

SDHA Gene

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succinate dehydrogenase complex flavoprotein subunit A

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1. Normal Function

The *SDHA* gene provides instructions for making one of four parts (subunits) of the succinate dehydrogenase (SDH) enzyme. The SDH enzyme plays a critical role in mitochondria, which are structures inside cells that convert the energy from food into a form that cells can use.

Within mitochondria, the SDH enzyme links two important pathways in energy conversion: the citric acid cycle (or Krebs cycle) and oxidative phosphorylation. As part of the citric acid cycle, the SDH enzyme converts a compound called succinate to another compound called fumarate. Negatively charged particles called electrons are released during this reaction. The SDHA protein is the active subunit of the enzyme that performs the conversion of succinate, and it also helps transfer electrons to the oxidative phosphorylation pathway. In oxidative phosphorylation, the electrons help create an electrical charge that provides energy for the production of adenosine triphosphate (ATP), the cell's main energy source.

Succinate, the compound on which the SDH enzyme acts, is an oxygen sensor in the cell and can help turn on specific pathways that stimulate cells to grow in a low-oxygen environment (hypoxia). In particular, succinate stabilizes a protein called hypoxia-inducible factor (HIF) by preventing a reaction that would allow HIF to be broken down. HIF controls several important genes involved in cell division and the formation of new blood vessels in a hypoxic environment.

The *SDHA* gene is a tumor suppressor gene, which means it prevents cells from growing and dividing in an uncontrolled way.

2. Health Conditions Related to Genetic Changes

2.1. Nonsyndromic paraganglioma

At least three mutations in the *SDHA* gene have been identified in people with paraganglioma or pheochromocytoma (a type of paraganglioma), which are noncancerous (benign) tumors associated with the nervous system. *SDHA* gene mutations are seen most commonly in people with paraganglioma, but they have been found in people with pheochromocytoma. Specifically, *SDHA* gene mutations are associated with nonsyndromic paraganglioma or pheochromocytoma, which means the tumors are not part of an inherited syndrome.

A single mutation in the *SDHA* gene increases the risk that an individual will develop the condition. However, an additional mutation that deletes the normal copy of the gene is needed to cause tumor formation. This second mutation, called a somatic mutation, is acquired during a person's lifetime and is present only in tumor cells.

The *SDHA* gene mutations associated with nonsyndromic paraganglioma or pheochromocytoma change single protein building blocks (amino acids) in the SDHA protein sequence or result in a shortened protein. As a result, there is little or no SDH enzyme activity. Because the mutated SDH enzyme cannot convert succinate to fumarate, succinate accumulates in the cell. The excess succinate abnormally stabilizes HIF, which also builds up in cells. Excess HIF stimulates cells to divide and triggers the production of blood vessels when they are not needed. Rapid and uncontrolled cell division, along with the formation of new blood vessels, can lead to the development of tumors.

2.2. Other disorders

Mutations in the *SDHA* gene have been identified in a small number of people with Leigh syndrome, a progressive brain disorder that typically appears in infancy or early childhood. Affected children may experience vomiting, seizures, delayed development, muscle weakness, and problems with movement. Heart disease, kidney problems, and difficulty breathing can also occur in people with this disorder.

The *SDHA* gene mutations responsible for Leigh syndrome change single amino acids in the SDHA protein or result in an abnormally short protein. These genetic changes disrupt the activity of the SDH enzyme, impairing the ability of mitochondria to produce energy. It is not known, however, how mutations in the *SDHA* gene are related to the specific features of Leigh syndrome.

3. Other Names for This Gene

- CMD1GG
- DHSA_HUMAN
- flavoprotein subunit of complex II
- FP
- SDH1
- SDH2
- SDHF
- succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
- succinate dehydrogenase complex flavoprotein subunit
- succinate dehydrogenase complex subunit A, flavoprotein (Fp)
- succinate dehydrogenase complex, subunit A, flavoprotein (Fp)

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