Transcript Details

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Fibrodysplasia Ossificans Progressiva: Mechanism of Disease

Announcer:
Welcome to ReachMD. This Medical Industry Feature titled Fibrodysplasia Ossificans Progressiva: Mechanism of Disease is sponsored by Ipsen Biopharmaceuticals. This program is intended for healthcare professionals only.

Narrator:
Fibrodysplasia ossificans progressiva, or FOP, is a severely disabling myopathy in which extraskeletal bone forms and accumulates over time within muscles and soft tissues. Eventually, this extraskeletal bone, known as heterotopic ossification, imprisons affected persons in a second skeleton.

Nearly all individuals with FOP are born with a hallmark malformation in which the big toes are shortened and bent inward, resembling a bunion. Shortened thumbs may also be present. In infancy, neck stiffness and scalp lumps that appear and disappear rapidly may occur. And as an affected child ages, episodes of soft tissue swelling, often referred to as flare-ups, begin.

Flare-ups can precede heterotopic ossification and may involve localized swelling, pain, redness, warmth, and loss or restriction of movement. Flare-ups can occur sporadically or can be provoked by even minor soft tissue damage caused by trauma, muscular stretching, overexertion and fatigue, intramuscular vaccinations, mandibular blocks for dental work, or flu-like infections. Biopsies or surgery should not be performed, as they exacerbate tissue damage and can cause flare-ups. Although the trigger for most flare-ups is unknown, the mechanisms of heterotopic ossification are better understood.

In FOP, the process of heterotopic ossification begins with tissue destruction and inflammation, followed by the recruitment and accumulation of stem cells within affected tissue. Individuals with FOP have a mutation in the ACVR1 gene that encodes for the ALK2 receptor, a BMP type I receptor. This receptor is part of the bone morphogenetic protein, or BMP, pathway and is critical in the regulation of cartilage and bone development and growth.

Scientists believe the mutation allows the ALK2 receptor to become more active, especially when bound by extracellular proteins called ligands. This abnormal activation results in increased BMP signaling, which is delivered to the nucleus by SMAD protein complexes. Excessive BMP signaling, along with other mechanisms, misdirects the recruited stem cells to differentiate into cartilage. The cartilage is then replaced by bone. Ultimately, the affected tissue is destroyed and replaced by heterotopic bone.

Researchers have made progress in understanding the genetic mysteries of FOP and continue to study the mechanisms of heterotopic ossification, seeking ways to attempt to treat this severely debilitating and life-limiting disease.

Announcer:
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