

## Gene Section Review

# CASP7 (caspase 7, apoptosis-related cysteine peptidase)

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### Abstract

Apoptosis is a selective process for deleting cells in various biological systems and plays an essential role in the development and maintenance of tissue homeostasis in multicellular organisms and inappropriate regulation of apoptosis is believed to be the cause of many human diseases, including cancer (Thompson, 1995).

Apoptosis relies on cysteine proteases called caspases (CASPs). Caspases are synthesized as proforms and become activated by cleavage at aspartate residues. Initiator caspases (1, 2, 4, 5, 8, 9, 10, 11, and 12) integrate molecular signals and activate the downstream effector caspases (3, 6, 7, and 14). Because caspases cleave and activate each other, the protease cascade amplifies, ensuring proper apoptotic cell death. In addition, caspases cleave numerous substrates, such as nuclear lamins, inhibitors of DNase, and cytoskeletal proteins, resulting in the typical morphological alterations of

apoptosis (Cohen, 1997; Denault and Salvesen, 2002; Boatright and Salvesen, 2003).

Caspase-7 is highly related to caspase-3, and these two caspases are activated by both death receptor- and mitochondria-induced apoptosis (Soung et al., 2003).

Besides its activation during apoptosis, proteolytic maturation of caspase-7 has also been observed under inflammatory conditions (Lamkanfi and Kanneganti, 2010).

### Keywords

Caspase-7, apoptosis, cancer, SNPs

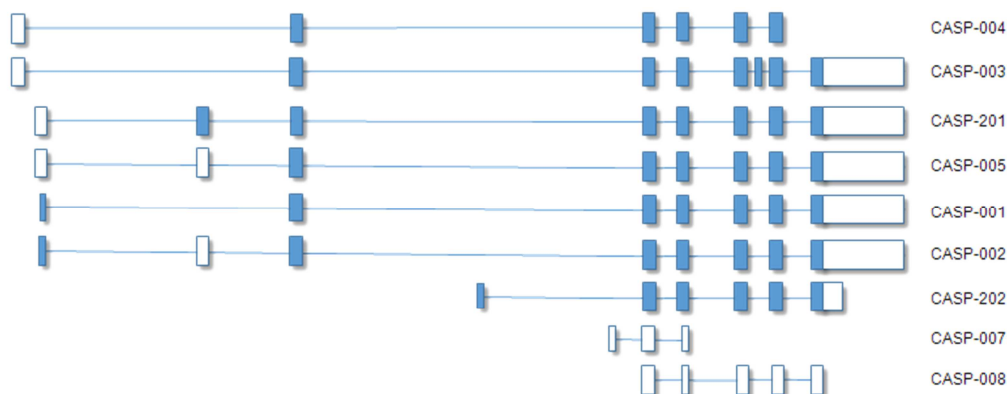
### Identity

**Other names:** CASP-7, CMH-1, ICE-LAP3, LICE2, MCH3

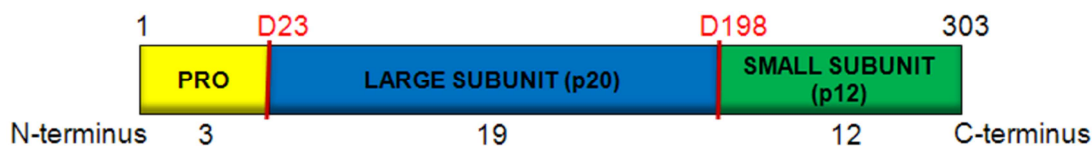
**HGNC (Hugo):** CASP7

**Location:** 10q25.3

**Local order:** Plus strand.



**CASP7 transcript variants.** Coding exons are marked by blue blocks, and non-coding exons, 5- and 3-UTRs are marked by white blocks.



**Structure of procaspase-7.** Numbers below the stick represents the approximate MWs of the resulting subunits and pro-regions. The proenzymes are cleaved at specific Asp residues (Dn, where n is the position in the protein).

## DNA/RNA

### Description

CASP7 gene contains 8 exons and spans 51.748 Kb of genomic DNA.

### Transcription

CASP7 gene has 9 transcripts (splice variants):

- CASP7-201: 2694 bp (8 exons; 7 coding exons)
- CASP7-005: 2659 bp (8 exons; 6 coding exons)
- CASP7-002: 2421 bp (8 exons; 6 coding exons)
- CASP7-003: 2380 bp (8 exons; 7 coding exons)
- CASP7-001: 2377 bp (7 exons; 6 coding exons)
- CASP7-202: 1148 bp (6 exons; 6 coding exons)
- CASP7-004: 834 bp (6 exons; 5 coding exons)
- CASP7-007: 607 bp (3 exons; 0 coding exons)
- CASP7-008: 799 bp (5 exons; 0 coding exons).

### Pseudogene

Not identified.

## Protein

### Description

Caspase-7 is an effector caspase and plays an central role in the execution phase of the apoptosis.

### Expression

Caspase-7 is widely expressed in human tissues. Highly expressed in lung, skeletal muscle, liver, kidney, spleen and heart, and moderately in testis.

### Localisation

Mainly in the cytoplasm, but also observed in the nucleus.

### Function

Effector caspases are responsible for initiating the hallmarks of the degradation phase of apoptosis, including DNA fragmentation, cell shrinkage and membrane blebbing.

Besides its activation during apoptosis, proteolytic maturation of caspase-7 has also been observed under inflammatory conditions.

### Homology

CASP7 (*P. troglodytes*, *M. mulatta*, *C. lupus*, *B. taurus*, *G. gallus*), Casp7 (*M. musculus*, *R. norvegicus*), casp7 (*X. tropicalis*, *D. rerio*), Ice (*D. melanogaster*), Dcp-1 (*D. melanogaster*), CASPS7 (*A. gambiae*).

## Mutations

Soung et al. (2003) detected CASP7 mutations in 2 of 98 colon carcinomas (2%), 1 of 50 esophageal carcinomas (2%), and 1 of 33 head/neck carcinomas (3%).

Expression of the tumor-derived CASP7 mutants in 293T cells showed that apoptosis was reduced compared to the wild-type caspase-7, suggesting that inactivating mutations of CASP7 might contribute to the pathogenesis of some human solid cancers.

Genetic polymorphisms in the CASP7 gene may affect cancer risk through altering expression levels and functions of this gene. Several polymorphisms have been associated with susceptibility of cancer development, as will be discussed later (Yan et al., 2013).

A detailed list of genetic variations could be found at: Ensembl.

## Implicated in

### Lung cancer

#### Note

Lee et al. (2009) showed that the CASP7 rs2227310 g.C>G polymorphism was associated with the risk of lung cancer.

Yoo et al. (2009) also demonstrated that the CASP7 rs2227310 polymorphism may affect survival in early-stage non-small cell lung cancer (NSCLC), suggesting that the analysis of this polymorphism can help identify patients at high risk for a poor disease outcome.

Qian et al. (2012) also provided evidence that genetic variations of CASP7 may modulate overall survival and progression-free survival of patients with advanced NSCLC treated with platinum-based chemotherapy.

### Esophageal cancer

#### Note

Liu et al. (2010) described that polymorphisms in CASP7 gene was associated with increased risk of esophageal cancer.

### Childhood leukemia

#### Note

Park et al. (2012) suggested that three SNPs in CASP7 acts as a strong apoptosis signal that block

or delay the apoptosis of childhood leukemia cancer cells.

### **Colorectal cancer**

#### **Note**

Palmerini et al. (2001) described a loss of caspase-7 in 84% of colon cancers, suggesting that caspase-7 deficiency might be used as a new immunohistochemical marker of colonic neoplasia. Chae et al. (2011) reported that CASP7 rs2227310 polymorphism may be useful marker to predict the prognosis of patients with surgically resected colorectal cancer.

### **Gastric cancer**

#### **Note**

Yoo et al. (2004) observed loss of capase-2, capase-6 and capase-7 expression in gastric cancers irrespective of depth of invasion and histological subtypes suggesting a role in the development of gastric cancers.

### **Endometrial cancer**

#### **Note**

The AA genotype of rs11196445b, the CC genotype of rs3124740, and the GG genotype of rs10787498 in the CASP7 gene were associated with increased risk compared with homozygotes of the major alleles, suggesting that genetic variants in CASP7 may play a role in endometrial cancer susceptibility in a Chinese population (Xu et al., 2009).

### **Renal carcinoma**

#### **Note**

Vilella-Arias et al. (2013) reported loss of CASP7 protein expression in renal cell carcinoma clear cell subtype (ccRCC) and this loss was associated with the aggressiveness of ccRCC, suggesting the potential use of CASP7 as a prognostic marker.

### **Oral squamous cell carcinoma**

#### **Note**

Coutinho-Camillo et al. (2011) reported that high expression level of CASP7 protein was associated with poor prognosis in oral squamous cell carcinoma (OSCC) patients.

### **Alzheimer's disease**

#### **Note**

Elevated mRNA levels of caspases-7 and 8 measured by a quantitative PCR method were observed in the Alzheimer's disease (AD) temporal neocortex as compared to the control brains, suggesting that the transcriptional activation of key components of the apoptotic cascade correlates with accumulation of Aβ42.

Thus, a principal caspase pathway from caspase-8 to caspase-3 and/or 7 may contribute to neuron loss in AD brain (Matsui et al., 2006).

### **Huntington's disease**

#### **Note**

Hermel et al. (2004) reported that caspase-7 immunoreactivity in post-mortem tissue from Huntington's disease (HD) patients is dramatically enhanced in the medium spiny neurons of the caudate nucleus and neurons in the putamen when compared to age-matched controls.

Caspase-7 is able to bind full-length huntingtin (Htt), accelerating the production of Htt fragments and resulting in the eventual induction of apoptosis both in the neuronal processes and somata.

### **Rheumatoid arthritis**

#### **Note**

CASP-7 gene is associated with the susceptibility to rheumatoid arthritis (RA). Genotyping of three single nucleotide polymorphisms (SNPs) of the CASP7 gene: rs11593766 (G/T), rs2227310 (C/G) and rs2227309 (G/A) revealed that rs2227309 SNP was found to be associated with susceptibility to RA.

Frequency of the G allele was significantly higher among RA patients and a higher frequency of GG homozygous individuals was found in the RA patient group (Garcia-Lozano et al., 2007).

Teixeira et al. (2008) found that CASP7 rs2227309 SNP was not associated with RA in a European Caucasian population. Nevertheless, CASP7 isoforms alpha and beta could be involved in the apoptosis process in RA.

### **Insulin-dependent diabetes mellitus**

#### **Note**

Babu et al. (2003) studied 18 SNPs in CASP7 and reported that 1 (SNP144692) differed significantly in frequency in the haplotypes found in affected individuals compared to control Bedouin Arab family haplotypes. This same SNP showed evidence of association with diabetes in a subset of patients (DR3/DR4\*0302) from Human Biological Data Interchange (HBDI) families, although these results are in conflict with other studies.

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*This article should be referenced as such:*

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