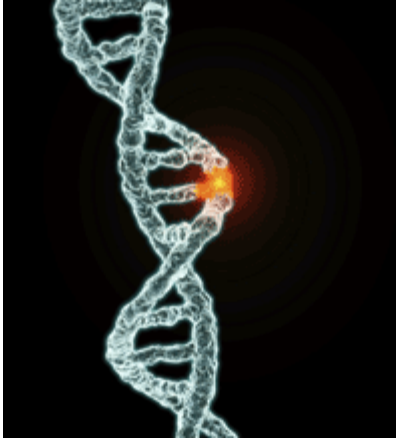


Genetics in Special Education Series

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Genetic disorders presented in this issue:

- [Achondroplasia](#)
 - [Alpha-1 antitrypsin deficiency](#)
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Achondroplasia

What is achondroplasia?

Achondroplasia is a disorder of bone growth. It is the most common form of disproportionate short stature. It occurs in one in every 15,000 to one in 40,000 live births. Achondroplasia is caused by a gene alteration (mutation) in the FGFR3 gene. The FGFR3 gene makes a protein called fibroblast growth factor receptor 3 that is involved in converting cartilage to bone. FGFR3 is the only gene known to be associated with achondroplasia. All people who have only a single copy of the normal FGFR3 gene and a single copy of the FGFR3 gene mutation have achondroplasia.

Most people who have achondroplasia have average-size parents. In this situation, the FGFR3 gene mutation occurs in one parent's egg or sperm cell before conception. Other people with achondroplasia inherit the condition from a parent who has achondroplasia.

What are the symptoms of achondroplasia?

People who have achondroplasia have abnormal bone growth that causes the following clinical symptoms: short stature with disproportionately short arms and legs, short fingers, a large head

(macrocephaly) and specific facial features with a prominent forehead (frontal bossing) and mid-face hypoplasia.

The intelligence and life span in individuals with achondroplasia is usually normal.

Infants born with achondroplasia typically have weak muscle tone (hypotonia). Because of the hypotonia, there may be delays in walking and other motor skills. Compression of the spinal cord and/or upper airway obstruction increases the risk of death in infancy.

People with achondroplasia commonly have breathing problems in which breathing stops or slows down for short periods (apnea). Other health issues include obesity and recurrent ear infections. Adults with achondroplasia may develop a pronounced and permanent sway of the lower back (lordosis) and bowed legs. The problems with the lower back can cause back pain leading to difficulty with walking.

How is achondroplasia diagnosed?

Achondroplasia is diagnosed by characteristic clinical and X-ray findings in most affected individuals. In individuals who may be too young to make a diagnosis with certainty or in individuals who do not have the typical symptoms, genetic testing can be used to identify a mutation in the FGFR3 gene.

Genetic testing can identify mutations in 99 percent of individuals who have achondroplasia. Testing for the FGFR3 gene mutation is available in clinical laboratories.

What is the treatment for achondroplasia?

No specific treatment is available for achondroplasia. Children born with achondroplasia need to have their height, weight and head circumference monitored using special growth curves standardized for achondroplasia. Measures to avoid obesity at an early age are recommended.

A magnetic resonance imaging (MRI) or CT scan may be needed for further evaluation of severe muscle weakness (hypotonia) or signs of spinal cord compression. To help with breathing, surgical removal of the adenoids and tonsils, continuous positive airway pressure (CPAP) by nasal mask, or a surgical opening in the airway (tracheostomy) may be needed to correct obstructive sleep apnea.

When there are problems with the lower limbs, such as hyperreflexia, clonus or central hypopnea, then surgery called suboccipital decompression is performed to decrease pressure on the brain.

Children who have achondroplasia need careful monitoring and support for social adjustment.

Is achondroplasia inherited?

Most cases of achondroplasia are not inherited. When achondroplasia is inherited, it is inherited in an [autosomal dominant manner](#) (PDF).

Over 80 percent of individuals who have achondroplasia have parents with normal stature and are born with achondroplasia as a result of a new (de novo) gene alteration (mutation). These parents have a small chance of having another child with achondroplasia.

A person who has achondroplasia who is planning to have children with a partner who does not have achondroplasia has a 50 percent chance, with each pregnancy, of having a child with achondroplasia. When both parents have achondroplasia, the chance for them, together, to have a child with normal stature is 25 percent. Their chance of having a child with achondroplasia is 50 percent. Their chance for having a child who inherits the gene mutation from both parents (called homozygous achondroplasia - a condition that leads to death) is 25 percent.

[To top](#)

Alpha-1 antitrypsin deficiency

What is alpha-1 antitrypsin deficiency?

Alpha-1 antitrypsin deficiency (AATD) is an inherited condition that causes low levels of, or no, alpha-1 antitrypsin (AAT) in the blood. AATD occurs in approximately 1 in 2,500 individuals. This condition is found in all ethnic groups; however, it occurs most often in whites of European ancestry.

Alpha-1 antitrypsin (AAT) is a protein that is made in the liver. The liver releases this protein into the bloodstream. AAT protects the lungs so they can work normally. Without enough AAT, the lungs can be damaged, and this damage may make breathing difficult.

Everyone has two copies of the gene for AAT and receives one copy of the gene from each parent. Most people have two normal copies of the alpha-1 antitrypsin gene. Individuals with AATD have one normal copy and one damaged copy, or they have two damaged copies. Most individuals who have one normal gene can produce enough alpha-1 antitrypsin to live healthy lives, especially if they do not smoke.

People who have two damaged copies of the gene are not able to produce enough alpha-1 antitrypsin, which leads them to have more severe symptoms.

What are the symptoms of alpha-1 antitrypsin deficiency (AATD)?

AATD can present as lung disease in adults and can be associated with liver disease in a small portion of affected children. In affected adults, the first symptoms of AATD are shortness of breath with mild activity, reduced ability to exercise and wheezing. These symptoms usually appear between the ages of 20 and 40. Other signs and symptoms can include repeated respiratory infections, fatigue, rapid heartbeat upon standing, vision problems and unintentional weight loss.

Some Individuals with AATD have advanced lung disease and have emphysema, in which the small air sacs (alveoli) in the lungs are damaged. Symptoms of emphysema include difficulty breathing, a hacking cough and a barrel-shaped chest. Smoking or exposure to tobacco smoke increases the appearance of symptoms and damage to the lungs. Other common diagnoses include COPD (chronic obstructive pulmonary disease), asthma, chronic bronchitis and bronchiectasis - a chronic inflammatory or degenerative condition of one or more bronchi or bronchioles.

Liver disease, called cirrhosis of the liver, is another symptom of AATD. It can be present in some affected children, about 10 percent, and has also been reported in 15 percent of adults with AATD. In its late stages signs and symptoms of liver disease can include a swollen abdomen, coughing up blood, swollen feet or legs, and yellowing of the skin and the whites of the eyes (jaundice).

Rarely, AATD can cause a skin condition known as panniculitis, which is characterized by hardened skin with painful lumps or patches. Panniculitis varies in severity and can occur at any age.

How is alpha-1 antitrypsin deficiency diagnosed?

Alpha-1 antitrypsin deficiency (AATD) is diagnosed through testing of a blood sample, when a person is suspected of having AATD. For example, AATD may be suspected when a physical examination reveals a barrel-shaped chest, or, when listening to the chest with a stethoscope, wheezing, crackles or decreased breath sounds are heard.

Testing for AATD, using a blood sample from the individual, is simple, quick and highly accurate.. Three types of tests are usually done on the blood sample:

- Alpha-1 genotyping, which examines a person's genes and determines their genotype.
- Alpha-1 antitrypsin PI type of phenotype test, which determines the type of AAT protein that a person has.
- Alpha-1 antitrypsin level test, which determines the amount of AAT in a person's blood.

Individuals who have symptoms that suggest AATD or who have a family history of AATD should consider being tested.

What is the treatment for alpha-1 antitrypsin deficiency?

Treatment of alpha-1 antitrypsin deficiency (AATD) is based on a person's symptoms. There is currently no cure. The major goal of AATD management is preventing or slowing the progression of lung disease.

Treatments include bronchodilators and prompt treatment with antibiotics for upper respiratory tract infections. Lung transplantation may be an option for those who develop end-stage lung disease. Quitting smoking, if a person with AATD smokes, is essential.

Replacement (augmentation) therapy with the missing AAT protein is available, although it is used only under special circumstances. It is not known how effective this is once disease has developed or which people would benefit most.

Is alpha-1 antitrypsin deficiency inherited?

Alpha-1 antitrypsin deficiency is inherited in families in an autosomal codominant pattern. Codominant inheritance means that two different variants of the gene (alleles) may be expressed, and both versions contribute to the genetic trait.

The M gene is the most common allele of the alpha-1 gene. It produces normal levels of the alpha-1 antitrypsin protein.

The Z gene is the most common variant of the gene. It causes alpha-1 antitrypsin deficiency. The S allele is another, less common variant that causes ATTD.

If a person inherits one M gene and one Z gene or one S gene ('type PiMZ' or 'type PiMS'), that person is a carrier of the disorder. While such a person may not have normal levels of alpha-1 antitrypsin, there should be enough to protect the lungs. However, carriers with the MZ alleles have an increased risk for lung disease, particularly if they smoke.

A person who inherits the Z gene from each parent is called 'type PiZZ.' This person has very low alpha-1 antitrypsin levels, allowing elastase - an enzyme especially of pancreatic juice that digests elastin - to damage the lungs. A person who inherits an altered version called S and Z is also likely to develop AATD.

[To top](#)