

Gene Section

Short Communication

AVEN (apoptosis, caspase activation inhibitor)

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Published in Atlas Database: October 2013

Online updated version : <http://AtlasGeneticsOncology.org/Genes/AVENID43158ch15q14.html>
DOI: 10.4267/2042/53640

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Abstract

Review on AVEN, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: PDCD12

HGNC (Hugo): AVEN

Location: 15q14

DNA/RNA

Description

The human AVEN gene is located on the reverse strand of chromosome 15 (bases 34158428 to 34331303; according to NCBI RefSeq gene database (gene ID: 57099; Refseq ID: NM_020371.2), genome assembly GRCh37 from February 2009) of the human genome and is comprised of 172876 bp. AVEN consists of 6

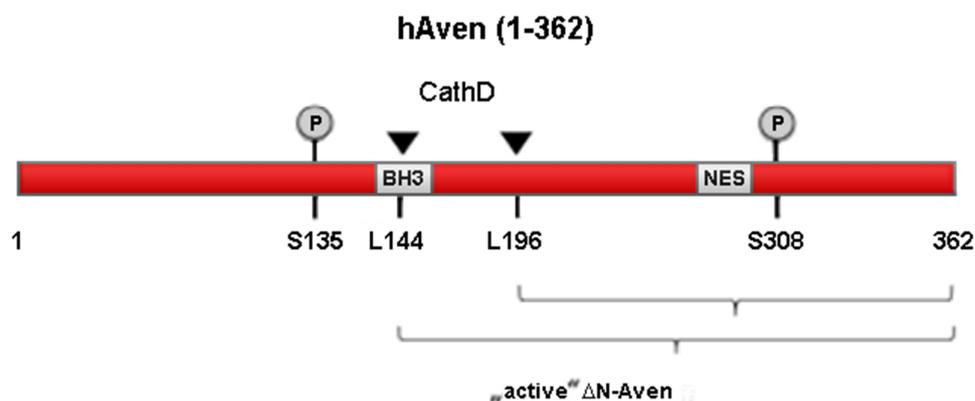
exons, ranging in length between 70 and appr. 500 bp and 5 introns varying largely in size (from few 100 bp to some Mb). According to the Ensembl genome browser database (ENSG00000169857), there are three transcript variants of AVEN of which only one leads to the translation of a functional protein whereas the other two are degraded by nonsense-mediated decay or do not encode for a functional protein product.

Transcription

According to the NCBI database, the human AVEN gene encodes for a 1551 bp mRNA transcript, the coding sequence ranging from bp 57 to 1145. The CDS in the Ensembl genome browser database (ENSG00000169857) is identical to the NCBI CDS (NM_020371.2). The transcript NM_020371.2 is also included in the human CCDS set and encodes for a protein of 362 aa.

Pseudogene

None known.



AVEN protein: 1-362 aa. Cathepsin D cleavage sites: L144 and L196; putative BH3 domain: aa141-153; NES: aa282-293. ATM kinase phosphorylation sites: S 135 and S 308.

Protein

Description

The AVEN protein possesses no predicted domains according to the NCBI database. However, a sequential proteolytic processing of AVEN by the lysosomal protease cathepsin D has been published (Melzer et al., 2012), leading to the cleavage of AVEN at aa 144 and 196 and the generation of a shorter isoform (deltaN Aven) that is supposed to be associated with the antiapoptotic function. Moreover, AVEN is able to bind to the DNA damage response regulating kinase ATM (ataxia telangiectasia mutated) and is phosphorylated by ATM at S135 and S308 (Guo et al., 2008). In addition, a potential nuclear export sequence (NES) to exists between aa 282-293 (Esmaili et al., 2010) and a putative BH3 motif (for binding to Bcl-xL) has been predicted to be located between aa 141-153 (Hawley et al., 2012).

Expression

Widely expressed throughout the human organism (Chau et al., 2000).

Localisation

Mostly cytosolic, punctuate, reticular pattern (associated with intracellular membrane localization, lysosomal?) in the cytosol (Chau et al., 2000), diffuse nuclear staining (Esmaili et al., 2010).

Function

Antiapoptotic:

AVEN was first discovered as an interactor of the antiapoptotic Bcl-xL protein by Chau et al. (2000). It was also shown to bind to the proapoptotic APAF-1 protein and postulated to prevent the oligomerization of APAF-1 (apoptosome formation) in the intrinsic apoptosis pathway and to stabilize the Bcl-xL protein by binding to it (Kutuk et al., 2010). Putative binding sites in Bcl-xL are predicted to be located in the Bcl-xL BH1 and BH4 domains (Hawley et al., 2012). Recently, it was shown that AVEN can be processed by the lysosomal protease Cathepsin D at aa 144 and 196, and that this processing is necessary to activate AVEN's antiapoptotic function (Melzer et al., 2012). It is still unclear whether it is the stabilization of Bcl-xL, the interference with apoptosome assembly or another feature of AVEN that is responsible for the antiapoptotic capacity of this protein.

DNA damage repair:

It was shown by Guo et al. (2008) that AVEN, in addition to binding to the apoptotic machinery, is also able to bind one of the key players in DNA damage repair, the ataxia telangiectasia mutated (ATM) kinase. Overexpression of AVEN in

Xenopus laevis egg extracts induced a cell cycle arrest at G2/M which is in large part ATM dependent, whereas the absence of AVEN impaired ATM-mediated checkpoint function. An intrinsic loop of activation exists between AVEN and ATM: AVEN binds to the kinase domain of ATM (appr. aa 2500-3000) and, in turn, is phosphorylated by ATM at S135 and S308.

This phosphorylation seems to enhance AVEN's activating influence on ATM. Esmaili et al. (2010) were able to demonstrate that AVEN possesses a nuclear export signal (NES) which is located between aa 282 and 293. Under normal physiological conditions, AVEN is shuttled outside of the nucleus by Exportin-1/CRM1 whereas inhibition of CRM1 by leptomycin or mutation of the AVEN NES leads to nuclear accumulation of the protein. The NES/nuclear-cytosolic shuttling of AVEN might be important for its cell cycle regulatory functions and its role in DNA damage repair.

Depending on the degree of DNA damage, AVEN is possibly a multifunctional protein, finetuning the cellular decisions of cell cycle arrest and apoptosis in the DNA damage response.

Homology

No close orthologs of AVEN in humans are known. However, Hawley et al. (2010) note homology to Bik (58% homology over a 77 aa region encompassing the putative BH3 homology domain). Homologs of AVEN can be found in several species, like mouse (NCBI acc. Nr. NP_083120), *Drosophila* (NP_572817), rat (NP_001101227), chicken (NP_001005791; Vezyri et al., 2011) and *Xenopus* (NP_001090621; Guo et al., 2008). Of note, two isoforms are postulated to exist in mouse, the second one (NP_001159407) possessing a distinctly shorter N-terminus than the full length protein. However, nothing is known about the function or biological relevance of this predicted second isoform. Functional similarity to the human protein in its cell cycle regulatory properties has been published for the *Drosophila* (Zou et al., 2011) and the *Xenopus* homologs (Guo et al., 2008).

Implicated in

Acute leukemias

Note

AVEN is a putative oncogene which is overexpressed in T- cell acute lymphoblastic leukemia.

First reports that AVEN is overexpressed on mRNA level in acute leukemias were published by Paydas et al. in 2003.

The authors investigated a study group consisting of 37 acute myeloblastic leukemias (AML) and 28 acute lymphoblastic leukemia (ALL) patients.

Details regarding the number of ALL patients who were either of the frequent B-cell type or had developed T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) were not given.

In this study, elevated Aven mRNA expression levels were noted in acute leukemias, and the authors suggest that AVEN could be a new prognostic marker in this cancer entity.

Choi et al. (2006) describe a positive correlation between Aven mRNA overexpression and poor prognosis in childhood ALL.

A recent study by Eissmann et al. (2013) shows proof that overexpression of AVEN contributes to increased malignancy in hematopoietic neoplasms. Here, the authors confirm overexpression of AVEN in T-ALL patient samples compared to healthy T cells on protein level.

Furthermore, using a transgenic mouse model with T-cell specific overexpression of AVEN, an oncogenic cooperation of AVEN with heterozygous loss of p53 is shown.

Additionally, in subcutaneous mouse xenograft models, the authors show that downregulation of AVEN expression via shRNA leads to significantly decreased, if not halted, tumor growth indicating AVEN as a putative novel therapy target for T-ALL and AML.

Breast cancer

Note

Two other studies implicate AVEN in breast cancer (Kutuk et al., 2010; Ouzounova et al., 2013).

Kutuk et al. describe decreased nuclear expression of AVEN in breast cancer tissue microarrays, in particular in infiltrative ductal carcinoma and papillary carcinoma compared to non-neoplastic breast tissue and infiltrating lobular breast cancer. They suggest that AVEN might be an important mediator in DNA damage-induced apoptotic signalling and its nuclear downregulation in breast cancer can lead to genomic instability.

A recent study by Ouzounova et al. shows that AVEN is an inversely regulated downstream target of the miR-30 family which is important for regulation of breast cancer cells under non-attachment conditions.

Overexpression of miR-30 family members reduces breast tumor progression and tumorsphere formation (and AVEN expression), an effect which could be partially rescued by AVEN re-/overexpression, suggesting, in contrast to the other study, that rather overexpression (than downregulation or nuclear depletion) of AVEN is important for breast tumor growth.

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This article should be referenced as such:

Melzer IM, Zörnig M. AVEN (apoptosis, caspase activation inhibitor). *Atlas Genet Cytogenet Oncol Haematol*. 2014; 18(5):311-313.
