

FH Gene

Subjects: **Genetics & Heredity**

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Fumarate hydratase

genes

1. Normal Function

The *FH* gene provides instructions for making an enzyme called fumarase (also known as fumarate hydratase). Fumarase participates in an important series of reactions known as the citric acid cycle or Krebs cycle, which allows cells to use oxygen and generate energy. Specifically, fumarase helps convert a molecule called fumarate to a molecule called malate.

2. Health Conditions Related to Genetic Changes

2.1 Fumarase Deficiency

More than 20 *FH* gene mutations have been identified in people with fumarase deficiency, a condition that primarily affects the brain and is often fatal in infancy. Fumarase deficiency occurs in individuals who inherit two mutated copies of the *FH* gene in each cell. Most of these mutations replace one protein building block (amino acid) with another amino acid in the fumarase enzyme. These changes disrupt the ability of the enzyme to help convert fumarate to malate, interfering with the function of this reaction in the citric acid cycle. Impairment of the process that generates energy for cells is particularly harmful to cells in the developing brain, and this impairment results in the signs and symptoms of fumarase deficiency.

2.2 Hereditary Leiomyomatosis and Renal Cell Cancer

More than 70 mutations in the *FH* gene that cause hereditary leiomyomatosis and renal cell cancer (HLRCC) have been reported. Most of these mutations replace one amino acid with another amino acid in the fumarase enzyme.

HLRCC is a disorder in which affected individuals tend to develop benign tumors containing smooth muscle tissue (leiomyomas) in the skin and, in females, the uterus. This condition also increases the risk of kidney cancer. People with HLRCC are born with one mutated copy of the *FH* gene in each cell. The second copy of the *FH* gene in certain cells may also acquire mutations as a result of environmental factors such as ultraviolet radiation from the sun or an error that occurs as DNA copies itself during cell division. These changes are called somatic mutations and are not inherited.

FH gene mutations may interfere with the enzyme's role in the citric acid cycle, resulting in a buildup of fumarate. Researchers believe that the excess fumarate may interfere with the regulation of oxygen levels in the cell. Chronic oxygen deficiency (hypoxia) in cells with two mutated copies of the *FH* gene may encourage tumor formation and result in the tendency to develop leiomyomas and renal cell cancer.

2.3 Primary Macronodular Adrenal Hyperplasia

3. Other Names for This Gene

- fumarase
- fumarase hydratase
- FUMH_HUMAN
- HLRCC
- LRCC
- MCL
- MCUL1

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