PRKAG2 Gene

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Contributor: Karina Chen

protein kinase AMP-activated non-catalytic subunit gamma 2

genes

1. Normal Function

The *PRKAG2* gene provides instructions for making one part (the gamma-2 subunit) of a larger enzyme called AMP-activated protein kinase (AMPK). This enzyme helps sense and respond to energy demands within cells. It is active in many different tissues, including heart (cardiac) muscle and muscles used for movement (skeletal muscles). AMP-activated protein kinase is likely involved in the development of the heart before birth, although its role in this process is unknown.

AMP-activated protein kinase regulates chemical pathways involving the cell's main energy source, a molecule called adenosine triphosphate (ATP). The breakdown of ATP releases energy to drive many types of chemical reactions. AMP-activated protein kinase is activated during times of cellular stress (such as low oxygen levels or muscle exercise), when ATP is broken down rapidly to produce energy. If ATP levels become too low, the enzyme restores the balance of energy by limiting chemical reactions that require ATP and stimulating pathways that generate ATP.

Studies suggest that AMP-activated protein kinase may play a role in controlling the activity of other genes, although many of these genes have not been identified. The enzyme may also regulate the activity of certain ion channels in the heart. These channels, which transport positively charged atoms (ions) into and out of heart muscle cells, play critical roles in maintaining the heart's normal rhythm.

2. Health Conditions Related to Genetic Changes

2.1. Wolff-Parkinson-White syndrome

At least seven mutations that cause Wolff-Parkinson-White syndrome have been identified in the *PRKAG2* gene. Some people with these mutations also have features of hypertrophic cardiomyopathy, a form of heart disease that enlarges and weakens the heart (cardiac) muscle. Researchers are uncertain how *PRKAG2* mutations lead to the development of these heart conditions. Research suggests that these mutations alter the activity of AMP-activated

protein kinase in the heart, disrupting the enzyme's ability to respond to changes in cellular energy demands. It is unclear, however, whether the genetic changes overactivate the enzyme or reduce its activity.

Studies indicate that changes in AMP-activated protein kinase activity allow a complex sugar called glycogen to build up abnormally within cardiac muscle cells. The accumulation of this substance enlarges these cells, which may lead to hypertrophic cardiomyopathy. Researchers continue to investigate whether an abnormal buildup of glycogen in the heart is also responsible for the problems with electrical signaling that are characteristic of Wolff-Parkinson-White syndrome.

Other studies have found that altered AMP-activated protein kinase activity is related to changes in the regulation of certain ion channels in the heart. These changes may help explain the increased risk of abnormal heart rhythms (arrhythmias) in people with Wolff-Parkinson-White syndrome.

2.2. Other disorders

Several mutations in the *PRKAG2* gene have been found in people with other heart conditions. For example, a specific mutation in this gene is responsible for a very severe form of heart disease called lethal congenital glycogen storage disease of the heart. People with this mutation are born with extremely enlarged hearts (cardiomegaly) and abnormal electrical signaling within the heart. These abnormalities lead to respiratory distress and heart failure early in life. The mutation responsible for this condition changes a single protein building block (amino acid) in the gamma-2 subunit of AMP-activated protein kinase. Specifically, this mutation replaces the amino acid arginine with the amino acid glutamine at position 531 (written as Arg531Gln or R531Q). Studies suggest that this severe disorder may be related to the abnormal buildup of glycogen within cardiac muscle cells.

Other mutations in the *PRKAG2* gene have been associated with disorders affecting both cardiac and skeletal muscle. These mutations change single amino acids in the gamma-2 subunit of AMP-activated protein kinase. Individuals with these genetic changes typically experience muscle pain and stiffness, particularly following exercise, in addition to hypertrophic cardiomyopathy and abnormal electrical signaling within the heart. It is not known why the effects of some *PRKAG2* mutations appear to be confined to the heart, while other mutations cause signs and symptoms affecting both cardiac and skeletal muscles.

3. Other Names for This Gene

- AAKG
- AAKG2
- AAKG2_HUMAN
- AMP-activated protein kinase gamma2 subunit

- AMPK gamma2
- CMH6
- H91620p
- protein kinase, AMP-activated, gamma 2 non-catalytic subunit
- WPWS

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