MAP2K1 Gene

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Mitogen-activated protein kinase kinase 1

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1. Introduction

The *MAP2K1* gene provides instructions for making a protein known as MEK1 protein kinase. This protein is part of a signaling pathway called the RAS/MAPK pathway, which transmits chemical signals from outside the cell to the cell's nucleus. RAS/MAPK signaling helps control the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (migration), and the self-destruction of cells (apoptosis). MEK1 protein kinase appears to be essential for normal development before birth and for survival after birth.

2. Health Conditions Related to Genetic Changes

2.1. Cardiofaciocutaneous Syndrome

At least 13 mutations in the *MAP2K1* gene have been identified in people with cardiofaciocutaneous syndrome. This condition affects many parts of the body, particularly the heart (cardio-), facial features (facio-), and the skin and hair (-cutaneous).

The *MAP2K1* gene mutations that cause cardiofaciocutaneous syndrome are germline mutations, which means that they are present in cells throughout the body. Each mutation changes a single protein building block (amino acid) in MEK1 protein kinase. The genetic changes abnormally activate the protein, which disrupts the tightly regulated RAS/MAPK signaling pathway in many types of cells. The altered signaling interferes with the normal development of many organs and tissues, resulting in the characteristic features of cardiofaciocutaneous syndrome.

2.2. Melorheostosis

At least three mutations in the *MAP2K1* gene have been identified in people with melorheostosis. This rare disease causes the abnormal growth of new bone tissue on the surface of existing bones. The new bone has a characteristic "dripping candle wax" or flowing appearance on x-rays.

The mutations associated with melorheostosis are described as somatic. Somatic mutations occur during a person's lifetime and are present only in certain cells, in this case, bone cells in a particular area of the body. The known mutations change single amino acids in MEK1 protein kinase. The mutations lead to the production of a version of the protein that is overactive, which increases RAS/MAPK signaling in bone tissue. The increased signaling disrupts the regulation of bone cell proliferation and allows new bone to grow abnormally. Studies suggest that increased RAS/MAPK signaling also stimulates excess bone remodeling, a normal process in which old bone is broken down and new bone is created to replace it. These changes in bone growth and turnover underlie the bone abnormalities characteristic of melorheostosis.

2.3. Noonan Syndrome with Multiple Lentigines

At least one mutation in the *MAP2K1* gene has been found to cause Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome). This condition is characterized by multiple brown skin spots (lentigines), heart defects, short stature, a sunken or protruding chest, and distinctive facial features.

The identified *MAP2K1* gene mutation is a germline mutation that replaces the amino acid glutamic acid with the amino acid glycine at position 102 (written as Glu102Gly or E102G) in MEK1 protein kinase. This change likely results in increased activation of the RAS/MAPK signaling pathway in cells throughout the body. The increased signaling interferes

with the normal development of many organs and tissues, resulting in the characteristic features of Noonan syndrome with multiple lentigines.

It is unclear why the E102G mutation causes Noonan syndrome with multiple lentigines and other germline mutations in the *MAP2K1* gene cause different disorders, such as cardiofaciocutaneous syndrome (described above).

2.4. Other Cancers

Mutations in the *MAP2K1* gene have also been found in several forms of cancer. Like the mutations that cause melorheostosis (described above), cancer-associated mutations in this gene are somatic. They occur only in the cells that ultimately give rise to cancer. Somatic mutations in the *MAP2K1* gene have been reported in several forms of blood cell cancer (leukemia and lymphoma), lung cancer, and a form of skin cancer called melanoma. The genetic changes lead to an overactive MEK1 protein kinase, which increases activation of the RAS/MAPK signaling pathway in particular tissues. The increased signaling allows cells to grow and divide too quickly, leading to cancer.

3. Other Names for This Gene

- Dual Specificity Mitogen-Activated Protein Kinase Kinase 1
- ERK Activator Kinase 1
- MAP Kinase Kinase 1
- MAPK/ERK kinase 1
- MAPKK1
- MEK-1
- MEK-1 Protein Kinase
- MEK1
- MKK-1 Protein Kinase
- MKK1
- MKK1 Protein Kinase
- MP2K1_HUMAN
- PRKMK1
- protein kinase, mitogen-activated, kinase 1 (MAP kinase kinase 1)

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