Hereditary angioedema

Description

Hereditary angioedema is a disorder characterized by recurrent episodes of severe swelling (angioedema). The parts of the body that are most often affected by swelling are the limbs, face, intestinal tract, and airway. Minor trauma or stress may trigger an attack, but swelling often occurs without a known trigger. Episodes involving the intestinal tract cause severe abdominal pain, nausea, and vomiting. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. About one-third of people with this condition develop a non-itchy rash called erythema marginatum during an attack.

Symptoms of hereditary angioedema typically begin in childhood and worsen during puberty. On average, untreated individuals have swelling episodes every 1 to 2 weeks, and most episodes last for about 3 to 4 days. The frequency and duration of attacks vary greatly among people with hereditary angioedema, even among people in the same family.

Hereditary angioedema is broadly divided into two types, which are distinguished by levels of a protein called C1 inhibitor (C1-INH) in the blood. These types are known as hereditary angioedema due to C1-INH deficiency and hereditary angioedema with normal C1-INH.

Hereditary angioedema due to C1-INH deficiency is further divided into two types: type I occurs when C1-INH levels are low, and type II occurs when the C1-INH protein is not functioning correctly.

The different types of hereditary angioedema have similar signs and symptoms.

Frequency

Hereditary angioedema is estimated to affect 1 in 50,000 people worldwide. Hereditary angioedema due to C1-INH deficiency accounts for the vast majority of cases.

Causes

Variants (also called mutations) in the *SERPING1* gene cause hereditary angioedema

due to C1-INH deficiency. The *SERPING1* gene provides instructions for making the C1-INH protein, which is important for controlling the immune response and inflammation. The C1-INH protein blocks the activity of certain proteins that promote inflammation.

SERPING1 gene variants that cause hereditary angioedema due to C1-INH deficiency type I lead to reduced levels of C1-INH in the blood, while variants that cause type II result in the production of a C1-INH protein that functions abnormally. When the body does not have enough normal C1-INH protein, it ends up with excessive amounts of a protein fragment (peptide) called bradykinin. Bradykinin promotes inflammation by increasing the amount of fluid that leaks through the walls of blood vessels into body tissues (vascular permeability). The accumulation of fluids in body tissues causes the episodes of swelling seen in individuals with hereditary angioedema due to C1-INH deficiency.

Variants in the *F12* gene cause most cases of hereditary angioedema with normal C1-INH. The *F12* gene provides instructions for making a protein called coagulation factor XII. In addition to playing a critical role in blood clotting (coagulation), factor XII is also an important stimulator of inflammation and is involved in the production of bradykinin.

In people with hereditary angioedema with normal C1-INH, variants in the *F12* gene cause cells to produce a factor XII protein that is easier to activate than normal. As a result, a greater-than-normal amount of bradykinin is released. More bradykinin leads to increased inflammation and leaky blood vessel walls, which causes the episodes of swelling seen in people with hereditary angioedema with normal C1-INH.

Variants in a few other genes are responsible for a small number of additional cases of hereditary angioedema with normal C1-INH. The cause of other cases of hereditary angioedema with normal C1-INH remain unknown.

Learn more about the genes associated with Hereditary angioedema

- F12
- PLG
- SERPING1

Additional Information from NCBI Gene:

- ANGPT1
- HS3ST6
- KNG1
- MYOF

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of an altered gene in each cell is sufficient to cause the disorder. In some cases, an

affected person inherits the variant from one affected parent. Other cases result from a new (de novo) variant in a gene that occur during the formation of reproductive cells (eggs or sperm) in an affected individual's parent or in early embryonic development. These affected individuals have no history of the disorder in their family.

Other Names for This Condition

- C1 esterase inhibitor deficiency
- C1 inhibitor deficiency
- HAE
- HANE
- Hereditary angioneurotic edema

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Angioedema, hereditary, 7 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5543526/)
- Genetic Testing Registry: Hereditary angioedema type 3 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1857728/)
- Genetic Testing Registry: Hereditary angioneurotic edema (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0019243/)
- Genetic Testing Registry: Hereditary C1 esterase inhibitor deficiency - dysfunctional factor (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0398776/)

Genetic and Rare Diseases Information Center

- Hereditary angioedema (https://rarediseases.info.nih.gov/diseases/5979/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Hereditary angioedema%22)

Catalog of Genes and Diseases from OMIM

- ANGIOEDEMA, HEREDITARY, 1; HAE1 (https://omim.org/entry/106100)

- ANGIOEDEMA, HEREDITARY, 3; HAE3 (https://omim.org/entry/610618)
- ANGIOEDEMA, HEREDITARY, 5; HAE5 (https://omim.org/entry/619361)
- ANGIOEDEMA, HEREDITARY, 8; HAE8 (https://omim.org/entry/619367)
- ANGIOEDEMA, HEREDITARY, 4; HAE4 (https://omim.org/entry/619360)
- ANGIOEDEMA, HEREDITARY, 6; HAE6 (https://omim.org/entry/619363)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(Angioneurotic+Edema%5BMAJR%5D)+AND+((hereditary+angioedema%5BTIAB%5D)+OR+(hereditary+angioneurotic+edema%5BTIAB%5D)+OR+(c1+esterase+inhibitor+deficiency%5BTIAB%5D)+OR+(c1+inhibitor+deficiency%5BTIAB%5D))+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1600+days%22%5Bdp%5D)

References

- Ariano A, D'Apolito M, Bova M, Bellanti F, Loffredo S, D'Andrea G, Intrieri M,Petraroli A, Maffione AB, Spadaro G, Santacroce R, Margaglione M. A myoferlingain-of-function variant associates with a new type of hereditary angioedema.Allergy. 2020 Nov;75(11):2989-2992. doi: 10.1111/all.14454. Epub 2020 Jul 1. Noabstract available. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32542751)
- Bork K, Machnig T, Wulff K, Witzke G, Prusty S, Hardt J. Clinical features ofgenetically characterized types of hereditary angioedema with normal C1inhibitor: a systematic review of qualitative evidence. Orphanet J Rare Dis. 2020Oct 15;15(1):289. doi: 10.1186/s13023-020-01570-x. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/33059692)
- Bork K, Wulff K, Mohl BS, Steinmuller-Magin L, Witzke G, Hardt J, Meinke P.Novel hereditary angioedema linked with a heparan sulfate 3-O-sulfotransferase 6gene mutation. J Allergy Clin Immunol. 2021 Oct;148(4):1041-1048. doi:10.1016/j.jaci.2021.01.011. Epub 2021 Jan 25. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/33508266)
- Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ,Craig T, Davis-Lorton M, Frank MM, Li HH, Lumry WR, Zuraw BL. US HAEA MedicalAdvisory Board 2020 Guidelines for the Management of Hereditary Angioedema. JAllergy Clin Immunol Pract. 2021 Jan;9(1):132-150.e3. doi:10.1016/j.jaip.2020.08.046. Epub 2020 Sep 6. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32898710)
- Cichon S, Martin L, Hennies HC, Muller F, Van Driessche K, Karpushova A,Stevens W, Colombo R, Renne T, Drouet C, Bork K, Nothen MM. Increased activity ofcoagulation factor XII (Hageman factor) causes hereditary angioedema type III. AmJ Hum Genet. 2006 Dec;79(6):1098-104. doi: 10.1086/509899. Epub 2006 Oct 18. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17186468) or Free article

on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1698720/)

- Cugno M, Zanichelli A, Foieni F, Caccia S, Cicardi M. C1-inhibitor deficiencyand angioedema: molecular mechanisms and clinical progress. Trends Mol Med. 2009Feb;15(2):69-78. doi: 10.1016/j.molmed.2008.12.001. Epub 2009 Jan 21. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19162547)
- Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hagemanfactor) gene in hereditary angioedema with normal C1 inhibitor. Biochem BiophysRes Commun. 2006 May 19;343(4):1286-9. doi: 10.1016/j.bbrc.2006.03.092. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16638441)
- Gosswein T, Kocot A, Emmert G, Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Bork K, Oldenburg J, Muller CR. Mutational spectrum of the C1INH(SERPING1) gene in patients with hereditary angioedema. Cytogenet Genome Res. 2008;121(3-4):181-8. doi: 10.1159/000138883. Epub 2008 Aug 28. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18758157)
- Krishnamurthy A, Naguwa SM, Gershwin ME. Pediatric angioedema. Clin RevAllergy Immunol. 2008 Apr;34(2):250-9. doi: 10.1007/s12016-007-8037-y. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18330729)
- Martin L, Raison-Peyron N, Nothen MM, Cichon S, Drouet C. Hereditaryangioedema with normal C1 inhibitor gene in a family with affected women and menis associated with the p.Thr328Lys mutation in the F12 gene. J Allergy ClinImmunol. 2007 Oct;120(4):975-7. doi: 10.1016/j.jaci.2007.07.002. Epub 2007 Sep 7.No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17825897)
- Pappalardo E, Caccia S, Suffritti C, Tordai A, Zingale LC, Cicardi M. Mutationscreening of C1 inhibitor gene in 108 unrelated families with hereditaryangioedema: functional and structural correlates. Mol Immunol. 2008Aug; 45(13):3536-44. doi: 10.1016/j.molimm.2008.05.007. Epub 2008 Jun 30. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18586324)
- Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, Ahmadzadeh S, Cornett EM, Shekoohi S, Kaye AD. Hereditary Angioedema: Diagnosis,Clinical Implications, and Pathophysiology. Adv Ther. 2023 Mar;40(3):814-827.doi: 10.1007/s12325-022-02401-0. Epub 2023 Jan 7. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/36609679)
- Veronez CL, Csuka D, Sheikh FR, Zuraw BL, Farkas H, Bork K. The ExpandingSpectrum of Mutations in Hereditary Angioedema. J Allergy Clin Immunol Pract.2021 Jun;9(6):2229-2234. doi: 10.1016/j.jaip.2021.03.008. Epub 2021 Mar 19. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/33746090)
- Wouters D, Wagenaar-Bos I, van Ham M, Zeerleder S. C1 inhibitor: just a serineprotease inhibitor? New and old considerations on therapeutic applications of C1inhibitor. Expert Opin Biol Ther. 2008 Aug;8(8):1225-40. doi:10.1517/14712598.8.8.1225. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18613773)
- Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008 Sep4;359(10):1027-36. doi: 10.1056/NEJMcp0803977. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18768946)

Last updated March 11, 2024