SMAD4 Gene

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SMAD family member 4

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1. Normal Function

The *SMAD4* gene provides instructions for making a protein involved in transmitting chemical signals from the cell surface to the nucleus. The SMAD4 protein is part of a signaling pathway, called the transforming growth factor beta (TGF-β) pathway, that allows the environment outside the cell to affect gene activity and protein production within the cell. The signaling process begins when a TGF-β protein attaches (binds) to a receptor protein on the cell surface, which turns on (activates) a group of related SMAD proteins. The SMAD proteins bind to the SMAD4 protein and form a protein complex, which then moves to the cell nucleus. In the nucleus, the SMAD protein complex binds to specific areas of DNA where it controls the activity of particular genes and regulates cell growth and division (proliferation). By controlling these cellular processes, the SMAD4 protein is involved in the development of many body systems.

The SMAD4 protein serves both as a transcription factor and as a tumor suppressor. Transcription factors help control the activity of particular genes, and tumor suppressors keep cells from growing and dividing too fast or in an uncontrolled way.

2. Health Conditions Related to Genetic Changes

2.1. Hereditary hemorrhagic telangiectasia

At least 27 mutations in the *SMAD4* gene have been found to cause a form of hereditary hemorrhagic telangiectasia, a disorder characterized by certain blood vessel abnormalities. In particular, some smaller arteries (arterioles) abnormally flow directly into veins rather than into other vessels called capillaries. These abnormalities are called arteriovenous malformations. When they occur in vessels near the surface of the skin, where they are visible as red markings, they are known as telangiectases (the singular is telangiectasia).

The form of hereditary hemorrhagic telangiectasia caused by *SMAD4* gene mutations is called juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome. People with this disorder have the blood vessel problems associated with hereditary hemorrhagic telangiectasia as well as an increased risk of developing intestinal growths (polyps) at an early age; the polyps may become cancerous.

SMAD4 gene mutations that cause this disorder affect the TGF-β signaling pathway. Disruption of this pathway may interfere with both the tumor suppressor function of the SMAD4 protein and the appropriate development of the boundaries between veins and arteries, resulting in the signs and symptoms of juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome.

2.2. Juvenile polyposis syndrome

At least 78 mutations in the *SMAD4* gene have been found to cause juvenile polyposis syndrome, a disorder characterized by multiple noncancerous (benign) growths called juvenile polyps. Most *SMAD4* gene mutations that cause juvenile polyposis syndrome result in the production of an abnormally short, nonfunctional protein. A lack of functional SMAD4 protein prevents binding to other SMAD proteins and interferes with the transmission of chemical signals from the cell surface to the nucleus. The SMAD protein complex is not activated and cannot be transported to the nucleus, where it is needed to regulate cell proliferation and the activity of certain genes. This unregulated cell growth can lead to polyp formation in people with juvenile polyposis syndrome.

2.3. Myhre syndrome

At least four mutations in the *SMAD4* gene have been identified in people with Myhre syndrome, a condition characterized by intellectual disability, a buildup of scar tissue (fibrosis) in the skin and internal organs, and other problems affecting multiple body systems and functions. These mutations affect the protein building block (amino acid) at protein position 496 or 500 by replacing it with a different amino acid. Studies suggest that these mutations result in an abnormally stable SMAD4 protein that remains active in the cell longer than it is needed. These mutations are classified as "gain-of-function" because they enhance the activity of the SMAD4 protein. Increased availability of active SMAD4 allows the protein more time to interact with other proteins and may result in abnormal TGF-β signaling in many cell types, which affects development of several body systems and leads to the signs and symptoms of Myhre syndrome.

2.4. Cancers

People with mutations in the *SMAD4* gene appear to have an increased risk of developing various cancers. Some of these gene mutations are inherited, while others are acquired during a person's lifetime. Such acquired (somatic) mutations are present only in certain cells. Cells with mutations in the *SMAD4* gene, whether inherited or somatic, may proliferate out of control and result in a tumor, often in the colon or pancreas.

2.5. Other disorders

SMAD4 gene mutations have also been identified in a small number of individuals with juvenile polyposis and blood vessel abnormalities other than hereditary hemorrhagic telangiectasia (described above). These abnormalities include weakening and stretching (dilation) of the aorta, which is the large blood vessel that distributes blood from the heart to the rest of the body. Aortic dilation may lead to a bulge in the blood vessel wall (an aneurysm), or may cause the aortic valve to leak, which can result in a sudden tearing of the layers in the aorta wall (aortic dissection). Aortic aneurysm and dissection can be life-threatening. Impaired functioning of the mitral valve, which connects two of the four chambers of the heart, has also been seen in combination with juvenile polyposis caused by *SMAD4* gene mutations.

3. Other Names for This Gene

- DPC4
- JIP
- MAD (mothers against decapentaplegic, Drosophila) homolog 4
- MAD, mothers against decapentaplegic homolog 4
- MAD, mothers against decapentaplegic homolog 4 (Drosophila)
- MADH4
- Mothers against decapentaplegic, Drosophila, homolog of, 4
- SMAD, mothers against DPP homolog 4 (Drosophila)
- SMAD4_HUMAN

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