



University of Pennsylvania School of Medicine
University of Pennsylvania Health System

Pennsylvania Researchers Discover Gene That Causes Second Skeleton to form
*Pinpointing Cause of Fibrodysplasia Ossificans Progressiva (FOP) Will Accelerate
Development of Treatments for FOP and Common Bone Disorders*

(Philadelphia, PA) – Researchers at the **University of Pennsylvania School of Medicine** have located the “skeleton key,” a gene that, when damaged, causes the body’s skeletal muscles and soft connective tissue to undergo a metamorphosis into bone, progressively locking joints in place and rendering movement impossible. Identifying the gene that causes fibrodysplasia ossificans progressiva (FOP), one of the rarest and most disabling musculoskeletal conditions known to humans and a condition that imprisons its childhood victims in a “second skeleton,” has been the focus at Penn’s Center for Research in FOP and Related Disorders for the past 15 years. This important discovery is relevant, not only for patients with FOP, but also for those with more common musculoskeletal conditions.

Senior authors **Eileen M. Shore, PhD**, and **Frederick S. Kaplan, MD**, both from the Penn Department of Orthopaedic Surgery, and their international consortium of colleagues, report their findings in the April 23 advanced online edition of *Nature Genetics*. “The discovery of the FOP gene is relevant to every condition that affects the formation of bone and every condition that affects the formation of the skeleton,” says Kaplan.

The discovery of the FOP gene was the result of painstaking work by the Penn scientists and their colleagues in the International FOP Research Consortium over many years. It involved the identification and clinical examination of multigenerational families, often in remote regions of the world; genome-wide linkage analysis; identification of candidate genes; and finally, the DNA sequencing and analysis of those candidate genes. The team found that FOP is caused by a mutation of a gene for a receptor called ACVR1 in the bone morphogenetic protein-signaling pathway.

Kaplan describes FOP as the “Mount Everest” of genetic musculoskeletal disorders. His lifelong ambition, as he puts it “is to conquer the summit of this daunting mountain range and see this emerging knowledge turned into novel therapies that can dramatically improve the life of these children. This is nothing less than a campaign for physical independence and personal freedom for these kids. If the knowledge helps us to see farther to help others, that will be great, but this work is for and about the children.”

One in Two Million

FOP is one of the rarest conditions known to medicine, found in only one in 2 million individuals, but, as Kaplan says, quoting from William Harvey who discovered the circulation of the blood, “Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path.” Of

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an estimated 2500 total FOP patients worldwide, there are approximately 600 known patients, and the FOP research group at Penn knows nearly all of them. Says Kaplan, “They are our children, our family.”

Early in life, because of a possible molecular short-circuit in the wound repair system of the body, tendons, ligaments, and skeletal muscle begin an inexorable transformation into an armament of bone, imprisoning its childhood victims in a second skeleton. “FOP bone is perfectly normal in every way, except it should not be there,” says Kaplan. “There are no other known examples of one normal organ system turning into another. It's like a runaway factory for making bone that just won't stop.”

Children with FOP seem normal at birth, except for telltale malformations of the great toes that look like congenital bunions. Early in childhood, painful swellings that are often mistaken for tumors seize the skeletal muscles and transform them into bone. Eventually, ribbons, sheets, and plates of bone cross the joints, lock them in place, and render movement impossible. Attempts to remove the extra bone leads to explosive growth of new bone. Even the slightest trauma such as bumps, bruises, childhood immunizations, and injections for dental work can cause the muscles to turn to bone.

For now, there is no effective prevention or treatment for the molecular sabotage of FOP. The discovery of the FOP gene and the unique mutation that causes FOP provides a highly specific target for future drug development that holds promise for altering not just the symptoms of the disease, but the disease itself.

Penn Team Builds on Past Findings

The Penn team originally surmised that FOP was caused by a mutation of a gene in the bone morphogenetic protein (BMP) signaling pathway, one of the most highly conserved signaling pathways in nature. BMPs are regulatory proteins involved in the embryonic formation and post-natal repair of the skeleton.

Indeed, the FOP gene encodes a BMP receptor called Activin Receptor Type IA, or *ACVR1*, one of three known BMP Type I receptors. BMP receptors are protein switches that help determine the fate of the stem cells in which they are expressed. The *ACVR1* protein is 509 amino acids long, and in FOP the amino acid histidine is substituted for the amino acid arginine at amino acid position 206 in all affected individuals.

FOP is the first human genetic disease ascribed to *ACVR1*. “Our identification of *ACVR1* as a critical regulator of endochondral bone formation during embryogenesis and in post-natal tissues will undoubtedly re-focus thinking and stimulate new research directions,” says Shore. “This discovery will have a major impact on the study of skeletal biology and regenerative medicine.

“This single amino acid substitution is predicted to change the sensitivity and activity of the receptor,” continues Shore. “As is the case for most genes, every cell has two copies of the *ACVR1* gene. In FOP patients, one of the two *ACVR1* gene copies harbors a mutation that causes the *ACVR1* protein to be incorrectly made.”

In FOP, the *ACVR1* gene is damaged by the substitution of a single genetic letter at a specific location in the gene. The single nucleotide substitution changes the meaning of the genetic message encoded by the *ACVR1* gene. “Thus, the substitution of one genetic letter for another

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out of six billion genetic letters in the human genome – the smallest and most precise change imaginable – is like a molecular terrorist that short circuits a functioning set of muscles and connective tissues and transforms them into a second skeleton – in essence turning a light bulb into an atom bomb,” says Kaplan.

ACVR1 is an important BMP signaling switch in cartilage cells of the growth plates of growing bones, especially in the hands and feet, as well as in the cells of skeletal muscle. In previous studies in chickens and zebrafish, other researchers have found that an artificially made “trigger happy” copy of the *ACVR1* gene (similar, but not identical to the FOP gene mutation) makes muscle cells behave like bone cells, upregulating BMP4 expression; downregulating BMP antagonist expression (such as noggin); expanding cartilage elements in growing bone, eventually inducing extra bone growth; and stimulating joint fusion - clinical and molecular features nearly identical to those seen in individuals with FOP.

In the definitive genetic linkage analysis described in the *Nature Genetics* paper, which located the FOP gene to a region on chromosome 2, the researchers used a subset of families in whom all affected individuals had unambiguous features of classic FOP, features that included typical congenital malformations of the great toes and a predictable pattern of extra-skeletal bone formation that mimics the embryonic patterns by which the normal skeleton forms. The researchers have found that every person with classic FOP has the identical mutation in the *ACVR1* gene.

Looking Forward

Computer modeling of the three-dimensional structure of the mutant ACVR1 protein suggests altered activation of this form of ACVR1. “Presumably, the FOP mutation causes a molecular short circuit or promiscuous activation of the receptor, but the detailed molecular physiology is still being deciphered,” says Kaplan. “Such knowledge will be essential to develop treatments and an eventual cure for FOP.”

“To really understand the physiological consequences, we have begun to develop a genetically engineered mouse with the FOP mutation,” notes Shore.

The *ACVR1* gene and protein have been encoded in the molecular machinery of vertebrate DNA for nearly 400 million years – long before the earliest dinosaurs appeared on Earth – suggesting that nature needs to maintain an arginine at codon 206 to support the normal functions of cells, tissues, and organs. Now it will be important to develop an animal model with the same mutation in *ACVR1* that is found in people who have FOP. The *ACVR1* gene is highly conserved throughout vertebrate evolution, from fish to mice to humans, but whether or not a mouse will develop FOP remains to be seen.

“We now know the cause for FOP at the genetic level, and we expect that it will not be long before we understand the mechanism at the molecular level,” says Kaplan. “That knowledge may someday be used, not just for understanding and treating FOP, but for treating many common disorders that affect the skeleton – conditions such as non-genetic forms of extra bone growth

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that may occur following total hip replacement, head injuries, spinal cord injuries, sports injuries, blast injuries from war, and even osteoarthritis and damaged heart valves. Perhaps someday we will be able to harness the gene mutation that causes the renegade bone formation in FOP and make bone in a controlled way – for patients who have severe osteoporosis, for those with severe bone loss from trauma, for those with fractures that fail to heal or spinal fusions that are slow to heal, or for those with congenital malformations of the spine and limbs. We have reached a summit on our epic journey to understand FOP – knowledge we desperately need to help the kids and that will likely help many others. We still have a long way to go, but finally we can see a therapeutic horizon above the clouds, and the view is promising.”

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Penn's School of Medicine is ranked #2 in the nation for receipt of NIH research funds; and ranked #3 in the nation in U.S. News & World Report's most recent ranking of top research-oriented medical schools. Supporting 1,400 fulltime faculty and 700 students, the School of Medicine is recognized worldwide for its superior education and training of the next generation of physician-scientists and leaders of academic medicine.

The University of Pennsylvania Health System includes three hospitals [Hospital of the University of Pennsylvania, which is consistently ranked one of the nation's few "Honor Roll" hospitals by U.S. News & World Report; Pennsylvania Hospital, the nation's first hospital; and Penn Presbyterian Medical Center]; a faculty practice plan; a primary-care provider network; two multispecialty satellite facilities; and home care and hospice.

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