CFH gene
complement factor H

Normal Function

The *CFH* gene provides instructions for making a protein called complement factor H. This protein helps regulate a part of the body's immune response known as the complement system. The complement system is a group of proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger an inflammatory response, and remove debris from cells and tissues. This system must be carefully regulated so it targets only unwanted materials and does not damage the body's healthy cells. Complement factor H, together with several related proteins, protects healthy cells by preventing the complement system from being turned on (activated) when it is not needed.

Health Conditions Related to Genetic Changes

**C3 glomerulopathy**

Several mutations in the *CFH* gene have been found to cause a rare form of kidney disease called C3 glomerulopathy. This disorder damages the kidneys and can lead to end-stage renal disease (ESRD), a life-threatening condition that prevents the kidneys from filtering fluids and waste products from the body effectively.

Most of the *CFH* gene mutations that cause C3 glomerulopathy change single protein building blocks (amino acids) in complement factor H. These mutations prevent cells from making this protein or lead to the production of a nonfunctional version of the protein. The resulting shortage (deficiency) of complement factor H overactivates the complement system, which damages structures called glomeruli in the kidneys. These structures are clusters of tiny blood vessels that help filter waste products from the blood. Damage to glomeruli prevents the kidneys from filtering waste products normally and can lead to ESRD.

Several other changes involving the *CFH* gene do not cause C3 glomerulopathy directly but appear to increase the likelihood of developing the disorder. The best-studied of these gene variations (polymorphisms) is written as Tyr402His or Y402H. Complement factor H usually has the amino acid tyrosine (Tyr/Y) at position 402, but sometimes it has the amino acid histidine (His/H) instead. People with C3 glomerulopathy are more likely than people in the general population to have histidine at this position. The version of complement factor H with histidine at position 402 is less effective at regulating the complement system on cell surfaces than the version with tyrosine at position 402, which may help explain the increased disease risk.
Age-related macular degeneration

Several variants in and near the CFH gene have been identified in people with age-related macular degeneration, an eye disease that is a common cause of vision loss in older adults. The Tyr402His polymorphism (described above) appears to be associated with an increased risk of this condition. People who carry one copy of this polymorphism in each cell have a 2.5-fold increased risk of developing age-related macular degeneration compared to people who do not have the polymorphism, and people who carry two copies of the polymorphism have a six-fold increased risk. However, most people with these variants never develop the disorder.

Age-related macular degeneration is characterized by the buildup of yellowish deposits called drusen underneath the light-sensitive tissue at the back of the eye (the retina). This buildup, together with other changes in the retina, leads to a progressive loss of central vision in late adulthood. Researchers suspect that changes in the CFH gene alter the production of complement factor H, although it is unclear how the abnormal protein is related to the buildup of drusen and progressive vision loss. Age-related macular degeneration is a complex condition that likely results from a combination of genetic and environmental factors.

Atypical hemolytic-uremic syndrome

More than 100 mutations in the CFH gene have been identified in people with atypical hemolytic-uremic syndrome, a condition that causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. Mutations in this gene increase the risk of a severe form of the disorder that usually appears early in life.

Most CFH gene mutations associated with atypical hemolytic-uremic syndrome affect a region of the complement factor H protein known as the C-terminal domain. These mutations result in the production of an abnormal or nonfunctional version of the protein. The resulting shortage of complement factor H can lead to uncontrolled activation of the complement system on the surface of cells. The overactive system attacks cells known as endothelial cells that line small blood vessels in the kidneys. Damage to these cells often leads to kidney failure and ESRD.

Although genetic changes increase the risk of atypical hemolytic-uremic syndrome, studies suggest that they are often not sufficient to cause the disease. In people with CFH gene mutations, the signs and symptoms of the disorder may be triggered by factors such as certain medications (such as anti-cancer drugs), chronic diseases, viral or bacterial infections, cancers, organ transplantation, or pregnancy.

Other disorders

Variations in the CFH gene, including the Tyr402His polymorphism (described above), have also been associated with an eye disease called basal laminar drusen (BLD). This condition is characterized by a buildup of drusen beneath the retina starting in early adulthood (in contrast to age-related macular degeneration, which begins later in life). It is unclear how changes in complement factor H are related
to the accumulation of drusen in people with BLD. A combination of genetic and environmental factors likely determines the risk of developing this complex disorder.

**Chromosomal Location**

Cytogenetic Location: 1q31.3, which is the long (q) arm of chromosome 1 at position 31.3

Molecular Location: base pairs 196,651,878 to 196,747,504 on chromosome 1 (Homo sapiens Updated Annotation Release 109.20200228, GRCh38.p13) (NCBI)

Credit: Genome Decoration Page/NCBI

**Other Names for This Gene**

- age-related maculopathy susceptibility 1
- AHUS1
- ARMD4
- ARMS1
- beta-1-H-globulin
- beta-1H
- C3b inactivator accelerator
- CFAH_HUMAN
- CFHL3
- factor H
- factor H-like 1
- FH
- FHL1
- H factor 1 (complement)
- H factor 2 (complement)
- HF
• HF1
• HF2
• HUS
• MGC88246

**Additional Information & Resources**

**Educational Resources**

- Immunobiology (fifth edition, 2001): The Complement System and Innate Immunity
  https://www.ncbi.nlm.nih.gov/books/NBK27100/

- The Merck Manual for Healthcare Professionals: Complement System
  https://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/complement-system.html?qt=&amp;sc=&amp;alt=

- Webvision: The Organization of the Retina and Visual System (2008): Molecular genetics of AMD
  https://www.ncbi.nlm.nih.gov/books/NBK27323/#macularde
gen.Molecular_genetics_of_AMD

**Clinical Information from GeneReviews**

- C3 Glomerulopathy
  https://www.ncbi.nlm.nih.gov/books/NBK1425

- Genetic Atypical Hemolytic-Uremic Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1367

**Scientific Articles on PubMed**

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28CFH%5BTI%5D%29+OR+%28complement+factor+H%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmhm%5D+AND+%22last+720+days%22%5Bdp%5D

**Catalog of Genes and Diseases from OMIM**

- BASAL LAMINAR DRUSEN
  http://omim.org/entry/126700

- COMPLEMENT FACTOR H
  http://omim.org/entry/134370

**Research Resources**

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_CFH.html

- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=CFH%5Bgene%5D
Sources for This Summary

- Abrera-Abeleda MA, Nishimura C, Smith JL, Sethi S, McRae JL, Murphy BF, Silvestri G, Skerka C, Józsi M, Zipfel PF, Hageman GS, Smith RJ. Variations in the complement regulatory genes factor H (CFH) and factor H related 5 (CFHR5) are associated with membranoproliferative glomerulonephritis type II (dense deposit disease). J Med Genet. 2006 Jul;43(7):582-9. Epub 2005 Nov 18. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16299065 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564553/

- Atkinson JP, Goodship TH. Complement factor H and the hemolytic uremic syndrome. J Exp Med. 2007 Jun 11;204(6):1245-8. Epub 2007 Jun 4. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17548524 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2118604/

- Boon CJ, Klevering BJ, Hoying CB, Zonneveld-Vrielin MN, Nabuurs SB, Blokland E, Cremers FP, den Hollander AI. Basal laminar drusen caused by compound heterozygous variants in the CFH gene. Am J Hum Genet. 2008 Feb;82(2):516-23. doi: 10.1016/j.ajhg.2007.11.007. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18252232 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427272/

- Boon CJ, van de Kar NC, Klevering BJ, Keunen JE, Cremers FP, Klaver CC, Hoyng CB, Daha MR, den Hollander AI. The spectrum of phenotypes caused by variants in the CFH gene. Mol Immunol. 2009 May;46(8-9):1573-94. doi: 10.1016/j.molimm.2009.02.013. Epub 2009 Mar 17. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19297022

- Despriet DD, Klaver CC, Witteeman JC, Bergen AA, Kardys I, de Maat MP, Boekhoorn SS, Vingerling JR, Hofman A, Oostra BA, Uitterlinden AG, Stijnen T, van Duijn CM, de Jong PT. Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA. 2006 Jul 19;296(3):301-9. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16849663

- Donoso LA, Vrabec T, Kuivaniemi H. The role of complement Factor H in age-related macular degeneration: a review. Surv Ophthamol. 2010 May-Jun;55(3):227-46. doi: 10.1016/j.survophthal.2009.11.001. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20385334
• Francis PJ, Schultz DW, Hamon S, Ott J, Weleber RG, Klein ML. Haplotypes in the complement factor H (CFH) gene: associations with drusen and advanced age-related macular degeneration. PLoS One. 2007 Nov 28;2(11):e1197. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18043728 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077927/

• Li M, Atmaca-Sonmez P, Othman M, Branham KE, Khanna R, Wade MS, Li Y, Liang L, Zareparsi S, Swaroop A, Abecasis GR. CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. Nat Genet. 2006 Sep;38(9):1049-54. Epub 2006 Aug 27. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16936733 Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1941700/

• Servais A, Noël LH, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey MA, Macher MA, Zuber J, Karras A, Provot F, Moulin B, Grünfeld JP, Niaudet P, Lesavre P, Frémeaux-Bacchi V. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012 Aug;82(4):454-64. doi: 10.1038/ki.2012.63. Epub 2012 Mar 28. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22456601

• Xiao X, Pickering MC, Smith RJ. C3 glomerulopathy: the genetic and clinical findings in dense deposit disease and C3 glomerulonephritis. Semin Thromb Hemost. 2014 Jun;40(4):465-71. doi: 10.1055/s-0034-1376334. Epub 2014 May 5. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24799308

• Zipfel PF, Skerka C, Chen Q, Wiech T, Goodship T, Johnson S, Fremaux-Bacchi V, Nester C, de Córdoba SR, Noris M, Pickering M, Smith R. The role of complement in C3 glomerulopathy. Mol Immunol. 2015 Sep;67(1):21-30. doi: 10.1016/j.molimm.2015.03.012. Epub 2015 Apr 28. Review. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25929733

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