ACVR1 gene

activin A receptor type 1

Normal Function

The *ACVR1* gene provides instructions for making the activin receptor type-1 (ACVR1) protein, which is a member of a protein family called bone morphogenetic protein (BMP) type I receptors. BMP receptors span the cell membrane, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This arrangement allows receptors to receive signals from outside the cell and transmit them inside to affect cell development and function.

The ACVR1 protein is found in many tissues of the body including skeletal muscle and cartilage. It helps to control the growth and development of the bones and muscles, including the gradual replacement of cartilage by bone (ossification). This process occurs in normal skeletal maturation from birth to young adulthood.

The ACVR1 protein is normally turned on (activated) at appropriate times by molecules called ligands. Activation may occur when these ligands, such as BMPs or a protein called activin A, attach (bind) to the receptor or to other proteins with which it forms a complex. Another protein called FKBP12 can turn off (inhibit) ACVR1 by binding to the receptor and preventing inappropriate (leaky) activation in the absence of ligands.

Health Conditions Related to Genetic Changes

Fibrodysplasia ossificans progressiva

Variants (also known as mutations) in the *ACVR1* gene cause fibrodysplasia ossificans progressiva, a disorder in which muscles and connective tissue such as tendons and ligaments are gradually replaced by bone (ossified). The formation of bone tissue outside the skeleton freezes joints and limits movement in affected individuals. The most common variant, which occurs in all individuals with the classic features of the condition, substitutes the protein building block (amino acid) histidine for the amino acid arginine at position 206 of the ACVR1 protein (written as Arg206His or R206H). Other variants in the *ACVR1* gene cause rarer forms of the condition that can be more severe and often involve skeletal abnormalities, such as multiple abnormally formed fingers and toes. The variants that cause fibrodysplasia ossificans progressiva occur as a random (de novo) event during the formation of reproductive cells (eggs or sperm) in an affected person's parent or in early embryonic development. The genetic change is found in all of

the affected person's cells.

Studies show that the R206H variant changes the shape of the ACVR1 protein. This shape change disrupts the binding of the inhibitor protein FKBP12. As a result, the receptor is constantly turned on (constitutively activated), even in the absence of ligands. Other *ACVR1* gene variants result in a receptor protein that is turned on by ligands more easily than the normal version of the protein. Too much receptor activity causes overgrowth of bone and cartilage, resulting in the signs and symptoms of fibrodysplasia ossificans progressiva. Although the same *ACVR1* gene variants that cause fibrodysplasia ossificans progressiva are associated with a rare brain cancer (described below), people with fibrodysplasia ossificans progressiva do not have an increased risk of developing cancer.

Other disorders

Variants in the *ACVR1* gene contribute to the development of a rare brain cancer in children called diffuse intrinsic pontine glioma (DIPG). Most people with DIPG have a particular genetic change in another gene, but a second variant in a different gene (such as *ACVR1*) is required for a tumor to develop. *ACVR1* variants are found in around 25 percent of children with DIPG.

Most of the *ACVR1* gene variants involved in DIPG are the same as those that cause fibrodysplasia ossificans progressiva (described above). However, in DIPG, the variant occurs during a person's lifetime and is found only in cells that become cancerous. (This type of genetic change is called a somatic variant.) As in fibrodysplasia ossificans progressiva, the *ACVR1* variant increases the activity of the ACVR1 receptor. In combination with other cellular changes, abnormal ACVR1 receptor activity can make cells grow and divide uncontrollably, leading to cancer.

Other Names for This Gene

- activin A receptor type I
- activin A receptor, type I
- activin A receptor, type II-like kinase 2
- activin A type I receptor
- activin A type I receptor precursor
- ActR-IA protein, human
- ACTRI
- ACVR1_HUMAN
- ACVR1A
- ACVRLK2
- ALK2
- hydroxyalkyl-protein kinase
- SKR1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ACVR1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=90[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28ACVR1%5BTIAB%5D%29+OR+%28%28ALK2%5BTIAB%5D%29+OR+%28SKR1%5BTIAB%5D%29+OR+%28ACTRI%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- ACTIVIN A RECEPTOR, TYPE I; ACVR1 (https://omim.org/entry/102576)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/90)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ACVR1[gene])

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Genomic Location

The *ACVR1* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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