HTRA1 Gene

Subjects: Genetics & Heredity
Contributor: Dean Liu

HtrA serine peptidase 1

Keywords: genes

1. Introduction

The *HTRA1* gene provides instructions for making a protein that is found in many of the body's organs and tissues. This protein is a type of enzyme called a serine protease, which has an active center that cuts (cleaves) other proteins into smaller pieces. The HTRA1 enzyme helps break down many other kinds of proteins in the space surrounding cells (the extracellular matrix).

The HTRA1 enzyme also attaches (binds) to proteins in the transforming growth factor-beta (TGF-β) family and slows down (inhibits) their ability to send chemical signals. TGF-β proteins normally help control many critical cell functions, including the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (motility), and the self-destruction of cells (apoptosis). TGF-β signaling also plays an important role in the formation of new blood vessels (angiogenesis).

Researchers have proposed several additional functions for the HTRA1 enzyme. It may play a role in the stabilization of microtubules, which are rigid, hollow fibers that make up the cell's structural framework (cytoskeleton). Additionally, the HTRA1 enzyme may be involved in depositing minerals, such as calcium and phosphorus, in developing bone (mineralization). Studies have also suggested that the HTRA1 enzyme acts as a tumor suppressor, a protein that helps prevent the development of cancerous tumors by keeping cells from growing and dividing in an uncontrolled way.

2. Health Conditions Related to Genetic Changes

2.1. Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

At least four mutations in the *HTRA1* gene have been found to cause cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, commonly known as CARASIL. This condition is characterized by a highly increased risk of stroke, deterioration of cognitive function (dementia), premature hair loss (alopecia), and attacks of low back pain. These signs and symptoms usually become apparent in early to mid-adulthood.

The *HTRA1* gene mutations responsible for CARASIL reduce or eliminate the function of the HTRA1 enzyme. As a result, the enzyme is not available to inhibit signaling by TGF-β proteins. Researchers suspect that abnormally increased TGF-β signaling alters the structure of small blood vessels, particularly in the brain. These blood vessel abnormalities increase the risk of stroke and lead to the death of nerve cells (neurons) in many areas of the brain. Dysregulation of TGF-β signaling may also underlie the hair loss and back pain seen in people with CARASIL, although the relationship between abnormal TGF-β signaling and these features is less clear.

2.2. Age-Related Macular Degeneration

The *HTRA1* gene is located on the long (q) arm of chromosome 10 in a region known as 10q26. This region has been strongly associated with the risk of developing age-related macular degeneration, a common cause of vision loss in older adults. Researchers have identified several variations (polymorphisms) in the *HTRA1* gene that may explain the association between the 10q26 region and age-related macular degeneration. One of the variants, known as rs11200638, is found in an area of the gene called the promoter region, which starts the production of the HTRA1 enzyme.

It is unclear how a polymorphism in the *HTRA1* gene might be related to age-related macular degeneration. In the 10q26 region, the *HTRA1* gene is located next to a gene called *ARMS2*; changes in this gene have also been studied as a risk factor for the disease. Because the two genes are so close together, it is difficult to tell whether changes in one gene or the other, or possibly changes in both genes, account for the increased disease risk. Age-related macular degeneration is a complex condition that likely results from a combination of multiple genetic and environmental factors.

2.3. Cancers

The *HTRA1* gene is less active (downregulated) in some cancerous tumors than in normal cells. Studies have found this gene downregulation in several forms of cancer, including ovarian cancer, cancer that occurs in the lining of the uterus (endometrial cancer), a form of skin cancer called melanoma, and a form of liver cancer called hepatocellular carcinoma. Having reduced amounts of the HTRA1 enzyme may be related to tumor progression, the risk that cancer will spread (metastasize) to other parts of the body, and resistance to treatment with chemotherapy. However, the mechanism by which downregulation of the *HTRA1* gene influences cancer development and growth is unknown.

3. Other Names for This Gene

- ARMD7
- HtrA
- HTRA1_HUMAN
- IGFBP5-protease
- L56
- ORF480
- protease, serine, 11 (IGF binding)
- PRSS11
- serine protease HTRA1

References

1. An E, Sen S, Park SK, Gordish-Dressman H, Hathout Y. Identification of novelsubstrates for the serine protease HTRA 1 in the human RPE secretome. InvestOphthalmol Vis Sci. 2010 Jul;51(7):3379-86. doi: 10.1167/iovs.09-4853.
2. Chien J, Ota T, Aletti G, Shridhar R, Boccellino M, Quagliuolo L, Baldi A,Shridhar V. Serine protease HtrA1 associates with microtubules and inhibits cell migration. Mol Cell Biol. 2009 Aug;29(15):4177-87. doi: 10.1128/MCB.00035-09.
3. Dewan A, Liu M, Hartman S, Zhang SS, Liu DT, Zhao C, Tam PO, Chan WM, Lam DS, Snyder M, Barnstable C, Pang CP, Hoh J. HTRA1 promoter polymorphism in wetage-related macular degeneration. Science. 2006 Nov 10;314(5801): 989-92.
4. Fukutake T. Cerebral autosomal recessive arteriopathy with subcorticalinfarcts and leukoencephalopathy (CARASIL): fr om discovery to geneidentification. J Stroke Cerebrovasc Dis. 2011 Mar-Apr;20(2):85-93. doi:10.1016/j.jstrokecerebrov asdis.2010.11.008.
5. Hara K, Shiga A, Fukutake T, Nozaki H, Miyashita A, Yokoseki A, Kawata H,Koyama A, Arima K, Takahashi T, Ikeda M, Shiota H, Tamura M, Shimoe Y, HirayamaM, Arisato T, Yanagawa S, Tanaka A, Nakano I, Ikeda S, Yoshida Y, Yamamot o T,Ikeuchi T, Kuwano R, Nishizawa M, Tsuji S, Onodera O. Association of HTRA1mutations and familial ischemic cere bral small-vessel disease. N Engl J Med. 2009Apr 23;360(17):1729-39. doi: 10.1056/NEJMoa0801560.
6. Kanda A, Chen W, Othman M, Branham KE, Brooks M, Khanna R, He S, Lyons R,Abecasis GR, Swaroop A. A variant of mitochondrial protein LOC387715/ARMS2, notHTRA1, is strongly associated with age-related macular degeneration. Proc NatlAcad Sci U S A. 2007 Oct 9;104(41):16227-32.
7. Shiga A, Nozaki H, Yokoseki A, Nihonmatsu M, Kawata H, Kato T, Koyama A, ArimaK, Ikeda M, Katada S, Toyoshima Y, Takahashi H, Tanaka A, Nakano I, Ikeuchi T,Nishizawa M, Onodera O. Cerebral small-vessel disease protein HTRA1 controls the amount of TGF-β1 via cleavage of proTGF-β1. Hum Mol Genet. 2011 May1;20(9):1800-10. doi: 10.1093/h mg/ddr063.

8. Tong Y, Liao J, Zhang Y, Zhou J, Zhang H, Mao M. LOC387715/HTRA1 genepolymorphisms and susceptibility to age-related macular degeneration: A HuGEreview and meta-analysis. Mol Vis. 2010 Oct 5;16:1958-81. Review.
9. Yang Z, Camp NJ, Sun H, Tong Z, Gibbs D, Cameron DJ, Chen H, Zhao Y, PearsonE, Li X, Chien J, Dewan A, Harmon J, Bernstein PS, Shridhar V, Zabriskie NA, Hoh J, Howes K, Zhang K. A variant of the HTRA1 gene increases susceptibility toage-related macular degeneration. Science. 2006 Nov 10;314(5801):992-3.
10. Yang Z, Tong Z, Chen Y, Zeng J, Lu F, Sun X, Zhao C, Wang K, Davey L, Chen H, London N, Muramatsu D, Salasar F, Carmona R, Kasuga D, Wang X, Bedell M, Dixie M,Zhao P, Yang R, Gibbs D, Liu X, Li Y, Li C, Li Y, Campochiaro B, Constantine R,Zack DJ, Campochiaro P, Fu Y, Li DY, Katsanis N, Zhang K. Genetic and functional dissection of HTRA1 and LOC387715 in age-related macular degeneration. PLoSGenet. 2010 Feb 5;6(2):e1000836. doi: 10.1371/journal.pgen.1000836.
