ACTG2 Gene

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1. Normal Function

The *ACTG2* gene provides instructions for making a protein called gamma (γ)-2 actin, which is part of the actin protein family. Actin proteins are organized into filaments, which are important for the tensing of muscle fibers (muscle contraction) and cell movement. These filaments also help maintain the cytoskeleton, which is the structural framework that determines cell shape and organizes cell contents.

The γ-2 actin protein is found in smooth muscle cells of the urinary and intestinal tracts. Smooth muscles line the internal organs; they contract and relax without being consciously controlled. The γ-2 actin protein is necessary for contraction of the smooth muscles in the bladder and intestines. These contractions empty urine from the bladder and move food through the intestines as part of the digestive process.

2. Health Conditions Related to Genetic Changes

2.1 Intestinal pseudo-obstruction

Several inherited mutations in the *ACTG2* gene have been identified in people with intestinal pseudo-obstruction, a condition that impairs the smooth muscle contractions that move food through the digestive tract (peristalsis). This condition mimics a physical blockage of the intestines without an actual obstruction. Problems with emptying the bladder can also occur in people with this disorder.

The *ACTG2* gene mutations that cause intestinal pseudo-obstruction are thought to hinder the formation of actin filaments in the cytoskeleton and reduce the ability of smooth muscles in the intestines and bladder to contract. As a result, peristalsis in the intestines is impaired and the bladder is less able to contract and expel urine, leading to the signs and symptoms of this condition.

2.2 Megacystis-microcolon-intestinal hypoperistalsis syndrome

At least 22 *ACTG2* gene mutations have been found to cause megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), which is characterized by impairment of peristalsis and emptying the bladder.

The *ACTG2* gene mutations that cause MMIHS are not inherited; rather they occur as a random (de novo) event during the formation of reproductive cells (eggs or sperm) or in early embryonic development. The alterations change single protein building blocks (amino acids) in the γ-2 actin protein. These changes hinder the formation of actin filaments and reduce the ability of smooth muscles in the bladder and intestines to contract. As a result, the bladder cannot empty normally, leading to an enlarged bladder (megacystis) and painful abdominal swelling (distention). In addition, partially digested food can build up in the intestines, which also contributes to distention. Poor digestion may lead to malnutrition in people with MMIHS.

2.3 Other disorders

ACTG2 gene mutations cause a spectrum of disorders (sometimes referred to as *ACTG2*-related disorders), with MMIHS (described above) at the severe end. As in MMIHS, most of these mutations change single amino acids in the γ-2 actin protein. However, in less severely affected individuals, the mutations are usually inherited. These mutations often cause intestinal pseudo-obstruction (described above). In some affected individuals, the smooth muscle problems are episodic and come and go throughout life. Intestinal malrotation can also occur in people with *ACTG2* gene mutations. This

condition occurs when the intestines do not fold properly; instead, they twist abnormally, which can impede the movement of food. Effects on the urinary tract include recurrent urinary tract infections and impaired bladder function. Individuals with inherited *ACTG2* gene mutations can have one or more of these intestinal or urinary tract abnormalities; they are usually milder than MMIHS, or they begin later in life. It is unclear why inherited and de novo mutations result in conditions with different severities.

3. Other Names for This Gene

- ACT
- ACTA3
- ACTE
- actin, gamma-enteric smooth muscle isoform 1 precursor
- actin, gamma-enteric smooth muscle isoform 2 precursor
- actin-like protein
- ACTL3
- ACTSG
- alpha-actin-3
- VSCM

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