Osteopetrosis

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Osteopetrosis is a bone disease that makes bones abnormally dense and prone to breakage (fracture). Researchers have described several major types of osteopetrosis, which are usually distinguished by their pattern of inheritance: autosomal dominant, autosomal recessive, or X-linked. The different types of the disorder can also be distinguished by the severity of their signs and symptoms.

Keywords: genetic conditions

1. Introduction

Autosomal dominant osteopetrosis (ADO), which is also called Albers-Schönberg disease, is typically the mildest type of the disorder. Some affected individuals have no symptoms. In these people, the unusually dense bones may be discovered by accident when an x-ray is done for another reason. In affected individuals who develop signs and symptoms, the major features of the condition include multiple bone fractures, abnormal side-to-side curvature of the spine (scoliosis) or other spinal abnormalities, arthritis in the hips, and a bone infection called osteomyelitis. These problems usually become apparent in late childhood or adolescence.

Autosomal recessive osteopetrosis (ARO) is a more severe form of the disorder that becomes apparent in early infancy. Affected individuals have a high risk of bone fracture resulting from seemingly minor bumps and falls. Their abnormally dense skull bones pinch nerves in the head and face (cranial nerves), often resulting in vision loss, hearing loss, and paralysis of facial muscles. Dense bones can also impair the function of bone marrow, preventing it from producing new blood cells and immune system cells. As a result, people with severe osteopetrosis are at risk of abnormal bleeding, a shortage of red blood cells (anemia), and recurrent infections. In the most severe cases, these bone marrow abnormalities can be life-threatening in infancy or early childhood.

Other features of autosomal recessive osteopetrosis can include slow growth and short stature, dental abnormalities, and an enlarged liver and spleen (hepatosplenomegaly). Depending on the genetic changes involved, people with severe osteopetrosis can also have brain abnormalities, intellectual disability, or recurrent seizures (epilepsy).

A few individuals have been diagnosed with intermediate autosomal osteopetrosis (IAO), a form of the disorder that can have either an autosomal dominant or an autosomal recessive pattern of inheritance. The signs and symptoms of this condition become noticeable in childhood and include an increased risk of bone fracture and anemia. People with this form of the disorder typically do not have life-threatening bone marrow abnormalities. However, some affected individuals have had abnormal calcium deposits (calcifications) in the brain, intellectual disability, and a form of kidney disease called renal tubular acidosis.

Rarely, osteopetrosis can have an X-linked pattern of inheritance. In addition to abnormally dense bones, the X-linked form of the disorder is characterized by abnormal swelling caused by a buildup of fluid (lymphedema) and a condition called anhydrotic ectodermal dysplasia that affects the skin, hair, teeth, and sweat glands. Affected individuals also have a malfunctioning immune system (immunodeficiency), which allows severe, recurrent infections to develop. Researchers often refer to this condition as OL-EDA-ID, an acronym derived from each of the major features of the disorder.

2. Frequency

Autosomal dominant osteopetrosis is the most common form of the disorder, affecting about 1 in 20,000 people. Autosomal recessive osteopetrosis is rarer, occurring in an estimated 1 in 250,000 people.

Other forms of osteopetrosis are very rare. Only a few cases of intermediate autosomal osteopetrosis and OL-EDA-ID have been reported in the medical literature.

3. Causes

Mutations in at least nine genes cause the various types of osteopetrosis. Mutations in the *CLCN7* gene are responsible for about 75 percent of cases of autosomal dominant osteopetrosis, 10 to 15 percent of cases of autosomal recessive osteopetrosis, and all known cases of intermediate autosomal osteopetrosis. *TCIRG1* gene mutations cause about 50 percent of cases of autosomal recessive osteopetrosis. Mutations in other genes are less common causes of autosomal dominant and autosomal recessive forms of the disorder. The X-linked type of osteopetrosis, OL-EDA-ID, results from mutations in the *IKBKG* gene. In about 30 percent of all cases of osteopetrosis, the cause of the condition is unknown.

The genes associated with osteopetrosis are involved in the formation, development, and function of specialized cells called osteoclasts. These cells break down bone tissue during bone remodeling, a normal process in which old bone is removed and new bone is created to replace it. Bones are constantly being remodeled, and the process is carefully controlled to ensure that bones stay strong and healthy.

Mutations in any of the genes associated with osteopetrosis lead to abnormal or missing osteoclasts. Without functional osteoclasts, old bone is not broken down as new bone is formed. As a result, bones throughout the skeleton become unusually dense. The bones are also structurally abnormal, making them prone to fracture. These problems with bone remodeling underlie all of the major features of osteopetrosis.

3.1. The Genes Associated with Osteopetrosis

- CLCN7
- IKBKG
- ITGB3
- TCIRG1
- TNFRSF11A

3.1.1. Additional Information from NCBI Gene

- CA2
- OSTM1
- PLEKHM1
- TNFSF11

4. Inheritance

Osteopetrosis can have several different patterns of inheritance. Most commonly, the disorder has an autosomal dominant inheritance pattern, which means one copy of an altered gene in each cell is sufficient to cause the disorder. Most people with autosomal dominant osteopetrosis inherit the condition from an affected parent.

Osteopetrosis can also be inherited in an autosomal recessive pattern, which means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

OL-EDA-ID is inherited in an X-linked recessive pattern. The *IKBKG* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

5. Other Names for This Condition

- congenital osteopetrosis
- marble bone disease
- osteopetroses

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