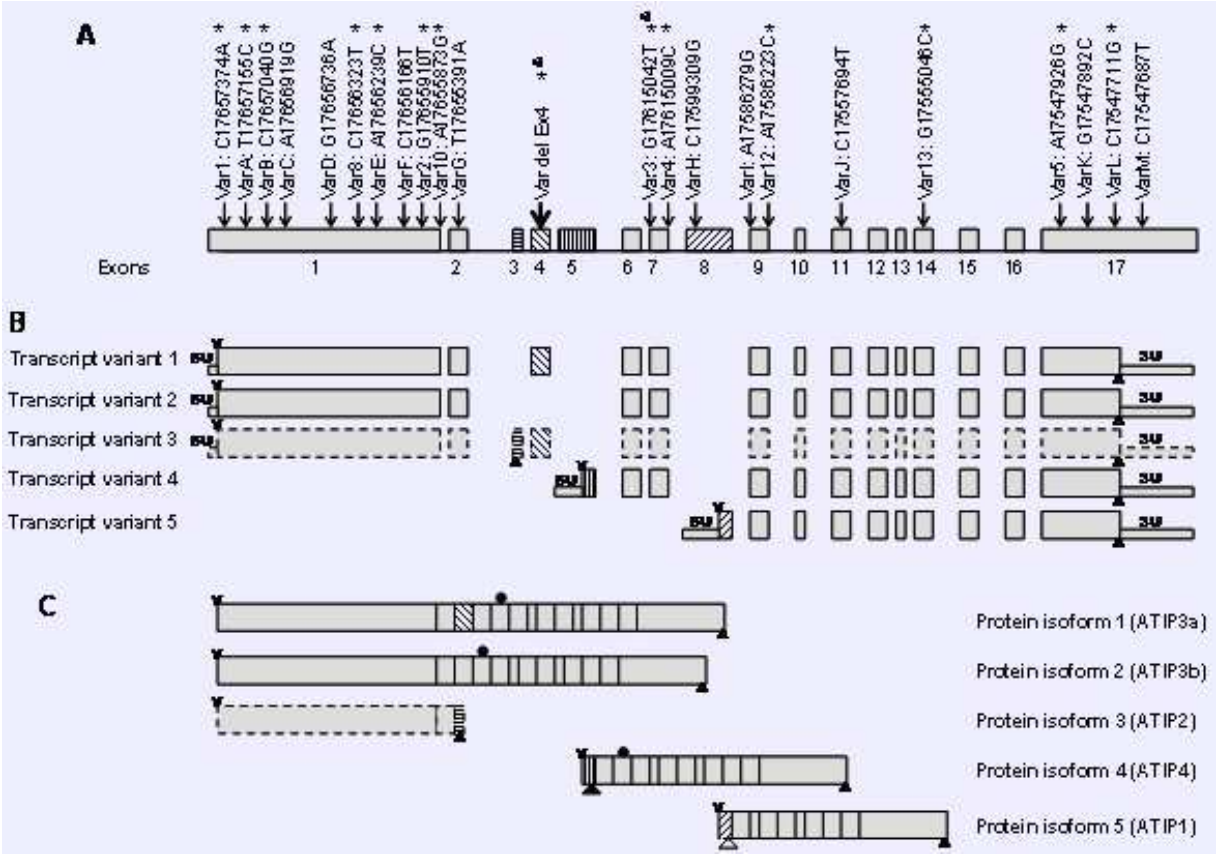
DNA/RNA

Note

The MTUS1 gene consists of 17 known exons. Alternative exon utilization leads to the generation of 5 known transcript variants (designated as variant 1 to 5), and consequentially 5 different protein isoforms (designated as isoform 1 to 5). It has been suggested that the transcription of variant 1, 2, and 3 are driven by a common gene promoter, while variant 4 and 5 are driven by 2 additional promoters. This hypothesis is supported by the observation of differential tissue distribution of different MTUS1 variants, which further suggests the differential regulation of MTUS1 gene transcription through these different promoters.

Transcription

The production of transcript variant 1, 2 and 3, which are driven by a common promoter, are produced by alternative splicing of exon 3 and exon 4. The splice junctions contain the conserved nucleotides (GT-AG) for the donor and acceptor splice sites. An in-frame stop codon in exon 3 indicates that the MTUS1 protein isoform 3 (the only isoform to utilize exon 3) may be interrupted at this position. This sequence feature also makes the transcript variant 3 a candidate for nonsense-mediated mRNA decay (NMD).



Organization of the MTUS1 gene. A) The schematic representation of genomic organization of MTUS1 gene located on the minus strand of chromosome 8p21.3-p22. The genomic locations of the detected nucleotide sequence variants (both polymorphisms and somatic mutations) for MTUS1 gene were indicated. The nucleotide sequence variants that lead to amino acid changes were identified with *. The indicates exon deletion. B) The alternative exon utilization by MTUS1 transcript variants. The **v** indicates translational initiating ATG codon. The ^ indicates stop codon. The 5U indicates 5' untranslated region, and the 3U indicates 3' untranslated region. An in-frame stop codon is located in exon 3. This in-frame stop codon makes the transcript variant 3 (dash-lined) a candidate for nonsense-mediated mRNA decay (NMD). C) The protein isoforms resulted from the MTUS1 transcript variants and cellular localization signals. The alternative names for the isoforms were given in parenthesis. Black circles indicate nuclear localization signals. Black triangle indicates a putative transmembrane region. White triangle indicates a mitochondrial targeting signal. The existence of the in-frame stop codon suggests that isoform 3 (dash-lined) is interrupted at exon 3.

Indeed, it is absent (or weakly expressed) in all normal tissues examined. While both transcript variant 1 and 2 show similar tissue distribution patterns, variant 1 is more expressed than variant 2 in most tissues. However, in the salivar gland, variant 2 accounts for more than 90% of all the MTUS1 transcript members. Apparently, the exon 4 is the only alternatively spliced exon out of 17 exons of the MTUS1 gene, which leads to the production of MTUS1 transcript variant 1 and 2. Alternatively, variant 2 may be a transcript from the MTUS1 gene with a recently identified polymorphic copy number variant at DNA level (Var del Ex4 that lacking the coding exon 4). Interestingly, an association of this MTUS1 gene Var del Ex4 polymorphism and familial breast cancer has been observed in a Germany patient cohort.

Protein

Expression

- MTUS1 isoform 1 and 2 are the major MTUS1 transcripts in all tissues except brain;
- MTUS1 isoform 3 is absent (or weakly expressed) in all normal tissues examined;
- MTUS1 isoform 4 is exclusively expressed in the brain, and is particularly abundant in the cerebellum and in the fetal brain.

Localisation

MTUS1 isoform 5 is the only isoform localized in mitochondria.

Function

The MTUS1 isoform 5 was the first one among the 5 different isoforms to be characterized independently in 2 laboratories, as a gene that is transiently upregulated during initiation of differentiation and quiescence in a 3-dimensional human umbilical vein endothelial cell culture, and as an early component of growth inhibitory signaling cascade that interacts with angiotensin II AT2 receptor. The exon 8, which is exclusively utilized by MTUS1 isoform 5, contains a mitochondrial targeting signal. This protein isoform has indeed been shown to co-localize with mitochondria, which eventually lead to its current name mitochondrial tumor suppressor 1. These early evidences on MTUS1 isoform 5 suggest the tumor suppressor function of this gene. As a consequence, the majority of the functional analyses have been focused on this specific isoform. As demonstrated in a pancreatic tumor cell line (MIA PaCa-2), recombinant expression of MTUS1 isoform 5 led to a 30% reduction in cell growth as measured by BrdU uptake. Using a CHO cell line stably transfected with both angiotensin II AT2 receptor and MTUS1 isoform 5, Nouet et al. demonstrated that the growth factors (insulin, bFGF, EGF) induced extracellular regulated kinase (ERK2) activation was inhibited. This MTUS1 isoform 5 mediated inhibitory effect was also observed at cell proliferation level as measured by DNA synthesis. The results from Nouet et al., 2006 study also suggested that MTUS1 isoform 5 functions through cooperating with the angiotensin II AT2 receptor to trans-inactivate growth factor receptor tyrosine kinases. The localization of the MTUS1 isoform 5 to mitochondria also lead to speculation that this protein achieves its tumor suppressor function by regulating different mitochondrial functions, such as the maintenance of energy supply, the production of reactive oxygen intermediates and their interactions with other cell cycle regulators.

While ample evidence suggested the tumor suppressor function of isoform 5, it is important to notice that **isoform 1 and 2** are the major MTUS1 transcripts in all tissues except brain, and account for an average of 72% of total MTUS1 mRNA. Evidence supporting the tumor suppressor function of MTUS1 isoform 1 and 2 come from the study on Xenopus Icis gene, a homolog of MTUS1 isoform 1/2. Using inactivating antibodies, Ohi et al. found that absence of Icis caused excessive microtubule growth and inhibited spindle formation, a function consistent with tumor suppressor activity. Prior to anaphase, Icis localized to inner centromeres in a Mitotic Centromere Associated Kinesin (Mcak)-dependent manner. From Xenopus extracts, Icis coimmunoprecipitated Mcak and the inner centromere proteins Incenp and AuroraB, which are thought to promote chromosome biorientation. Immunoelectron microscopy detected Icis on the surface of inner centromeres, in an ideal location to depolymerize microtubules associated laterally with inner centromeres. Ohi et al. hypothesized that Mcak-Icis may destabilize these microtubules and provide a mechanism that prevents kinetochore-microtubule attachment errors.

The MTUS1 isoform 1 and isoform 2 differ in their use of exon 4; exon 4 is contained in isoform 1 but not in isoform 2 (Figure 2). This difference may be a result of alternative splicing. Alternatively, this isoform 2 may be a protein product from the MTUS1 gene with a recently identified polymorphic copy number variant at DNA level (Var del Ex4 that lacking the exon 4).

The existence of **MTUS1 isoform 3** is not entirely certain. The expression of MTUS1 isoform 3 appears to be under the control of the same gene promoter that drives the expression of the isoform 1 and 2. However, as a result of alternative splicing, exon 3, which contains an in-frame stop codon, is incorporated into the transcript. This sequence feature makes the transcript variant 3 a candidate for nonsense-mediated mRNA decay (NMD). Indeed, it is absent (or weakly expressed) in all normal tissues examined. Hence, the sequence for this variant in the GenBank (NM_001001927) was permanently suppressed. Nevertheless, it is possible that this alternative splice to include exon 3 in the transcript may provide a mechanism to switch-off the expression of isoform 1 and 2 at posttranscriptional level.

The MTUS1 isoform 4 is exclusively expressed in the brain, and is particularly abundant in the cerebellum and in the fetal brain. It appears that the expression of isoform 4 is driven by a gene promoter specific to central nervous system. These findings suggest multiple cellular/physiological functions of MTUS1 gene, including tumor suppression as well as brain function and/or development.

Homology

Xenopus Icis gene is a homolog of MTUS1 isoform 1 and 2.

Mutations

Somatic

Sequence analyses of this gene in liver cancer and head and neck cancer revealed that MTUS1 gene is prone to various point mutations and small deletions. Many of these mutations lead to substitutions of conserved amino acid residues or interfere with the physiological splice sites that may functionally silence the MTUS1 gene. In particular, a point mutation in exon 7 (Var3 G17615042T), identified in an 8p21.3-p22 LOH-positive liver cancer cell line, abolished a physiological splicing acceptor site of exon 7. Additional experiment confirmed that this point mutation indeed leads to a transcript that lacking exon 7. Thus, this point mutation results in the deletion of the entire exon 7, which codes for several important motifs, including a nuclear localization signal.

Implicated in

Various Cancers

Note

Mitochondrial tumor suppressor gene 1 (MTUS1) is a recently identified tumor suppressor gene that resides in a frequent LOH region (8p21.3-p22) in many tumor types. Sequence analyses of MTUS1 gene suggest that this gene is rich in genetic polymorphisms, including single nucleotide polymorphism (SNP) and copy number variation (CNV), and it is susceptible to various point mutations during tumorigenesis. Consistent down-regulation of MTUS1 gene expression was observed in various cancer cell lines and tissue samples.

Breast cancer

Note

A copy number variant in MTUS1 gene is significantly associated with a decreased risk for both familial and high-risk familial breast cancer in a Germany patient cohort. This finding was made based on a case-control study on a large homogeneous study cohort (case n = 593, control n = 732) of a single ethnic group. These authors hypothesized that the lack of this exon 4 may lead to increased tumor suppressor activity. Further molecular analyses will be needed to functionally characterize this apparent phenotypic difference. While the true biological consequence(s) of this MTUS1 exon 4 deletion is still unknown, this study clearly suggested a functional difference between MTUS1 isoform 1 and isoform 2.

Pancreatic cancer

Note

In a pancreatic tumor cell line (MIA PaCa-2), recombinant expression of MTUS1 isoform 5 led to a 30% reduction in cell growth as measured by BrdU uptake.

Head and neck squamous cell carcinoma

Note

Consistent down-regulation in expression was observed in HNSCC for MTUS1 as measured by real-time quantitative RT-PCR. Sequence analysis of MTUS1 gene in HNSCC revealed several important sequence variants in the exon regions of this gene.

Hepatocellular carcinoma

Note

Sequence analysis of MTUS1 gene in hepatocellular carcinoma revealed several important sequence variants in the exon regions of this gene.

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