SDHC gene

succinate dehydrogenase complex subunit C

Normal Function

The *SDHC* gene provides instructions for making one of four 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. The SDHC protein helps anchor the SDH enzyme in the mitochondrial membrane.

Within mitochondria, the SDH enzyme links two important cellular 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 electrons are transferred through the SDH subunits, including the SDHC protein, 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 *SDHC* gene is a tumor suppressor, which means it prevents cells from growing and dividing in an uncontrolled way.

Health Conditions Related to Genetic Changes

Gastrointestinal stromal tumor

Changes affecting the *SDHC* gene have been found in people with a gastrointestinal stromal tumor (GIST), which is a type of tumor that occurs in the gastrointestinal tract. Alteration of this gene cause SDH-deficient GIST, which accounts for less than 10 percent of GIST cases. SDH-deficient GISTs usually occur in childhood or early adulthood and are almost always found in the stomach. Individuals with an SDH-

deficient GIST have a high risk of developing other types of tumors, particularly noncancerous tumors in the nervous system called paragangliomas (described below) and noncancerous lung tumors called pulmonary chondromas.

The most common genetic alteration affecting the *SDHC* gene involved in GIST is known as promoter hypermethylation. (This genetic change is also called an epimutation.) The promoter is a region of DNA near the gene that controls gene activity (expression). Hypermethylation occurs when too many small molecules called methyl groups are attached to the promoter region. The extra methyl groups reduce the expression of the *SDHC* gene, which means that less SDHC subunit is produced.

Other genetic changes alter the sequence of DNA building blocks in the *SDHC* gene. These mutations are present in all of the body's cells and are known as germline mutations. The germline mutations prevent the production of a functional SDHC subunit from the altered copy of the gene.

A single change impairing the *SDHC* gene, either promoter hypermethylation or a germline mutation, increases the risk that an individual will develop a tumor. However, an additional change that alters the normal copy of the gene is needed to cause tumor formation. Some people with GIST inherit a germline mutation in one copy of the gene and have promoter hypermethylation affecting the other copy. Other affected individuals have promoter hypermethylation affecting both copies of the *SDHC* gene. As a result, little or no functional SDHC enzyme is produced.

Without the SDHC subunit, the SDH enzyme either cannot form or is unstable and broken down quickly. As a result, there is little or no SDH enzyme activity. Without the SDH enzyme, succinate is not converted to fumarate, and succinate builds up in cells. The excess succinate abnormally stabilizes the HIF protein, which also builds up in cells. Excess HIF protein 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.

The *SDHC* promoter hypermethylation is usually associated with the development of GIST, paraganglioma, and pulmonary chondroma; this combination of tumors is a condition known as Carney triad. Less commonly, individuals with *SDHC* gene mutations or promoter hypermethylation develop only GIST or a different combination of tumors. The combination of GIST and paraganglioma is known as known as Carney-Stratakis syndrome; and the combination of GIST and pulmonary chondroma is known as incomplete Carney triad.

Hereditary paraganglioma-pheochromocytoma

More than 30 mutations in the *SDHC* gene have been found to increase the risk of hereditary paraganglioma-pheochromocytoma type 3. People with this condition have paragangliomas, pheochromocytomas, or both. An inherited (germline) *SDHC* gene mutation predisposes an individual to the condition, and a somatic mutation that deletes the normal copy of the *SDHC* gene is needed to cause hereditary paraganglioma-pheochromocytoma type 3.

Most of the inherited *SDHC* gene mutations involved in hereditary paraganglioma-pheochromocytoma type 3 change single protein building blocks (amino acids) in the SDHC protein sequence or result in a shortened protein. As a result, there is little or no SDH enzyme activity. As in GIST (described above), the reduction of SDH enzyme activity stabilizes the HIF protein, causing it to build up in cells. Excess HIF protein abnormally stimulates cell division and the formation of blood vessels, which can lead to tumor formation.

Cowden syndrome

MedlinePlus Genetics provides information about Cowden syndrome

Other Names for This Gene

- C560_HUMAN
- CYB560
- CYBL
- cytochrome B large subunit of complex II
- integral membrane protein CII-3
- integral membrane protein CII-3b
- PGL3
- QPs-1
- QPS1
- SDH3
- succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa
- succinate dehydrogenase cytochrome b560 subunit, mitochondrial
- succinate-ubiquinone oxidoreducatase cytochrome B large subunit
- succinate-ubiquinone oxidoreductase cytochrome B large subunit

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SDHC (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6391[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SDHC%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT C; SDHC (https://omim.org/entry/602413)
- PARAGANGLIOMA AND GASTRIC STROMAL SARCOMA (https://omim.org/entry/606864)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6391)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SDHC[gene])

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Genomic Location

The *SDHC* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

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