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Mini Review

Treatment of Aggrecan Deficiency (ACAN) in Short Stature Pediatric Patients

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Abstract

An ACAN deficiency, mutations in the Aggrecan gene on chromosome 15q26.1, leads to a genetically inherited skeletal disorder characterized by familial short stature, advanced bone age in childhood, and significantly reduced adult height. Symptoms include joint problems, facial dysmorphia, and premature growth cessation. Main features and symptoms of ACAN deficiency are pronounced familial short stature, often combined with advanced bone maturation compared to actual age by premature epiphyseal closure. Skeletal changes include early joint pain with osteochondritis dissecans, degenerative joint diseases, spinal changes like scoliosis, and a tendency towards early-onset osteoarthritis. Facial features show craniofacial abnormalities such as a flatter midface area may occur. The growth spurt in puberty is often absent or significantly shortened, leading to a low final height. Diagnosis can be made by autosomal dominant inherited mutations in the ACAN gene, responsible for the protein Aggrecan, a major component of cartilage. Diagnosis is done through molecular genetic testing and gene panel for skeletal disorders. There is no curative treatment. Treatment focuses on symptom relief, such as growth hormone therapy to improve final height, often in combination with GnRH analogs to delay puberty. Curing options on the DNA level are not on the market in this rare genetic defect. The manuscript gives an overview of extremely rare aggrecan deficiency in childhood.

Introduction

An ACAN gene mutation affects the gene that provides the blueprint for the cartilage protein aggrecan [1-9]. This protein is essential for the normal development of cartilage and bone growth plates. Alterations in this gene typically result in hereditary growth disorders and joint diseases. Heterozygous mutations usually lead to mild to moderate short stature. Bone age is often advanced in children, resulting in premature cessation of growth after the onset of puberty and reduced adult height [2-4]. The mutation can significantly increase the risk of premature joint wear (osteoarthritis) as well as painful cartilage and bone damage with osteochondritis dissecans in the knees, hips, or ankles. Severe forms, homozygous, are extremely rare, more severe mutations can lead to very extreme short stature and skeletal malformations, for example aggrecan-type spondyloepimetaphyseal dysplasia.

Corresponding Diseases with ACAN Mutations

Spondyloepiphyseal dysplasia, Kimberley type

Kimberley-type spondyloepiphyseal dysplasia (SEDK) is an extremely rare genetic skeletal disorder. It is classified as one of the milder forms of spondyloepiphyseal dysplasia. The clinical presentation is primarily characterized by proportionate short stature and premature, progressive osteoarthritis of the weight-

bearing joints. The disorder is caused by heterozygous mutations in the ACAN gene on chromosome 15q26.1. This gene encodes the protein aggrecan, a major component of cartilage tissue that is essential for normal bone growth. The mutations result in conditions known as aggrecanopathies. The disorder follows an autosomal dominant inheritance pattern. An affected parent passes the predisposition on to their offspring with a 50% probability. Signs of the disorder may become apparent as early as the neonatal period or infancy. Affected individuals typically exhibit short stature, proportionate but below average (often below the 5th percentile), and a stocky build. Early-onset, progressive joint disease (osteoarthropathy) develops, placing significant strain primarily on the hips and knees. Axial leg deformities, such as knock-knees or bowlegs, frequently occur. X-rays reveal typical skeletal changes with flattened vertebral bodies (platyspondyly) with irregular endplates and areas of increased bone density (sclerosis). Flattened growth zones at the ends of the thigh bones (femoral epiphyses). Due to the extremely low prevalence (less than 1 in 1,000,000), the diagnosis is usually confirmed via molecular genetic testing of the ACAN gene. As there is no curative treatment, medical care focuses on alleviating joint discomfort, providing physiotherapy, and performing orthopedic interventions to preserve joint function when necessary.

Familial Osteochondritis Dissecans

Familial Osteochondritis Dissecans (OCD) is a rare, genetic skeletal disorder characterized by damage to multiple joints, short stature, and premature osteoarthritis. Unlike the common, sporadic (randomly occurring) form of OCD, the familial type systemically affects multiple joints simultaneously and stems from an inherited genetic defect. The disorder is caused by mutations in the ACAN gene. This gene encodes the protein aggrecan, a major component of cartilage. The mutation causes the cartilage to attract less water, lose its gel-like density, and become mechanically unstable. A single copy of the altered gene from one parent is sufficient to pass the disorder on to offspring and therefore has an autosomal dominant inheritance.

Spondyloepimetaphyseal Dysplasia, Aggrecan type (SEMDAG)

Spondyloepimetaphyseal Dysplasia, Aggrecan type (SEMDAG) is an extremely rare genetic skeletal disorder characterized by severely stunted growth (dwarfism), facial abnormalities, and characteristic radiographic findings. The condition belongs to the group of disorders known as aggrecanopathies. It occurs when a child inherits an altered copy of the ACAN gene from both parents (autosomal recessive inheritance). The affected ACAN gene encodes aggrecan, a key protein proteoglycan in cartilage tissue. Aggrecan provides cartilage with its elasticity and compressive strength and is essential for normal longitudinal bone growth. In the SEMDAG variant, a mutation typically occurs in the C-type lectin domain of the aggrecan protein. This disrupts its interaction with other proteins in the extracellular matrix. While a single (heterozygous) mutation in the *ACAN* gene often results only in milder short stature or premature osteoarthritis, the presence of two mutated copies (homozygous) is required to cause the severe clinical presentation of SEMDAG. National Symptoms are evident as early as the neonatal or infancy period as a marked short stature with short limbs (micromelia) and a short trunk. A relatively large head (macrocephaly), a strikingly flat midface (midface hypoplasia) due to the near-absence of nasal cartilage, a slightly protruding lower jaw (prognathism), and low-set ears. A short neck, a barrel-shaped chest, and pronounced swayback (lumbar lordosis). The fingers are usually strikingly short (brachydactyly).

Discussion

The ACAN gene (aggrecan gene) is a crucial human gene that provides the instructions for producing the protein aggrecan [1,2,3]. Aggrecan is a key component of cartilage tissue and intervertebral discs. It binds water, giving cartilage its elasticity and its ability to absorb pressure. The key facts regarding mutations and disorders associated with the ACAN gene are that mutations in the ACAN gene can lead to various forms of skeletal and growth disorders [1,2,5,8] Alterations in the gene cause affected children to grow significantly more slowly and result in short stature in adulthood. In SEMD cases, severe mutations, particularly homozygous mutations, can lead to extreme short stature and other skeletal abnormalities, such as joint malformations [3,5,6]. Children with ACAN gene mutations can often be successfully treated with growth hormones if diagnosed early. 2. Effects in animals (dwarfism) In horses, the ACAN gene is responsible for certain forms of dwarfism (chondrodysplasia) that occur particularly in small horse breeds such as miniature horses, Falabellas, and Shetland ponies. There are four known mutations (D1, D2, D3*, and D4) that can trigger dwarfism, either individually or in combination. Affected foals often exhibit abnormal leg length, a disproportionately large head, jaw deformities, cleft palates, and joint problems. The mode of inheritance is autosomal recessive. This means that a foal develops the condition only if it inherits two mutated copies of the gene, one from each parent. To date, there are no curing options for these rare pediatric diseases in childhood. Further research is ongoing to develop further treatment and curing options for aggrecanopathies for the future.

Disclaimer (Artificial Intelligence)

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Consent and Ethical Approval

It is not applicable.

Competing Interests

Author has declared that no competing interests exist.

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