Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin deficiency is an inherited disorder that may cause lung disease and liver disease. The signs and symptoms of the condition and the age at which they appear vary among individuals.

People with alpha-1 antitrypsin deficiency usually develop the first signs and symptoms of lung disease between ages 20 and 50. The earliest symptoms are shortness of breath following mild activity, reduced ability to exercise, and wheezing. Other signs and symptoms can include unintentional weight loss, recurring respiratory infections, fatigue, and rapid heartbeat upon standing. Affected individuals often develop emphysema, which is a lung disease caused by damage to the small air sacs in the lungs (alveoli). Characteristic features of emphysema include difficulty breathing, a hacking cough, and a barrel-shaped chest. Smoking or exposure to tobacco smoke accelerates the appearance of emphysema symptoms and damage to the lungs.

About 10 percent of infants with alpha-1 antitrypsin deficiency develop liver disease, which often causes yellowing of the skin and whites of the eyes (jaundice). Approximately 15 percent of adults with alpha-1 antitrypsin deficiency develop liver damage (cirrhosis) due to the formation of scar tissue in the liver. Signs of cirrhosis include a swollen abdomen, swollen feet or legs, and jaundice. Individuals with alpha-1 antitrypsin deficiency are also at risk of developing a type of liver cancer called hepatocellular carcinoma.

In rare cases, people with alpha-1 antitrypsin deficiency develop a skin condition called panniculitis, which is characterized by hardened skin with painful lumps or patches. Panniculitis varies in severity and can occur at any age.

Frequency

Alpha-1 antitrypsin deficiency occurs worldwide, but its prevalence varies by population. This disorder affects about 1 in 1,500 to 3,500 individuals with European ancestry. It is uncommon in people of Asian descent. Many individuals with alpha-1 antitrypsin deficiency are likely undiagnosed, particularly people with a lung condition called chronic obstructive pulmonary disease (COPD). COPD can be caused by alpha-1 antitrypsin deficiency; however, the alpha-1 antitrypsin deficiency is often never diagnosed. Some people with alpha-1 antitrypsin deficiency are misdiagnosed with asthma.

Causes

Mutations in the *SERPINA1* gene cause alpha-1 antitrypsin deficiency. This gene provides instructions for making a protein called alpha-1 antitrypsin, which protects the body from a powerful enzyme called neutrophil elastase. Neutrophil elastase

is released from white blood cells to fight infection, but it can attack normal tissues (especially the lungs) if not tightly controlled by alpha-1 antitrypsin.

Mutations in the *SERPINA1* gene can lead to a shortage (deficiency) of alpha-1 antitrypsin or an abnormal form of the protein that cannot control neutrophil elastase. Without enough functional alpha-1 antitrypsin, neutrophil elastase destroys alveoli and causes lung disease. Abnormal alpha-1 antitrypsin can also accumulate in the liver and damage this organ.

Environmental factors, such as exposure to tobacco smoke, chemicals, and dust, likely impact the severity of alpha-1 antitrypsin deficiency.

Inheritance Pattern

This condition is inherited in an autosomal codominant pattern. Codominance means that two different versions of the gene may be active (expressed), and both versions contribute to the genetic trait.

The most common version (allele) of the *SERPINA1* gene, called M, produces normal levels of alpha-1 antitrypsin. Most people in the general population have two copies of the M allele (MM) in each cell. Other versions of the *SERPINA1* gene lead to reduced levels of alpha-1 antitrypsin. For example, the S allele produces moderately low levels of this protein, and the Z allele produces very little alpha-1 antitrypsin. Individuals with two copies of the Z allele (ZZ) in each cell are likely to have alpha-1 antitrypsin deficiency. Those with the SZ combination have an increased risk of developing lung diseases (such as emphysema), particularly if they smoke.

Worldwide, it is estimated that 161 million people have one copy of the S or Z allele and one copy of the M allele in each cell (MS or MZ). Individuals with an MS (or SS) combination usually produce enough alpha-1 antitrypsin to protect the lungs. People with MZ alleles, however, have a slightly increased risk of impaired lung or liver function.

Other Names for This Condition

- AAT
- AATD
- alpha-1 protease inhibitor deficiency
- alpha-1 related emphysema
- genetic emphysema
- hereditary pulmonary emphysema
- inherited emphysema

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Alpha-1-antitrypsin deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0221757/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22alpha-1+antitrypsin+deficiency%22

Other Diagnosis and Management Resources

- Alpha-1 Foundation: Testing for Alpha-1
  https://www.alpha1.org/Newly-Diagnosed/Learning-about-Alpha-1/Testing-for-Alpha-1
- GeneReview: Alpha-1 Antitrypsin Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK1519
- MedlinePlus Encyclopedia: Alpha-1 antitrypsin deficiency
  https://medlineplus.gov/ency/article/000120.htm
- MedlinePlus Encyclopedia: Pulmonary function tests
  https://medlineplus.gov/ency/article/003853.htm
- MedlinePlus Encyclopedia: Wheezing
  https://medlineplus.gov/ency/article/003070.htm

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Alpha-1 antitrypsin deficiency
  https://medlineplus.gov/ency/article/000120.htm
- Encyclopedia: Pulmonary function tests
  https://medlineplus.gov/ency/article/003853.htm
- Encyclopedia: Wheezing
  https://medlineplus.gov/ency/article/003070.htm
- Health Topic: Alpha-1 Antitrypsin Deficiency
  https://medlineplus.gov/alpha1antitrypsindeficiency.html
- Health Topic: Cirrhosis
  https://medlineplus.gov/cirrhosis.html
- Health Topic: Emphysema
  https://medlineplus.gov/emphysema.html

Genetic and Rare Diseases Information Center

- Alpha-1 antitrypsin deficiency
  https://rarediseases.info.nih.gov/diseases/5784/alpha-1-antitrypsin-deficiency

Additional NIH Resources

- National Heart, Lung, and Blood Institute
  https://www.nhlbi.nih.gov/health-topics/alpha-1-antitrypsin-deficiency
- National Human Genome Research Institute
  https://www.genome.gov/Genetic-Disorders/Alpha-1-Antitrypsin-Deficiency

Educational Resources

- Alpha-1 Foundation: What is Alpha-1?
  https://www.alpha1.org/what-is-alpha1
- Childhood Liver Disease Research and Education Network
  https://childrennetwork.org/Clinical-Studies/Alpha-1-Antitrypsin-Deficiency
- Cincinnati Children's Hospital Medical Center
  https://www.cincinnatichildrens.org/health/a/alpha
- MalaCards: alpha-1-antitrypsin deficiency
  https://www.malacards.org/card/alpha_1_antitrypsin_deficiency_2
- Merck Manual Consumer Version
  https://www.merckmanuals.com/home/lung-and-airway-disorders/chronic-obstructive-pulmonary-disease-copd/alpha-1-antitrypsin-deficiency
- Orphanet: Alpha-1-antitrypsin deficiency
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=60
- University of Utah Genetic Science Learning Center
  https://learn.genetics.utah.edu/content/disorders/singlegene/

Patient Support and Advocacy Resources

- Alpha-1 Foundation
  https://www.alpha1.org/
- American Liver Foundation
  https://liverfoundation.org/for-patients/about-the-liver/diseases-of-the-liver/alpha-1-antitrypsin-deficiency/
- American Lung Association
  https://www.lung.org/
- Canadian Lung Association
  https://www.lung.ca/lung-health/lung-disease/alpha-1-antitryspin-deficiency/causes
- Children's Liver Disease Foundation
  https://childliverdisease.org/

- Lung Foundation Australia
  https://lungfoundation.com.au/resources/?search=fact%20sheet&condition=3
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/alpha-1-antitrypsin-deficiency/
- Resource List from the University of Kansas Medical Center
  http://www.kumc.edu/gec/support/alpha1.html

Clinical Information from GeneReviews

- Alpha-1 Antitrypsin Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK1519

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28alpha+1-Antitrypsin+Deficiency%5BMAJR%5D%29+OR+%28alpha-1+antitrypsin+deficiency%5BTIAB%5D%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- ALPHA-1-ANTITRYPSIN DEFICIENCY
  http://omim.org/entry/613490

Medical Genetics Database from MedGen

- Alpha-1-antitrypsin deficiency
  https://www.ncbi.nlm.nih.gov/medgen/67461

Sources for This Summary

- Carrell RW, Lomas DA. Alpha1-antitrypsin deficiency--a model for conformational diseases. N Engl J Med. 2002 Jan 3;346(1):45-53. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11778003
- DeMeo DL, Silverman EK. Alpha1-antitrypsin deficiency. 2: genetic aspects of alpha(1)-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. Thorax. 2004 Mar;59(3):259-64. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14985567
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1746953/
- Fairbanks KD, Tavill AS. Liver disease in alpha 1-antitrypsin deficiency: a review. Am J Gastroenterol. 2008 Aug;103(8):2136-41; quiz 2142. doi: 10.1111/j.1572-0241.2008.01955.x. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18796107
- Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. Orphanet J Rare Dis. 2008 Jun 19;3:16. doi: 10.1186/1750-1172-3-16. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18565211
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2441617/

- Lomas DA, Parfrey H. Alpha1-antitrypsin deficiency. 4: Molecular pathophysiology. Thorax. 2004 Jun;59(6):529-35. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15170041
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1747018/
- Luisetti M, Seersholm N. Alpha1-antitrypsin deficiency. 1: epidemiology of alpha1-antitrypsin deficiency. Thorax. 2004 Feb;59(2):164-9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14760160
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1746939/
- Needham M, Stockley RA. Alpha 1-antitrypsin deficiency. 3: Clinical manifestations and natural history. Thorax. 2004 May;59(5):441-5. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15115878
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1746985/
- Perlmutter DH, Brodsky JL, Balistreri WF, Trapnell BC. Molecular pathogenesis of alpha-1-antitrypsin deficiency-associated liver disease: a meeting review. Hepatology. 2007 May;45(5): 1313-23. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17464974
- Ranes J, Stoller JK. A review of alpha-1 antitrypsin deficiency. Semin Respir Crit Care Med. 2005 Apr;26(2):154-66. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16088434
- Stoller JK, Aboussouan LS. Myths and misconceptions about {alpha}1-antitrypsin deficiency. Arch Intern Med. 2009 Mar 23;169(6):546-50. doi: 10.1001/archinternmed.2009.25.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19307516
- Stoller JK, Lacbawan FL, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006 Oct 27 [updated 2017 Jan 19]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from http://www.ncbi.nlm.nih.gov/books/NBK1519/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301692
- Teckman JH, Lindblad D. Alpha-1-antitrypsin deficiency: diagnosis, pathophysiology, and management. Curr Gastroenterol Rep. 2006 Feb;8(1):14-20. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16510030
- Teckman JH. Alpha1-antitrypsin deficiency in childhood. Semin Liver Dis. 2007 Aug;27(3):274-81. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17682974
- de Serres FJ, Blanco I, Fernández-Bustillo E. Estimated numbers and prevalence of PI*S and PI*Z deficiency alleles of alpha1-antitrypsin deficiency in Asia. Eur Respir J. 2006 Dec;28(6):1091-9. Epub 2006 Sep 27.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17005586
- de Serres FJ, Blanco I, Fernández-Bustillo E. Estimating the risk for alpha-1 antitrypsin deficiency among COPD patients: evidence supporting targeted screening. COPD. 2006 Aug;3(3):133-9. Erratum in: COPD. 2006 Dec;3(4):245.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17240615
- de Serres FJ, Blanco I, Fernández-Bustillo E. Health implications of alpha1-antitrypsin deficiency in Sub-Sahara African countries and their emigrants in Europe and the New World. Genet Med. 2005 Mar;7(3):175-84. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15775753

- de Serres FJ, Blanco I, Fernández-Bustillo E. PI S and PI Z alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. Monaldi Arch Chest Dis. 2007 Dec; 67(4):184-208. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18309698
- de Serres FJ. Alpha-1 antitrypsin deficiency is not a rare disease but a disease that is rarely diagnosed. Environ Health Perspect. 2003 Dec;111(16):1851-4. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14654440
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241756/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/alpha-1-antitrypsin-deficiency

Reviewed: January 2013
Published: May 14, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services