Collagen VI-related Myopathy

Subjects: Genetics & Heredity
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Collagen VI-related myopathy is a group of disorders that affect skeletal muscles (which are the muscles used for movement) and connective tissue (which provides strength and flexibility to the skin, joints, and other structures throughout the body). Most affected individuals have muscle weakness and joint deformities called contractures that restrict movement of the affected joints and worsen over time. Researchers have described several forms of collagen VI-related myopathy, which range in severity: Bethlem myopathy is the mildest, an intermediate form is moderate in severity, and Ullrich congenital muscular dystrophy is the most severe.

Keywords: genetic conditions

1. Introduction

People with Bethlem myopathy usually have loose joints (joint laxity) and weak muscle tone (hypotonia) in infancy, but they develop contractures during childhood, typically in their fingers, wrists, elbows, and ankles. Muscle weakness can begin at any age but often appears in childhood to early adulthood. The muscle weakness is slowly progressive, with about two-thirds of affected individuals over age 50 needing walking assistance. Older individuals may develop weakness in respiratory muscles, which can cause breathing problems. Some people with this mild form of collagen VI-related myopathy have skin abnormalities, including small bumps called follicular hyperkeratosis on the arms and legs; soft, velvety skin on the palms of the hands and soles of the feet; and abnormal wound healing that creates shallow scars.

The intermediate form of collagen VI-related myopathy is characterized by muscle weakness that begins in infancy. Affected children are able to walk, although walking becomes increasingly difficult starting in early adulthood. They develop contractures in the ankles, elbows, knees, and spine in childhood. In some affected people, the respiratory muscles are weakened, requiring people to use a machine to help them breathe (mechanical ventilation), particularly during sleep.

People with Ullrich congenital muscular dystrophy have severe muscle weakness beginning soon after birth. Some affected individuals are never able to walk and others can walk only with support. Those who can walk often lose the ability, usually in adolescence. Individuals with Ullrich congenital muscular dystrophy develop contractures in their neck, hips, and knees, which further impair movement. There may be joint laxity in the fingers, wrists, toes, ankles, and other joints. Some affected individuals need continuous mechanical ventilation to help them breathe. As in Bethlem myopathy, some people with Ullrich congenital muscular dystrophy have follicular hyperkeratosis; soft, velvety skin on the palms and soles; and abnormal wound healing.

Individuals with collagen VI-related myopathy often have signs and symptoms of multiple forms of this condition, so it can be difficult to assign a specific diagnosis. The overlap in disease features, in addition to their common cause, is why these once separate conditions are now considered part of the same disease spectrum.

2. Frequency

Collagen VI-related myopathy is rare. Bethlem myopathy is estimated to occur in 0.77 per 100,000 individuals, and Ullrich congenital muscular dystrophy is estimated to occur in 0.13 per 100,000 individuals. Only a few cases of the intermediate form have been described in the scientific literature.

3. Causes

Mutations in the *COL6A1*, *COL6A2*, and *COL6A3* genes can cause the various forms of collagen VI-related myopathy. These genes each provide instructions for making one component of a protein called type VI collagen. Type VI collagen makes up part of the extracellular matrix that surrounds muscle cells and connective tissue. This matrix is an intricate

lattice that forms in the space between cells and provides structural support. The extracellular matrix is necessary for cell stability and growth. Research suggests that type VI collagen helps secure and organize the extracellular matrix by linking the matrix to the cells it surrounds.

Mutations in the *COL6A1*, *COL6A2*, and *COL6A3* genes result in a decrease or lack of type VI collagen or the production of abnormal type VI collagen. While it is difficult to predict which type of mutation will lead to which form of collagen VI-related myopathy, in general, lower amounts of type VI collagen lead to more severe signs and symptoms that begin earlier in life.

Changes in type VI collagen structure or production lead to an unstable extracellular matrix that is no longer attached to cells. As a result, the stability of the surrounding muscle cells and connective tissue progressively declines, which leads to the muscle weakness, contractures, and other signs and symptoms of collagen VI-related myopathy.

3.1. The Genes Associated with Collagen VI-Related Myopathy

- COL6A1
- COL6A2
- COL6A3

4. Inheritance

Collagen VI-related myopathy can be inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Bethlem myopathy is typically inherited in an autosomal dominant manner, as are some cases of the intermediate form and a few rare instances of Ullrich congenital muscular dystrophy. Most cases result from new mutations in the gene and occur in people with no history of the disorder in their family. In other cases, an affected person inherits the mutation from one affected parent.

Collagen VI-related myopathy can be inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. Ullrich congenital muscular dystrophy is typically inherited in an autosomal recessive manner, as are some cases of the intermediate form and a few rare instances of Bethlem myopathy. 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.

5. Other Names for This Condition

- collagen type VI-related disorders
- collagen VI-related myopathies
- ColVI myopathies

References

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