

# How Fibrodysplasia Ossificans Progressiva (FOP) Works

by Katie Lambert

## Introduction to How FOP Works

You might not think about your bones very often unless you break one. When you break a bone, the bone heals itself and begins to regrow. But, what if your muscles, tendons and ligaments turned to bone? What if you formed a second skeleton on top of the one you already have? That's what happens with **Fibrodysplasia Ossificans Progressiva**, or **FOP**.

An FOP skeleton doesn't look like the ones you see at Halloween or the kind that hangs in an anatomy classroom. Instead of having lots of bones linked to one another with functioning joints, an FOP skeleton's bones fuse together, essentially forming a second skeleton out of the tendons, ligaments and muscles -- a true metamorphosis. The skeleton is almost one solid piece, and sheets of **bone exist where they should not**.

The most common sign of FOP can be seen at birth: malformed big toes. Doctors aren't sure why this happens -- it just appears as an early indicator of FOP. Aside from the malformed big toes, other initial signs of FOP usually show up in the first two decades of life. One day, a large lump suddenly begins to form on a child's body, usually in the neck or back area. It can appear rapidly, often overnight, and grows much faster than most tumors. It's warm to the touch, red and painful. A person's first reaction is often to assume it must be some sort of tumor -- what if it's cancer? But then the lump stops being painful, eventually gets smaller, and turns to bone -- normal bone, but in the wrong place -- where the body neither needs it nor wants it.

These lumps are called **flare-ups**, and they appear all through the life of a person with FOP. Doctors aren't always sure what triggers them, but they do know that any kind of injury, even a small one, can cause a flare-up. For someone with FOP, a fall is not just a fall, and the typical bumps and bruises of daily life are a major threat to the mobility and independence. If a person with FOP bumps his elbow or knee, bone could begin to grow there and lock the arm or leg.

In FOP patients, extra bone formation almost always starts at the neck, spine and shoulders. Only then does it move to the other joints. Eventually, people with FOP will probably lose most of their mobility. Joints lock, and bones can twist into odd positions. Some people with FOP develop scoliosis, and their spine twists. Often, the jaw fuses together either spontaneously or as a result of an injection for dental work, which makes eating and brushing teeth extremely difficult. The skeleton will fuse into one position, and that is the position a person with FOP will stay in for the rest of his or her life. Any attempt to remove the extra (or **heterotopic**) bone only leads to extra bone formation. Only 700 people worldwide are known to have FOP, which makes this disorder extremely rare [source: IFOPA].

In this article, we'll learn how FOP bone compares to normal bone, how doctors treat FOP and what other kinds of rare bone disorders exist.

## FOP Bone versus Normal Bone

Bone is a living tissue. Each bone in your body is an organ, made up of tissues and cartilage. FOP bone is just like normal bone -- it's just in the wrong place.

**Ossification** and **osteogenesis** are words for bone formation. There are two methods of bone formation: **intramembranous** and **endochondral**. Intramembranous bone formation is the simpler process, and it's responsible for forming a person's skull and lower jawbone. It's also how long bones like the humerus and femur grow in width.

Most bones in the body grow and heal after a break through endochondral bone formation. It's also how FOP bone grows. First, cartilage forms, and then bone gradually takes the place of the cartilage.

Both kinds of ossification begin with **mesenchyme**. Mesenchyme is a connective tissue that all other connective tissues come from. Mesenchymal cells can turn into different kinds of specialized cells that form tissues. Here is how the process of endochondral bone formation works:

1. Mesenchymal cells come together in the shape of the bone they will form. They turn into **chondroblasts** -- cells that secrete cartilage matrix. A membrane called the **perichondrium** surrounds this cartilage.
2. After the chondroblasts cover themselves in cartilage matrix, they turn into **chondrocytes**. The chondrocytes keep dividing while new chondroblasts continue to make cartilage matrix, causing the cartilage to grow.
3. Some of the chondrocytes burst, and others die. The bursting of the cells causes **calcification**, or hardening of the cartilage. The dying cells make small spaces in the cartilage.
4. A **nutrient artery** enters the cartilage, triggering cells in the perichondrium to turn into **osteoblasts**. Osteoblasts are just like chondroblasts, but they secrete bone matrix instead of cartilage matrix. The osteoblasts start to secrete compact bone, and the perichondrium becomes the **periosteum** -- the covering of the outside of the bone.
5. Blood vessels grow into the cartilage and bring red bone marrow cells and other bone cells with them. The blood vessels stimulate a **primary ossification center** to grow -- this is the place where bone tissue will begin to take the place of cartilage. Osteoblasts start covering the broken-down cartilage with bone matrix.
6. Osteoclasts follow behind the osteoblasts and break down the spongy bone, making a cavity for red bone marrow to fill.

At this point, the long part of the bone, which started as cartilage, is compact bone with red bone marrow in the center. The endochondral bone formation finishes with the **epiphyses**, the ends of the bones. **Secondary ossification centers** develop to form bone, although unlike with the primary ossification center, spongy bone stays at the center of epiphyses instead of marrow.

This process uses **undifferentiated cells**, or cells that can grow into any type of cell, to make bones. The amazing thing about FOP is that the body convinces undifferentiated cells in tendons, ligaments and muscles to turn into something completely different. The body doesn't normally work this way. With FOP, ligaments and tendons and other connective tissues all go through this process of bone formation. It's normal bone, but in the wrong place at the wrong time. This is called **heterotopic ossification**.

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So what happens with FOP? A mutation in the gene encoding activin receptor IA (ACVR1) tells the body to make an extra skeleton. This gene helps control **bone morphogenetic proteins**, or **BMPs**. In FOP, the gene is active without BMPs -- operating like a leaky faucet. When BMPs are present, the faucet explodes with activity. This clue might someday help scientists figure out how to make extra bone for people who need it, like people with osteoporosis.

## FOP Treatment

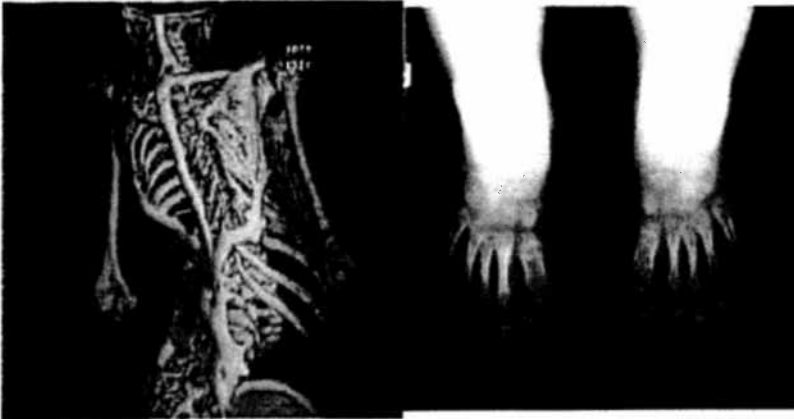


Image courtesy Eileen Shore, PhD and Frederick Kaplan, MD, University of Pennsylvania School of Medicine; Nature Genetics, 23 April 2006, DOI: 10.1038/ng1783

**Some clinical features of FOP: extra bone and malformed big toes**

You might wonder if FOP bone can be removed. Well yes, it can -- but that actually makes things worse. The bone will simply grow back, possibly with even more bone than before. Any kind of trauma to the body can cause a flare-up, resulting in new bone. Even injections into the muscle (like for vaccines or local anesthesia) can cause flare-ups, so you can see why a full operation might spark a traumatic reaction.

There isn't any real proven treatment for FOP, so doctors use medications to treat the symptoms of FOP. Reports are **anecdotal** -- they rely on the unscientific observations of people using the medications, rather than a double-blind clinical study. There aren't many people with FOP, so it's hard to get a large enough sample to conduct a study that could produce significant results. Eventually, it should be possible to design new medications to block the overactive receptor that triggers bone formation in FOP.

Some of the medicines that have been reported to be helpful are:

- **Corticosteroids** like prednisone during the early part of a flare-up in major joint. Corticosteroids help decrease inflammation and swelling.
- **NSAIDs** also reduce inflammation. If you've ever taken Advil or aspirin, you've taken an NSAID. **COX-2 inhibitors** (like Vioxx, which is no longer on the market, and Celebrex) are a particular kind of NSAID that seems to be very helpful in FOP treatment.
- **Aminobiphosphonates** are **anti-angiogenic**, which means that they prevent the formation of blood vessels, which bone tissue needs to grow. They also keep too much bone resorption from happening by shortening the life span of osteoclasts. You would think that decreased bone resorption would be a bad thing in FOP, but it turns out that it seems to help people. Doctors aren't sure why.
- **Thalidomide** is also an anti-angiogenic. It appears to modify immune system responses and functions in a way that might help with flare-ups. To some people, thalidomide brings to mind news stories of birth defects in the 1960s, after doctors gave it to pregnant women to help with morning sickness. However, thalidomide is supposed to be safe in people who aren't pregnant.

For an adult with FOP, trying to stay as independent as possible can be a challenge. People with financial means or good insurance coverage could modify their homes to be wheelchair-friendly, making everything easier. For some people, it might be necessary to hire a caregiver.

## Other Rare Bone Disorders

Are there other diseases like FOP? Not quite, but there are many rare bone diseases we don't completely understand yet. **Osteogenesis imperfecta** (OI) is also known as "brittle bone disease," and it's just like it sounds -- someone with OI could have literally hundreds of fractures in his lifetime. Unlike with FOP, the actual structure of the bones is faulty in people with OI. Remember that osteogenesis is another word for bone formation -- here, that very bone formation is imperfect. Collagen fibers in bones help keep them strong and structurally sound. In people with osteogenesis imperfecta, one of two things happens -- either the collagen isn't formed right or there isn't enough of it. Without that internal support, the bones can't withstand stress. You could break a bone just by coughing. Samuel L. Jackson's character in "Unbreakable" suffers from a form of brittle bone disease.

**Melorheostosis** is another rare disease affecting the bones and soft tissues. In melorheostosis patients, the compact bone thickens in a way it shouldn't. In X-rays, observers say that the bones look like they are covered in dripping candle wax [source: Melorheostosis Association]. As with FOP, melorheostosis often limits motion -- the muscles contract because connective tissues, such as ligaments and tendons, are shortened. Sometimes the joints turn to bone and freeze, and connective tissues calcify. One limb is often longer than the other, and limbs and hands or feet can be deformed. Like FOP and the other diseases on this page, melorheostosis is a painful disease.

**Paget's disease** enlarges and deforms bones. Osteoblasts, the bone-building cells, make bone that is too weak. Osteoclasts, the cells that break bones down, destroy too much bone. Paget's is painful and sometimes results in scoliosis and bowed limbs. When Paget's affects the skull, sometimes the head looks too big and the person loses his hearing. And surprisingly, even though many of the bones are dense and some are too large in Paget's patients, the bones can also break very easily.

Like with Paget's, people who suffer from **osteopetrosis** (not to be confused with osteoporosis), have lots of bone mass, but the bone is fragile. In osteopetrosis, the osteoclasts don't do their job. Osteoclasts are supposed to reabsorb bone. They work together with osteoblasts to make sure that the right amount of bone is in the body -- osteoblasts make the bone matrix, and osteoclasts eat it up. With osteopetrosis, there's too much new bone and the old bone isn't disappearing fast enough, which throws the whole system out of whack. Osteopetrosis is sometimes called **marble bone** disease -- in some forms of the disorder, the appearance of the bones is changed.



Mütter Museum

The Mütter Museum in Philadelphia houses all kinds of odd medical relics, including a gigantic colon, a tumor from Grover Cleveland and a cast of Siamese twins. The museum also owns the skeleton of Harry Eastlack, an FOP patient (at left).

## **FOP Article Questions**

1. In your own words, describe FOP:
2. What is mesenchyme?
3. What is the cause of FOP?
4. Why is surgery for FOP not an option?
5. Why haven't there been any good scientific studies to find a treatment for FOP?
6. In your own words, describe one other rare bone disease and what causes it:

## **FOP Video Questions**

7. What were Ashley Kurpiel's first symptoms, and what did doctor's think was the proper treatment?
8. What usually causes death in FOP patients?

