ACVR1

Analyzing the Various Mutations of ACVR1 and How They Result in Fibrodysplasia ossificans progressiva

William Weatherby
University of North Alabama
wweatherby@una.edu

Abstract

Various mutations in ACVR1 that result in Fibrodysplasia ossificans progressiva (FOP), a rare connective tissue disease in which cartilage and other connective tissue are gradually ossified, were examined via virtual modeling in order to view the effects of each mutation on the structure and function of the ACVR1 protein. ACVR1's function was also examined using mouse gene knockouts and string protein maps. The structure for wild-type ACVR1 and its mutations were modeled using YASARA (Yet Another Scientific Artificial Reality Application) with the wild-type optimal model being created by analyzing and comparing models created from UniProt and I-Tasser using the homology modeling tool of YASARA. Pathogenic mutations in ACVR1 that result in FOP were taken from ClinVar and modeled in YASARA to be compared to the wild-type. Analysis and comparison of these mutations showed the common link of Guanine in each mutation being the nucleotide changed.

Introduction

Activin A Receptor, Type I (ACVR1) is a 509 amino acid long gene located on the long arm of Chromosome 2 at the locus 2q24.1 that encodes a protein of the same name. It is important in the Bone Morphogenic Protein Pathway due to its roll in the development and repair of the skeletal system, such as the gradual replacement of cartilage by bone in skeletal maturation. Fibrodysplasia ossificans progressiva is a very rare disease that affects every 1 person per 2 million people, that turns connective tissue such as muscles or ligaments into bone, forming a metaphorical cage around the person, trapping them in their own body. This eventually prevents adult patients from moving altogether, giving it the name "Stone Man Syndrome". Fibrodysplasia ossificans progressiva is caused by a mutation in ACVR1 that changes the shape of the protein, which disrupts the binding of inhibitor proteins or interferes with other mechanisms that control activation. This leads to constitutive activation of ACVR1, causing an overgrowth of bone and cartilage and fusion of joints, resulting in the signs and symptoms of Fibrodysplasia ossificans progressiva as seen in figure 1.

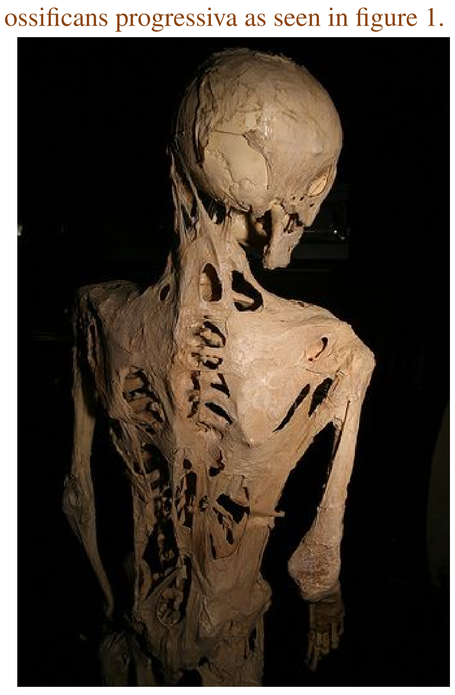

Figure 1: Skeleton exhibiting symptoms of FOP, showing how constrictive the overgrowth of bone is

Mouse gene knockouts, as shown in figure 2, were also analyzed to delve more into the role and function of ACVR1. The figure shows ACVR1's expression affects many phenotypes of the body, confirming ACVR1's role in the skeletal system. A string map, figure 3, was also examined to compare ACVR1 to proteins it is connected to. One such gene family associated with ACVR1, the Bone morphogenetic proteins, handle a similar role to ACVR1 in that they are a group of growth factor signaling molecules that induce bone and cartilage formation, providing a crucial role in all organ systems by constructing and arranging tissue structure throughout the body in a similar vein to ACVR1's role.

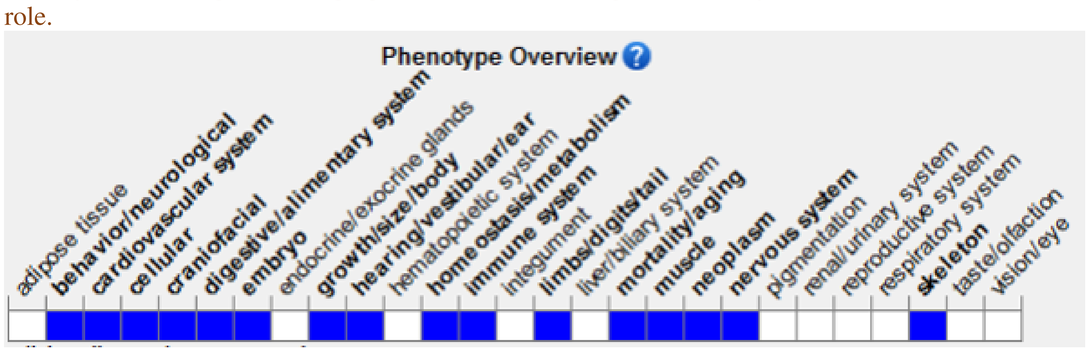

Figure 2: List of all phenotypes that are impacted by ACVR1 knockout in Mice

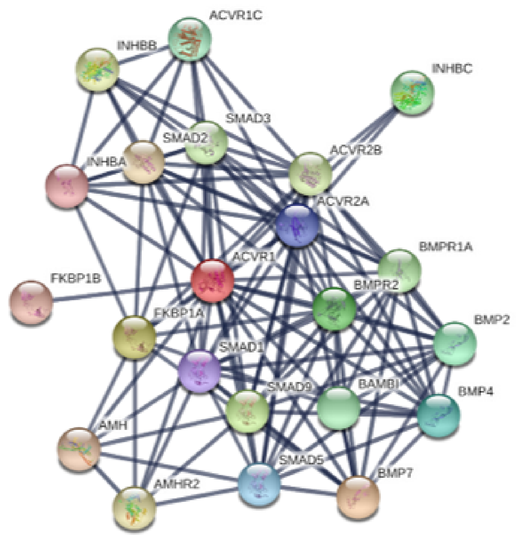

Figure 3: Map of ACVR1 and its related proteins

Methods

The wild-type for ACVR1, shown in figure 4, that would serve as the baseline for comparisons to mutations was modeled using a FASTA sequence taken from UniProt. Then this sequence was modeled using both YASARA (Yet Another Scientific Artificial Reality Application) slow homology modeling tool and I-Tasser, an online tool that predicts protein structure and function by analyzing the amino acid sequence. The mutations to be compared to the wild-type were taken from Clinvar, an online repository of various known mutations that occur in different genes. Each mutation is a change in ACVR1 that results in Fibrodysplasia ossificans progressiva that is considered pathogenic. Each mutation was modeled in YASARA then compared to the wild-type homology model created by I-Tasser.

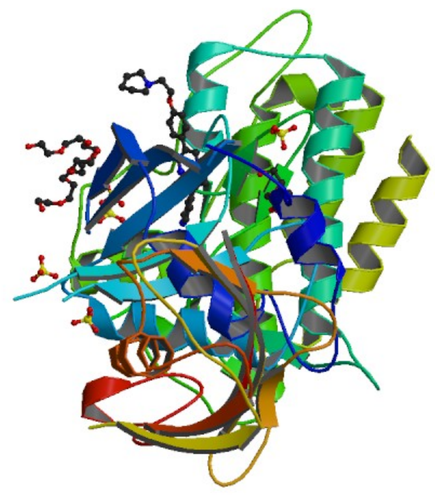

Figure 4: The wild-type form of ACVR1

Results

After analyzing all the mutations and comparing them to their normal wild-type counterparts, a few patterns emerged. The nucleotide, Guanine, was present in every mutation, always being either the nucleotide changed or one of the nucleotides changed. This change in Guanine resulted in each time a radical change in structure and charge of the Amino Acid Residue. Figure 5 shows the normal form of ACVR1 at position 328, where it encodes the amino acid Glycine. The mutation in ACVR1 that causes Fibrodysplasia ossificans progressiva changes the first Guanine the sequence GGG to the nucleotide Uracil. This change from Guanine to Uracil results in the change from the amino acid Glycine to the amino acid Tryptophan, resulting in the radical change in structure shown in figure 5. For future research, it would be explored why exactly the nucleotide that is always changed is Guanine, and why exactly this mutation causes Fibrodysplasia ossificans progressiva every time.

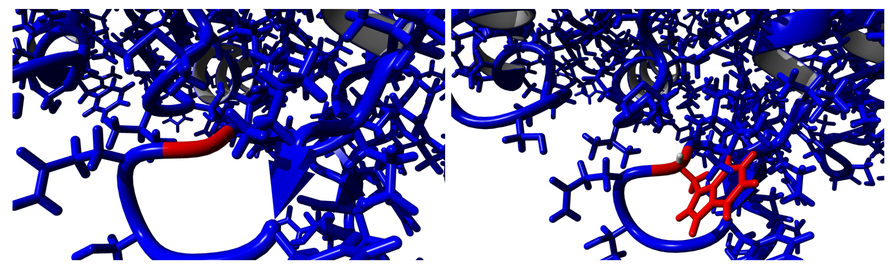

Figure 5: ACVR1 wild-type (left) compared with a mutation at the same point

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