

## **BRAF gene**

B-Raf proto-oncogene, serine/threonine kinase

### **Normal Function**

The *BRAF* gene provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell's nucleus. This protein is part of a signaling pathway known as the RAS/MAPK pathway, which controls several important cell functions. Specifically, the RAS/MAPK pathway regulates 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). Chemical signaling through this pathway is essential for normal development before birth.

The *BRAF* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous.

### **Health Conditions Related to Genetic Changes**

#### Cardiofaciocutaneous syndrome

Mutations in the *BRAF* gene are the most common cause of cardiofaciocutaneous syndrome. This condition affects many parts of the body, particularly the heart (cardio-), facial features (facio-), and the skin and hair (cutaneous). At least 49 *BRAF* mutations have been identified in people with this disorder. These mutations change single protein building blocks (amino acids) in the BRAF protein. Almost all of these genetic changes abnormally activate the protein, which disrupts the tightly regulated RAS/MAPK signaling pathway in cells throughout the body. The altered signaling interferes with the normal development of many organs and tissues, resulting in the characteristic features of cardiofaciocutaneous syndrome.

#### Erdheim-Chester disease

At least one mutation in the *BRAF* gene has been identified in some people with Erdheim-Chester disease. This rare condition is characterized by the abnormal production and accumulation of immune system cells called histiocytes in many of the body's tissues. The disease most commonly affects the bones, causing bone thickening and pain, but the accumulation of histiocytes can also cause signs and symptoms affecting the brain, eyes, lungs, liver, kidneys, and other organs.

The *BRAF* gene mutation that causes this condition is somatic, meaning that it occurs during a person's lifetime and is present only in certain cells. The mutation affects a single amino acid in the BRAF protein. Specifically, the mutation replaces the amino acid valine with the amino acid glutamic acid at position 600 (written as Val600Glu or V600E). This mutation leads to production of a BRAF protein that is abnormally active, which disrupts regulation of cell proliferation and may allow histiocytes to grow and divide uncontrollably, leading to the abnormal accumulation of histiocytes that occurs in Erdheim-Chester disease.

### Giant congenital melanocytic nevus

The V600E mutation (described above) in the *BRAF* gene has also been found to cause giant congenital melanocytic nevus. This condition is characterized by a large, noncancerous patch of abnormally dark skin that is present from birth and an increased risk of a type of skin cell cancer called melanoma (described below). In giant congenital melanocytic nevus, a somatic V600E mutation occurs during embryonic development in cells that will develop into pigment-producing skin cells (melanocytes). This mutation leads to production of a BRAF protein that is abnormally active, which disrupts regulation of cell proliferation. The unregulated cell proliferation of early melanocytes leads to a large patch of darkly pigmented skin characteristic of giant congenital melanocytic nevus. Additional gene mutations in cells within the nevus after birth can lead to melanoma in people with giant congenital melanocytic nevus.

### Noonan syndrome

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### Noonan syndrome with multiple lentigines

At least two mutations in the *BRAF* gene have 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 *BRAF* gene mutations change single amino acids in the BRAF protein: One mutation replaces the amino acid threonine with the amino acid proline at position 241 (written as Thr241Pro or T241P) and the other mutation replaces the amino acid leucine with the amino acid phenylalanine at position 245 (written as Leu245Phe or L245F).

The *BRAF* gene changes that cause Noonan syndrome with multiple lentigines are believed to abnormally activate the BRAF protein, which disrupts the regulation of the RAS/MAPK signaling pathway that controls cell functions such as proliferation. This misregulation can result in the various features of Noonan syndrome with multiple lentigines.

### Cholangiocarcinoma

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## Gastrointestinal stromal tumor

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## Langerhans cell histiocytosis

Somatic mutations in the *BRAF* gene, most frequently the V600E mutation (described above), have been identified in some individuals with Langerhans cell histiocytosis. This disorder causes an abnormal accumulation of certain immune cells called Langerhans cells in multiple tissues and organs, which often leads to the formation of tumors called granulomas. Many researchers consider Langerhans cell histiocytosis to be a form of cancer, but this classification is controversial.

The *BRAF* gene mutations, which are found only in the abnormal Langerhans cells, cause the BRAF protein to be continuously active. The overactive protein may contribute to the development of Langerhans cell histiocytosis by allowing the Langerhans cells to grow and divide uncontrollably.

In some other forms of histiocytosis such as Erdheim-Chester disease (described above), the histiocytes do not include Langerhans cells; a disorder of that type is classified as a non-Langerhans cell histiocytosis. It is not clear why the V600E mutation can cause different forms of histiocytosis.

## Lung cancer

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## Melanoma

The V600E mutation (described above) in the *BRAF* gene has also been found in about half of noninherited (sporadic) cases of melanoma. Melanoma is a type of skin cancer that begins in pigment-producing cells called melanocytes. In this cancer, a somatic V600E mutation occurs during a person's lifetime, likely caused by ultraviolet (UV) radiation from the sun or other environmental risk factors. This mutation often leads only to the formation of a noncancerous mole. At least one additional mutation is necessary for the development of melanoma.

## Multiple myeloma

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## Cancers

Somatic mutations in the *BRAF* gene are common in several types of cancer. Normally, the BRAF protein is switched on and off in response to signals that control cell growth and development. Somatic mutations cause the BRAF protein to be continuously active and to transmit messages to the nucleus even in the absence of these chemical signals. The overactive protein may contribute to the growth of cancers by allowing abnormal cells to grow and divide without external signals.

The V600E mutation (described above) is the most common *BRAF* gene mutation found in human cancers. This mutation has frequently been found in cancers of the colon and rectum, ovary, and thyroid gland. Several other somatic mutations in the *BRAF* gene have also been associated with cancer.

### Other Names for This Gene

- 94 kDa B-raf protein
- B-raf 1
- B-Raf proto-oncogene serine/threonine-protein kinase
- BRAF1
- BRAF1\_HUMAN
- Murine sarcoma viral (v-raf) oncogene homolog B1
- p94
- RAFB1
- v-raf murine sarcoma viral oncogene homolog B

### Additional Information & Resources

#### Tests Listed in the Genetic Testing Registry

- Tests of BRAF ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=673\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=673[geneid]))

#### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28BRAF%5BTI%5D%29+OR+%28B-RAF%5BTI%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+180+days%22%5Bdp%5D%29%29%29>)

#### Catalog of Genes and Diseases from OMIM

- B-RAF PROTOONCOGENE, SERINE/THREONINE KINASE; BRAF (<https://omim.org/entry/164757>)

#### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/673>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=BRAF\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=BRAF[gene]))

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## Genomic Location

The *BRAF* gene is found on chromosome 7 (<https://medlineplus.gov/genetics/chromosome/7/>).

**Last updated August 1, 2018**