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Gene Section

Review

CASP8AP2 (caspase 8 associated protein 2)

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Abstract

CASP8AP2 was initially identified as a pro-apoptotic protein that transmits an apoptosis indication through the death-inducing signaling complex.

More recently, diverse functions have been described including TNF-induced NF-kappaB activation, cell-cycle progression and cell division, regulation of histone gene transcription and histone mRNA processing.

Keywords

CASP8AP2

Identity

Other names: FLASH, CED-4, FLJ11208, KIAA1315, RIP25

HGNC (Hugo): CASP8AP2

Location

6q15 ; CASP8AP2 gene is located on the long arm of chromosome 6 NC_000006.12, in opposite orientation

DNA/RNA

Description

44,537 bp; 10 exons

Transcription

Three transcripts reported at NCBI: Variant1, 6,821bp NM_012115.3; Variant2, 6,782bp NM_001137667.1; Variant3, 6,649bp NM_001137668.1. Alternative splicing results in multiple transcript variants encoding the same protein.

Protein

Description

Size 1982 amino acids; 222,658 kDa protein.

It contains a motif structurally related to CED4/Apaf1 (602233) and a C-terminal death effector domain (DED)-recruiting domain (DRD); a NCOA2-binding domain (position 1709-1982aa); a SUMO interaction motifs: SIM1 (position 1683-1687aa), SIM2 (position 1737-1741aa, SIM3 (position 1794-1798aa) which mediate the binding to polysumoylated substrates.

The FLASH activity is regulated by sumoylation (Alm-Kristiansen et al., 2009).

Localisation

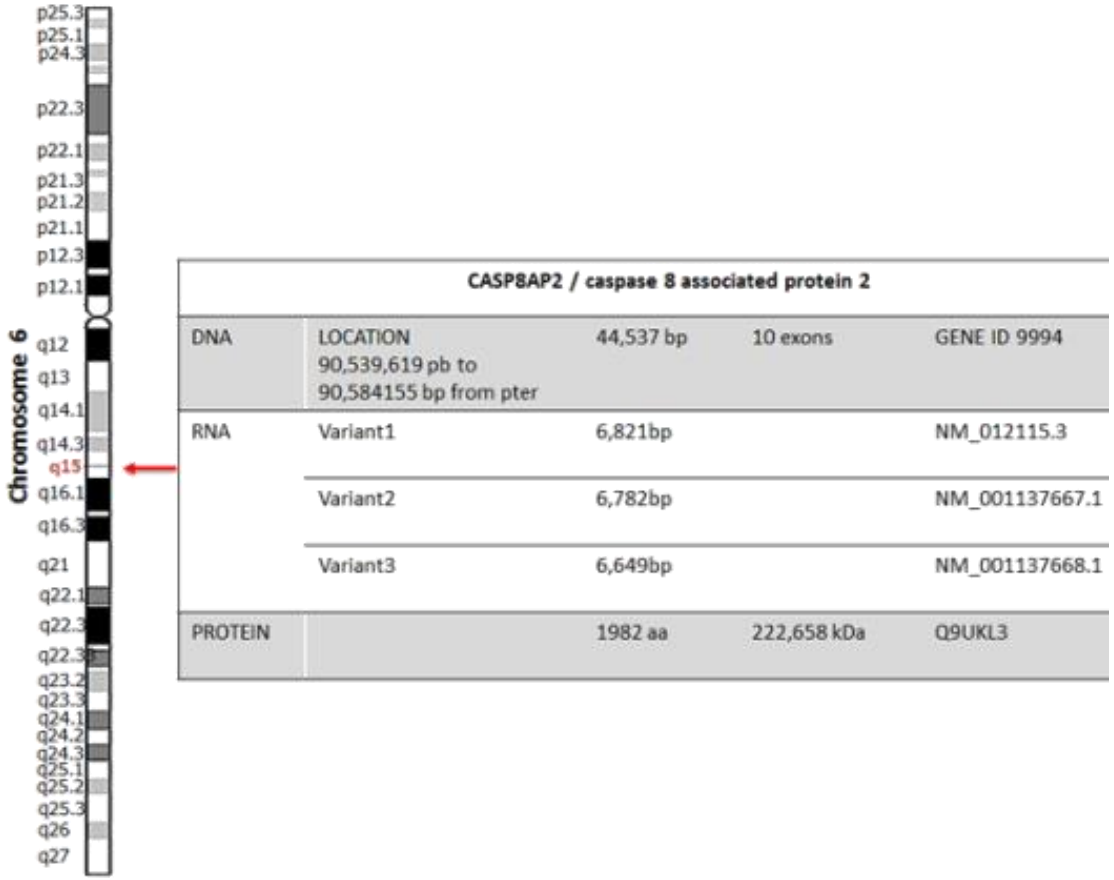
Nucleus, cytoplasm, mitochondrion.

Function

Component of the apoptosis signaling pathway required for the activation of CASP8 in Fas-mediated apoptosis (Imai Y et al., 1999).

Component of the machinery required for histone precursor mRNA expression and essential for 3end maturation of histone mRNAs (Barcaroli D et al., 2006; De Cola et al., 2012; Yang XC et al., 2009).

It participates in TNF-alpha-induced blockade of glucocorticoid receptor transactivation at the nuclear receptor coactivator level, upstream and independently of NF-kappa-B (Kino and Chrousos, 2003). It also contributes to cell cycle progression at S phase (Kiriyama et al., 2009; Barcaroli D et al., 2006).



Genomic location and gene products of CASP8AP2. The gene is located at 6q15, it has three transcripts, and all of them encode the same protein.

Homology

Caenorhabditis elegans protein CED-4; Mus musculus protein FLASH

Implicated in

t(6;11)(q15;q23)

Disease

Acute myeloid leukemia. A t(6;11)(q15;q23) in a 50-year-old Korean woman with acute myeloid leukemia has been reported (Park TS et al., 2009).

Hybrid/Mutated gene

A MLL/CASP8AP2 fusion was identified by LDI-PCR and sequencing, a rearrangement between MLL (intron 8) and CASP8AP2 (intron 7) was detected at the genomic DNA level. The breakpoint analysis at the transcription level was not performed due to lack of a cDNA specimen

Oncogenesis

MLL/CASP8AP2 seems to be related to poor clinical outcome, however, further studies are needed to evaluate prognosis.

Acute lymphoblastic leukemia

CASP8AP2 low expression

Prognosis

The clinical significance of CASP8AP2 was first reported by (Flotho C et al., 2006), the differences in its expression levels were significantly associated with early response to treatment and the presence of minimal residual disease (MRD). CASP8AP2 expression was analyzed in 99 children with acute lymphoblastic leukemia (ALL) enrolled in the St. Jude Total Therapy Study XIII protocol. Patients with low levels of expression presented a lower event-free survival and higher incidence of relapse, in contrast to patients with higher expression levels. High expression was associated with greater propensity of leukemic cells to undergo apoptosis. In this study CASP8AP2 was considered as an independent prognostic marker for relapse (Flotho C et al., 2006).

The usefulness of CASP8AP2 expression as a potential marker of response to treatment has been analyzed in leukemic patients from different populations. In a cohort of 39 newly diagnosed ALL children treated with the Beijing Children`s Hospital (BCH)-ALL 2003 protocol, the bone marrow expression of CASP8AP2 at diagnosis resulted a suitable indicator of relapse. In the same study, another cohort of 106 patients enrolled in the

Chinese Childrens Leukemia Group (CCLG)-ALL 2008 protocol were also analyzed, patients with low CASP8AP2 expression showed higher relapse rates, lower relapse-free survival and lower overall-survival, in comparison to the higher-expression group (Jiao Y et al., 2012).).
In an independent study a gene signature of 14 genes, including CASP8AP2 and H2AFZ, was identified (Flotho C et al., 2007); their low expressions were associated to relapse. Based on this result, the expressions of CASP8AP2 and H2AFZ were analyzed in a cohort of 88 ALL Mexican children treated with the Popular Medical Insurance protocols (Juárez-Velázquez R et al., 2014). An increased risk for early relapse in patients with low expression of CASP8AP2 was found, confirming its usefulness as a risk marker; the H2AFZ expression did not showed the same effect. The CASP8AP2 expression was not an independent marker of relapse, but combined characteristics as the low expressions of both genes and high white blood cell count, identified more accurately patients at greater risk of relapse (Juárez-Velázquez R et al., 2014). Although the prognostic value of CASP8AP2 expression as an independent factor is controversial (Yang YL et al., 2010), combined with expressions of other genes such as H2AFZ (Juárez-Velázquez R et al., 2014) and ARS2 (Cui L et al., 2015), could more precisely predict high risk of relapse in ALL.).
Epigenetic modifications are also related to the down-regulation of CASP8AP2. DNA hypermethylation of the gene promoter was analyzed in 86 children with ALL, treated according to the BCH-2003 and CCLG-2008 protocols. The percentage of methylation of two CpG sites at positions -1189 and -1176 were inversely correlated with mRNA expression. The patients with higher methylation presented MRD and poor treatment outcome. The results suggested that combination of methylation level and MRD might improve current risk stratification (Li ZG et al., 2013). In regard to these findings, it has been demonstrated that methylation of the CASP8AP2 promoter in somatic stem cells and cancer cells increase their resistance to drugs (Lee KD et al., 2012). These data associate this epigenetic modification with the development of drug resistance.

T-cell acute lymphoblastic leukemia) (T-ALL)

A del(6)(q15-q16.1) has been reported in approximately 12% of T-ALL patients. This deletion includes the CASP8AP2 gene, whose mRNA expression was the single most down-regulated gene of all 7 genes located in the deleted region.

Prognosis

The lower expression of CASP8AP2 has been also associated to deletions at band 6q15-q16.1, which are often detected in patients with T-ALL (Remke M et al., 2009). These deletions result in down regulation of the gene and poor early response to treatment. In 73 T-cell ALL samples obtained from patients enrolled in the multicenter ALL-BFM 1990, ALL-BFM 1995 and ALL-BFM 2000 protocols, deletion 6q15-q16.1 was associated with unfavorable MRD levels. Although deletion 6q15-q16.1 involves several genes, CASP8AP2 was the single one with a better association between the deletion and the less efficient induction of apoptosis by chemotherapy (Remke M et al., 2009).

Cytogenetics

The del(6)(q15-q16.1)comprises 2.54 Mb.

Diffuse large B-cell lymphomas)(activated B-cell like subtype)

Loss of CASP8AP2 in 35% of cases. Imbalance with possible pathogenic relevance (Scholtysik R et al., 2015).

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