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Gene Section
Review

HTRA1 (HtrA serine peptidase 1)

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Identity

Other names: ARMD7; HtrA; L56; ORF480; PRSS11

HGNC (Hugo): HTRA1

Location: 10q26.13

Local order: Genes flanking HTRA1 in centromere to telomere direction:
- PLEKHA1: pleckstrin homology domain-containing family A (phosphoinositide-binding specific) member 1;
- ARMS2/LOC387715: age-related maculopathy susceptibility 2 (hypothetical protein);
- **HTRA1**;
- DMBT1: deleted in malignant brain tumors;
- C10orf120/LOC399814: chromosome 10 open reading frame (hypothetical protein).

Note

Abberrations on 10q26.3 are reported to be associated with ovarian cancer. The 10q26.3 region shows high frequency of deletion in ovarian cancer.

Genetic variations on chromosome 10q26 (outside variations in the complement genes) are associated with an increased risk of the development of AMD (age-related macular degeneration).

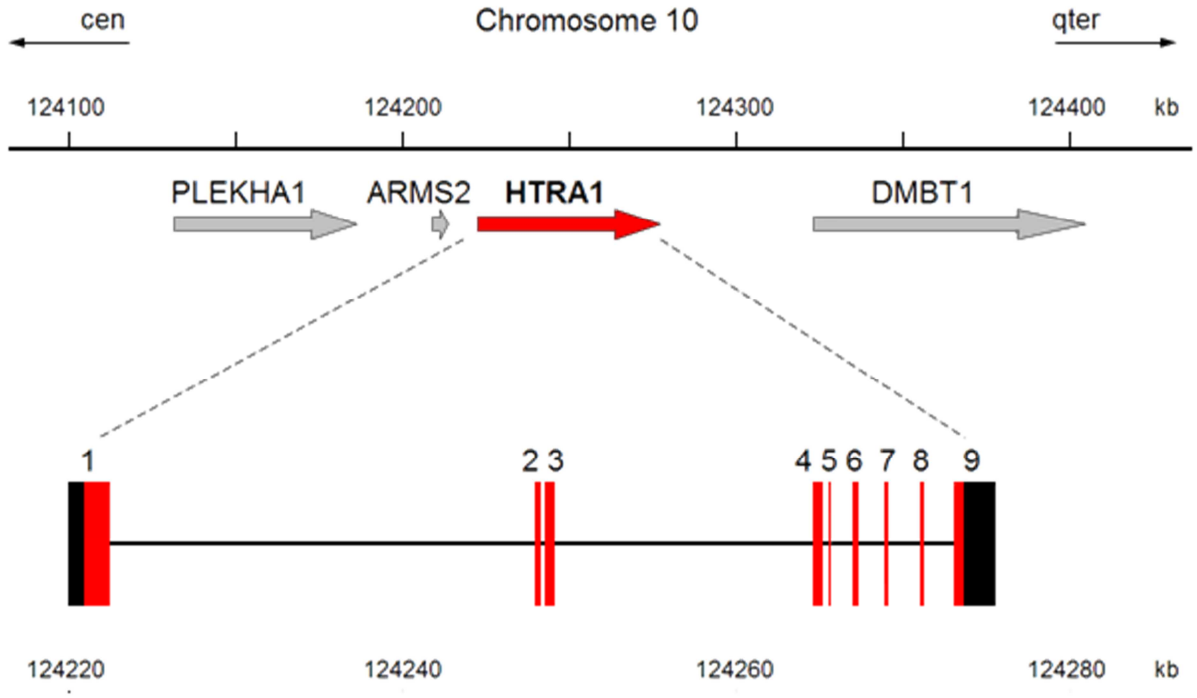

Figure 1. Localization and schematic organization of the HTRA1 gene on chromosome 10. The numbers indicate the length in kilo bases. Red boxes represent exons. Black boxes indicate untranslated regions.

Several single-nucleotide polymorphisms (SNPs) of the ARMS2/HTRA1 region of chromosome 10q26 have been identified. They contribute to the development of typical neovascular AMD, polypoidal choroidal vasculopathy (PCV), which is classified as a subtype of neovascular AMD, and nonneovascular AMD as well (Cameron et al., 2007; Gotoh et al., 2010; Tong et al., 2010; Friedrich et al., 2011).

DNA/RNA

Description

The gene encompasses 53384 bases of DNA. The coding part is composed of nine exons.

Transcription

HTRA1 mRNA product, length of 2138 bases, has an open frame of 1443 bp. The gene encodes a 50 kDa polypeptide of 480 amino acids residues.

A single-nucleotide polymorphism (SNP) rs11200638 located in the HTRA1 promoter has been found in AMD (age-related macular degeneration) patients. The sequence change is located 512 basepairs upstream of the transcriptional start site of the HTRA1 gene (-512G/A) within a CpG island. It resides within the putative binding sites for transcription factors, AP2alpha (adaptor-related protein complex 2alpha) and SRF (serum response factor) (Yang et al., 2006; DeWan et al., 2006). Much debate exists regarding the functional significance of the HTRA1 promoter SNP and its influence on the HTRA1 gene expression. It was demonstrated that the HTRA1 promoter SNP is associated with the enhanced expression of the HTRA1 gene in lymphocytes and retinal pigment epithelium from AMD patients (Yang et al., 2006; DeWan et al., 2006). An et al. (2010) showed that increased expression of HTRA1 in retinal pigment epithelium cells form AMD patients harbouring homozygous risk genotype in comparison to wild type genotype. However, two independent studies did not show any influence of the risk variant on the HTRA1 expression in human lymphocytes and retina (Kanda et al., 2007; Chowers et al., 2008). Moreover, Kanda et al. (2010) did not find association between the rs11200638 SNP and steady-state expression of HTRA1 in retina of AMD patients. Results of reporter gene assays with HTRA1 promoter sequence provide no evidence for the influence of the rs1120638 SNP on the HTRA1 promoter activity (Friedrich et al., 2011). Friedrich et al. (2011) revealed also the presence of a Muller glia-specific cis-regulatory region located between -3550 and -2770 bp upstream of the HTRA1 transcription start site.

Pseudogene

No pseudogenes have been identified.

Protein

Note

HtrA1 protein belongs to the HtrA family of proteins. Members of the family are homologs of the HtrA protein from the bacterium Escherichia coli. They are evolutionarily conserved ATP-independent serine proteases, widely distributed from bacteria to humans. Structurally, the HtrA proteins are characterized by the presence of a trypsin-like protease domain and at least one PDZ domain at the C-terminus. The defence against cellular stresses inducing abberrations in protein structure is believed to be a general function of HtrAs (reviewed by Clausen et al., 2002). At least four human homologous HtrA proteins have been identified. They are involved in maintenance of mitochondrial homeostasis, apoptosis and cell signaling and disturbances in their functions may contribute to the development of several diseases including cancer, arthritis and neurodegenerative disorders (reviewed by Zurawa-Janicka et al., 2010). HTRA1 was originally identified as a gene downregulated in SV40-transformed fibroblasts (Zumbrunn and Trueb, 1996).

Description

The HTRA1 gene encodes a polypeptide of 480 aa and of a mass of approximately 50 kDa.

The full-length HtrA1 protein contains a signal secretory peptide at the N-terminus (residues 1-22), a domain with homology to the insulin-like growth factor binding proteins (residues 25-111), a Kazal-type inhibitor motif (residues 115-135), and the evolutionarily conserved trypsin-like domain (residues 206-364) with the amino acid residues of serine protease catalytic triad (H220, D250, S328), and the PDZ domain (residues 382-473) at the C-terminus.

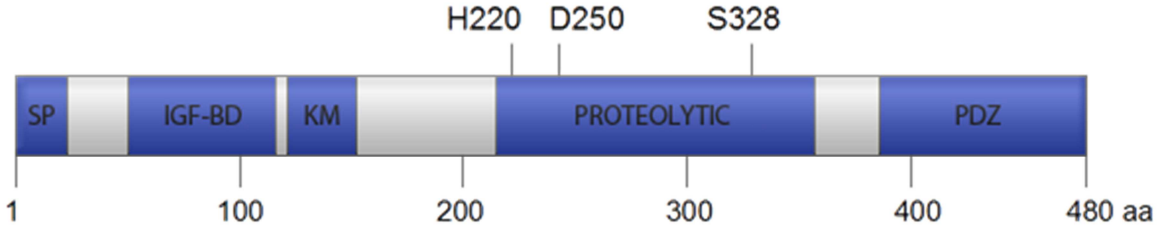

Figure 2. Domain organization of human HtrA1 protein. SP: signal peptide, IGF-BD: domain with homology to insulin-like growth factor binding proteins, KM: Kazal type serine protease inhibitor motif, PROTEOLYTIC: trypsin-like domain, PDZ: PDZ domain. Amino acid residues of the HtrA1 catalytic triad are marked (numbers indicate the position of the given residue in a polypeptide chain).

Under treatment of ovarian cancer cells with chemotherapeutic agents (cisplatin, paclitaxel) a removal of the N-terminal Mac25 domain was observed. The resulting product, mass of 35 kDa, expressed more active phenotype than the full-length protein (Chien et al., 2006). The proteolytic processing is believed to be an autocatalytic process since the catalytically inactive mutant did not undergo such modification.

The processed form of HtrA1, mass of 29 kDa was detected in CaSki cells (human cervical cancer line) and in 293T cells (human embryonic kidney line). The 29 kDa product was found to be a predominant active form in the nuclear fraction (Clawson et al., 2008).

The lower molecular weight products were also generated under overproduction of proteolytically active HtrA1 in heterologous expression systems (Hu et al., 1998).

Expression

HTRA1 is widely expressed in human tissues. High expression was detected in secretory breast epithelium, duct cells of liver, kidney tubules of cortex and in the glandular epithelium of proliferating endometrium. The highest expression was detected in mature layers of epidermis (De Luca et al., 2003).

It was demonstrated that HTRA1 expression in glandular and stromal cells increases gradually across menstrual cycle and reaches the maximum level at the mid- and late secretory phases (Nie et al., 2006). It was also reported that HTRA1 expression changes during pregnancy both in placental and endometrial cells. Up-regulation of HTRA1 was observed in endometrial glands and decidual cells during preparation of endometrium for embryo implantation and during the first trimester of placentation (Nie et al., 2006). However, the highest expression of HTRA1 was detected in placenta in the third trimester of gestation (De Luca et al., 2004). These data suggest an important role of HtrA1 in placenta development and function.

Changes in HTRA1 expression were observed in response to stress-inducing agents. Upon treatment of ovarian cancer cells expressing HTRA1 with the commonly used chemotherapeutics the HtrA1 protein level estimated by the Western blotting technique was increased (Chien et al., 2006).

Abnormal expression of the gene is associated with several diseases, including arthritis and many types of cancers.

Localisation

HtrA1 is classified as a secreted protein. However, processed forms of HtrA1 have been found in the cytoplasm and in the nuclear fraction (Clawson et al., 2008; Chien et al., 2009; He et al., 2010).

Function

HtrA1 acts as an ATP-independent serine protease.

HtrA1 has been shown to function as a regulator of TGF-beta signaling. HtrA1 binds to several members of the TGF-beta proteins family, including TGF-beta1, TGF-beta2, BMP2, BMP4, activin and Gdf5, and suppresses signal transduction mediated by these extracellular cytokines (Oka et al., 2004). It was demonstrated that the proteolytic activity of HtrA1 is indispensable for this inhibitory function (Oka et al., 2004). Recent studies showed also that TGF-beta1 is a substrate for HtrA1 in vitro (Launay et al., 2008). However, a hypothesis that degradation of TGF-beta proteins is the underlying mechanism of TGF-beta signaling regulation by HtrA1 needs further studies.

HtrA1 is involved in the programmed cell death, apoptosis. Treatment of the ovarian cancer cells with cisplatin or paclitaxel resulted in upregulation of HtrA1 expression. Under these conditions HtrA1 underwent autocatalytic activation resulting in activation of caspases 3 and 7 associated with apoptotic cell death. However, the mechanism of the process is unknown and needs to be elucidated (Chien et al., 2006).

HtrA1 is implicated in anoikis, a cell death induced by anchorage-dependent cells detaching from the surrounding extracellular matrix. Resistance to anoikis is a common feature of cancer cells and contributes to metastasis. HtrA1 regulates anoikis by modulating the EGFR/AKT pathway (He et al., 2010). HtrA1 binds to EGFR and inhibits EGRF/AKT pathway in a protease-dependent manner. It was demonstrated that HtrA1 expression was upregulated and underwent autocatalytic activation in response to loss of anchorage in suspended culture of ovarian cancer cells. Enhanced expression of HtrA1 in ovarian cancer cells suppressed EGFR/AKT signaling, which contributed to increased cell death, whereas downregulation of the gene attenuated anoikis in vitro and also promoted peritoneal dissemination of ovarian cancer cells in mouse model (He et al., 2010).

Homology

The HtrA1 protein is evolutionarily conserved among mammalian species. At the amino acid level the human HtrA1 shares a 98% identity with its orthologues from mouse, cow, rabbit, guinea pig (Hu et al., 1998) and hamster (Zurawa-Janicka et al., 2008). At least three paralogs of HtrA1 have been identified in humans: HtrA2 (Omi), HtrA3 (PRSP) and HtrA4. HtrA1 protein shares the 54, 58 and 54% identity with HtrA2, HtrA3 and HtrA4 respectively. The homology between HtrA1 and its paralogs HtrA2, HtrA3 and HtrA4 reaches 75, 74 and 71%, respectively.

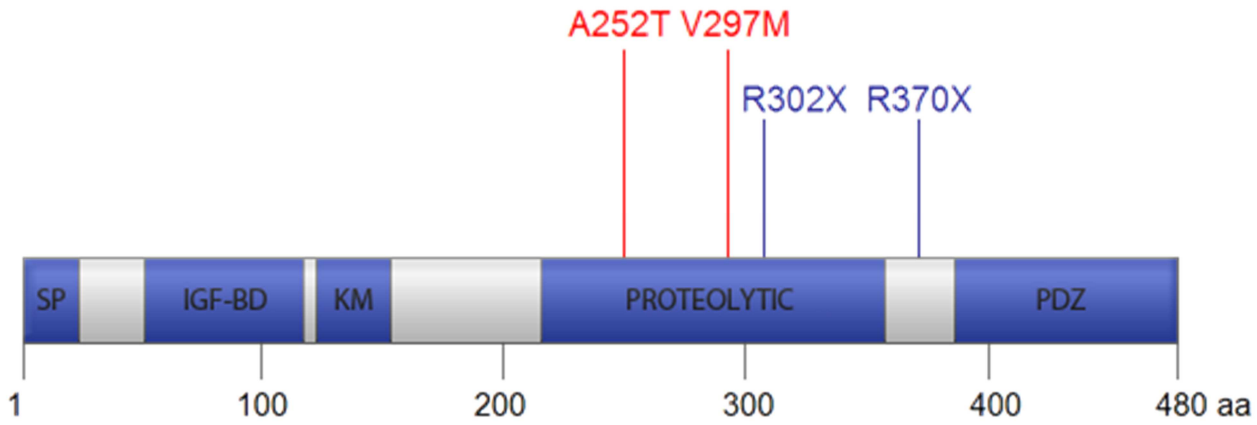

Figure 3. Distribution of HTRA1 mutations associated with CARASIL. Missense mutations are marked in red and nonsense mutations are marked in blue. SP: signal peptide, IGF-BD: domain with homology to insulin-like growth factor binding proteins, KM: Kazal type serine protease inhibitor motif, PROTEOLYTIC: trypsin-like domain, PDZ: PDZ domain.

Mutations

Germinal

Two missense mutations G754A (the amino acid substitution A252T) and G889A (the amino acid substitution V297M) and two nonsense mutations C904T and C1108T (resulting in a stop codon at position 302 and 370, respectively) localized in exon 3 and 4, associated with the development of cerebral autosomal recessive arteriopathy with subcortical infarts and leukoencephalopathy (CARASIL) have been identified in the HTRA1 gene (Hara et al., 2009). The nonsense mutation C1108T resulted in the loss of protein product by nonsense-mediated mRNA decay. Three other mutations reduced the HtrA1 proteolytic activity in vitro and also failed to repress the TGF-beta signaling pathway (Hara et al., 2009).

Somatic

Not known.

Implicated in

Various cancers

Note

The HTRA1 expression was found to be down-regulated in many types of cancers such as melanoma (Baldi et al., 2002), glioma (Kotliarov et al., 2006), mesothelioma (Baldi et al., 2008), ovarian tumors (Chien et al., 2004; Chien et al., 2006; Narkiewicz et al., 2008), endometrial (Bowden et al., 2006; Narkiewicz et al., 2009) and lung cancers (Esposito et al., 2006) as well as in the ovarian, some brain, breast and liver cancer cell lines (Chien et al., 2004).

The HTRA1 expression was reported to be down-regulated in ovarian cancer cells lines and tumors (Chien et al., 2004; Chien et al., 2006; Narkiewicz et al., 2008). In the primary ovarian tumors downregulation of the HTRA1 expression was correlated with a loss of heterozygosity of the gene and hypermethylation (Chien et al., 2004). Moreover, a progressive decrease of HTRA1 expression with degree of malignancy has been observed (Narkiewicz et al., 2008).

The HTRA1 mRNA and HtrA1 protein levels were also significantly decreased in the endometrial cancer (Bowden et al., 2006; Narkiewicz et al., 2009). The HTRA1 level decreased with increasing grades of endometrial cancer (Bowden et al., 2006). A significant negative correlation between HtrA1 and TGF-beta1 protein levels found in endometrial cancer suggests that HtrA1 is involved in regulation of the TGF-beta1 signaling pathway in this type of cancer (Narkiewicz et al., 2009).

The decreased expression of HTRA1 was found to be correlated with metastasis in melanoma and lung cancer. HTRA1 expression was significantly lower in the lymph node metastases than in primary tumors (Baldi et al., 2002; Esposito et al., 2006).

Prognosis

Downregulation of the HTRA1 gene, frequently observed in ovarian cancer was correlated with poor clinical response to chemoteraphy. In patients with primary ovarian tumors higher expression of HTRA1 corresponded to a better response to platinum-based chemotherapy. Similar clinical response to the cisplatin-based therapy was observed in a group of patients with gastric tumors (Chien et al., 2006). Loss of HtrA1 was also correlated with poor prognosis in glioma (Kotliarov et al., 2006) and mesothelioma (Baldi et al., 2008).

Cytogenetics

A loss of heterozygosity of the gene was observed in ovarian cancer (Chien et al., 2004). In the primary ovarian cancers HTRA1 expression was diminished or lost in 59% of cases. Analysis of tumor samples revealed that decreased expression of HTRA1 was associated with the loss of heterozygosity of the gene. On the other hand the HTRA1 locus was subjected to hypermethylation which might be another mechanism

of the HTRA1 gene silencing observed in ovarian cancer (Chien et at., 2004).

Hybrid/Mutated gene
Not known.

Abnormal protein
Not known.

Oncogenesis
HtrA1 is believed to function as a tumor supressor, promoting cell death due to its proapoptotic function and implication in anoikis. Thereby downregulation of the HTRA1 gene expression contributes to survival of cancer cells in vitro, and facilitates tumor growth, malignant progression and metastasis in vivo (Baldi et al., 2002; Chien et al., 2004; Chien et al., 2006; He et al., 2010). Lower expression of HTRA1 in ovarian and gastric tumors contributes to poor response to platinum-based chemotherapy (Chien et al., 2006).

Age-related macular degeneration (AMD)

Note
Several single nucleotide polymorphisms (SNP) associated with the development of AMD have been identified within the HTRA1 gene. Among them, the rs11200638 (G>A) SNP serves as a strong marker for AMD contributing to increased risk for the disease and association of the rs11200638 SNP with susceptibility to AMD in studies of Caucasian and Asian populations have been revealed (DeWan et al., 2006; Kondo et al., 2007; Yoshida et al., 2007; Cameron et al., 2007; DeAngelis et al., 2008; Tong et al., 2010). The SNP is located in the HTRA1 promoter, however its influence on HTRA1 expression in AMD patients is a matter of controversy (Yang et al., 2006; DeWan et al., 2006; Kanda et al., 2007; Kanda et al., 2010; Chowers et al., 2008; Friedrich et al., 2011; An et al., 2010).
The rs2672598 (C>T) SNP found within the promoter region was associated with decreased risk for neovascular AMD (DeAngelis et al., 2008).
Two minor SNPs, rs1049331 (C>T) and rs2293870 (G>T,C) were found within the coding region of HTRA1 and they resulted in synonymous substitutions in amino acid sequence. They were associated with an increased risk of neovascular AMD development (DeAngelis et al., 2008).
The rs2672587 (C>G) SNP was also demonstrated to be significantly associated with the development of neovascular AMD in Japanese patients (Goto et al., 2009).
Recent studies by An et al. (2010) showed that various regulators of the complement pathway such as vitronectin, clusterin, fibronectin are substrates for HtrA1 in vitro. It suggests an association between HtrA1 and the complement pathway in AMD (An et al., 2010).

Disease
AMD is a leading cause of irreversible blindness in the world and is associated with degeneration of the central retina. The neovascular, wet type of AMD is prevalent among Asian population, whereas Caucasians are predominantly affected by nonneovascular, dry form of AMD. Environmental and genetic risk factors have been found to be involved in the pathogenesis of AMD. Results of genetic analysis have demonstrated that susceptibility to AMD is strongly associated with genetic variants at chromosomes 1q31, encompassing the complement factor H (CFH) gene and 10q26, encompassing ARMS2/HTRA1 loci.

Alzheimer's disease (AD)

Note
Neuropathological analysis of brain samples from AD patients revealed colocalization of HtrA1 with beta-amyloid deposits. HtrA1 was detected in astrocytes and cortical neurons of AD patients in contrast to neuroglial cells of the healthy adult brains. Grau et al. (2005) demonstrated that HtrA1 performs in vitro proteolysis of various fragments of amyloid precursor protein, including beta40 and beta42. Using human astrocytoma cell line they showed that inhibition of HtrA1 proteolytic activity resulted in accumulation of beta-amyloid in cell culture supernatant. These results indicate that HtrA1 is involved in metabolism of beta-amyloid proteins and suggest that HtrA1 could protect against the development of AD (Grau et al., 2005).

Disease
AD is a neurodegenerative disorder characterized by progressive memory loss and cognitive decline. The pathological features of AD are neuronal and synaptic loss, formation of neurofibrillary tangles within neurons and accumulation of extracellular neurotoxic deposites of amyloid beta protein (Abeta), called senile plaques. Major components of senile plagues are Abeta40 and Abeta42, exhibiting tendency to aggregation and generated by hydrolysis of amyloid precursor protein (APP) amyloid in beta-amyloid pathway involving secretase beta and gamma.

Arthritic diseases (osteoarthritis and rheumatoid arthritis)

Note
Elevated level of HtrA1 was detected in cartilage of joints from patients with osteoarthritis (Hu et al., 1998) and in synovial fluid derived from patients with rheumatoid arthritis (Grau et al., 2006).
HtrA1 is believed to be involved in pathogenesis of arthritic disorders due to inhibition of TGF-beta signalling, proteolysis of extracellular matrix proteins and components of cartilage, and activation of metalloproteases. TGF-beta proteins are implicated in the maintenance of a normal joint cartilage by preventing joint chondrocytes from terminal differentiation. HtrA1 inhibits TGF-beta signaling and thereby might contribute to the replacement of articular cartilage by bone (Tsuchiya et al., 2005). Several proteins of the extracellular matrix and components of

cartilage such as aggrecan, decorin, fibromodulin, fibronectin, soluble type II collagen are substrates of the protease in vitro (Tsuchiya et al., 2005; Grau et al., 2006; Hadfield et al., 2008). HtrA1 is involved in activation of matrix metalloproteases -1 and -3 which contribute to extracellular matrix destruction (Grau et al., 2006).

Disease

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease characterized by a deforming symmetrical polyarthritis of varying extent and severity, articular cartilage loss and erosion of juxta-articular bone. RA can occur at any age. Osteoarthritis (OA) is a degenerative joint disease characterized by loss of articular chondrocytes and destruction of extracellular matrix components, leading to cartilage degeneration and restriction of joint mobility. The prevalence of OA increases with age.

Cerebral autosomal recessive arteriopathy with subcortical infarts and leukoencephalopathy (CARASIL)

Note

Hara et al. (2009) showed that CARASIL is associated with mutations in the coding sequence of the HTRA1 gene. Two missense mutations and two nonsense mutations have been identified in CARASIL patients. These mutations have been found to be liable for the loss of HtrA1 protein and generation of the HtrA1 variants with a reduced activity in vitro and lacking the ability to inhibit signalling mediated by TGF-beta proteins. Hara et al. (2009) postulated that the increased TGF-beta signalling, associated with the reduced activity of HtrA1 protease in the cerebral small arteries, contributes to the development of CARASIL.

Disease

CARASIL is a hereditary form of ischemic, nonhypertensive, cerebral small-vessel disease with associated deterioration in brain functions, progressive dementia, alopecia, spondylosis and disk degeneration linked to osteophytosis. Histopathologically, CARASIL is characterized by intense arteriosclerosis, limited to cerebral small arteries, associated with intimal thickening and dense collagen fibres, loss of vascular smooth muscle cells and hyaline degeneration of the tunica media.

Breakpoints

Note

No breakpoints described so far.

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