SDHD gene

succinate dehydrogenase complex subunit D

Normal Function

The *SDHD* 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 SDHD protein helps anchor the SDH enzyme in the mitochondrial membrane.

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 electrons are transferred through the SDH subunits, including the SDHD protein, to the oxidative phosphorylation pathway. In oxidative phosphorylation, the electrons 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 *SDHD* 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

Mutations in the *SDHD* gene are a rare cause of gastrointestinal stromal tumor (GIST), which is a type of tumor that occurs in the gastrointestinal tract. Mutation 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. People with SDH-deficient GIST caused by *SDHD* gene mutations tend to also develop paragangliomas (described below); this combination of tumors is a condition known as Carney-Stratakis syndrome.

An inherited (germline) mutation in the *SDHD* gene increases the risk that an individual will develop a GIST. However, an additional mutation that alters or 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.

SDHD gene mutations associated with GIST prevent the production of functional SDHD protein. Without this 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 the cell. 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.

Hereditary paraganglioma-pheochromocytoma

More than 100 mutations in the *SDHD* gene have been identified in people with hereditary paraganglioma-pheochromocytoma type 1. People with this condition have paragangliomas, pheochromocytomas, or both. These noncancerous (benign) tumors are associated with the nervous system. An inherited *SDHD* gene mutation predisposes an individual to the condition. An additional, somatic mutation that deletes the normal copy of the gene is needed to cause hereditary paraganglioma-pheochromocytoma type 1.

Most of the inherited *SDHD* gene mutations associated with hereditary paraganglioma-pheochromocytoma type 1 change single protein building blocks (amino acids) in the SDHD 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.

Nonsyndromic paraganglioma

Mutations in the *SDHD* gene are found in some cases of nonsyndromic paraganglioma or pheochromocytoma, which are forms of the condition that occur in people with no history of these tumors in their families. Most of these mutations change single amino acids in the SDHD protein. As in GIST and hereditary paraganglioma-pheochromocytoma type 1 (described above), these mutations are expected to decrease SDH enzyme activity, which 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

- CBT1
- CII-4
- cybS
- DHSD_HUMAN
- PGL
- PGL1
- QPs3
- SDH4
- succinate dehydrogenase [ubiquinone] cytochrome b small subunit, mitochondrial
- succinate dehydrogenase complex subunit D, integral membrane protein
- succinate dehydrogenase complex, subunit D, integral membrane protein
- succinate dehydrogenase ubiquinone cytochrome B small subunit
- succinate-ubiquinone oxidoreductase cytochrome b small subunit
- succinate-ubiquinone reductase membrane anchor subunit

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SDHD (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6392[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SDHD%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 D; SDHD (https://omim.org/entry/602690)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6392)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SDHD[gene])

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Genomic Location

The *SDHD* gene is found on chromosome 11 (https://medlineplus.gov/genetics/chromosome/11/).

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