SDHB gene
succinate dehydrogenase complex iron sulfur subunit B

**Normal Function**

The *SDHB* 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.

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 SDHB protein provides an attachment site for electrons as they are transferred 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 *SDHB* gene is a tumor suppressor, which means it prevents cells from growing and dividing in an uncontrolled way.

**Health Conditions Related to Genetic Changes**

**Hereditary paraganglioma-pheochromocytoma**

More than 150 mutations in the *SDHB* gene have been identified in people with hereditary paraganglioma-pheochromocytoma type 4. People with this condition have paragangliomas, pheochromocytomas, or both. Paragangliomas and pheochromocytomas (a type of paraganglioma) are noncancerous tumors associated with the nervous system. An inherited *SDHB* gene mutation predisposes an individual to the condition, and a somatic mutation that deletes the normal copy of the gene is needed to cause hereditary paraganglioma-pheochromocytoma type 4.

Most of the inherited *SDHB* gene mutations change single protein building blocks (amino acids) in the SDHB 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 in people with hereditary paraganglioma-pheochromocytoma.

**Nonsyndromic paraganglioma**

Mutations in the *SDHB* gene are found in some cases of nonsyndromic paraganglioma or pheochromocytoma, which are non-hereditary forms of the condition. Most of these mutations change single amino acids in the SDHB protein. As in hereditary paraganglioma-pheochromocytoma type 4, 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**

At least 10 variants in the *SDHB* gene have been identified in people with Cowden syndrome or a similar disorder called Cowden-like syndrome. These conditions are characterized by multiple tumor-like growths called hamartomas and an increased risk of developing certain cancers, particularly breast cancer, thyroid cancer, and cancer of the uterine lining (endometrial cancer).

The *SDHB* gene variants associated with Cowden syndrome and Cowden-like syndrome change single amino acids in the SDHB protein, which likely alters the function of the SDH enzyme. Studies suggest that the defective enzyme could allow cells to grow and divide unchecked, leading to the formation of hamartomas and cancerous tumors. However, researchers are uncertain whether the identified *SDHB* gene variants are directly associated with Cowden syndrome and Cowden-like syndrome. Some of the variants described above have rarely been found in people without the features of these conditions.

**Gastrointestinal stromal tumor**

**Other cancers**

The *SDHB* gene is involved in several cancers. Mutations in the *SDHB* gene have been found in a small number of people with gastrointestinal stromal tumors (GISTs), which are a type of tumor that occurs in the gastrointestinal tract, or renal cell carcinoma, which is a type of kidney cancer. *SDHB* gene mutations have been identified in people a condition called Carney-Stratakis syndrome in which affected individuals have both paraganglioma and GIST or in people with both renal cell cancer and paraganglioma. An inherited *SDHB* gene mutation predisposes an individual to cancer formation. An additional mutation that deletes the normal copy of the gene is needed to cause these forms of GIST, renal cell cancer, and
paraganglioma. This second mutation, called a somatic mutation, is acquired during a person's lifetime and is present only in tumor cells.

Mutations of the *SDHB* gene lead to a reduction in the amount of SDHB protein in the cell and loss of SDH enzyme activity. Furthermore, even without a *SDHB* gene mutation, a subset of gastrointestinal stromal tumors have reduced SDHB protein and loss of SDH enzyme activity. Lack of SDH enzyme activity results in abnormal hypoxia signaling and formation of tumors.

**Chromosomal Location**

Cytogenetic Location: 1p36.13, which is the short (p) arm of chromosome 1 at position 36.13

Molecular Location: base pairs 17,018,722 to 17,054,032 on chromosome 1 (Homo sapiens Updated Annotation Release 109.20200522, GRCh38.p13) (NCBI)

Credit: Genome Decoration Page/NCBI

**Other Names for This Gene**

- DHSB_HUMAN
- FLJ92337
- IP
- iron-sulfur subunit of complex II
- PGL4
- SDH
- SDH1
- SDH2
- SDHIP
- succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial
- succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial precursor
- succinate dehydrogenase complex subunit B, iron sulfur (Ip)
- succinate dehydrogenase complex, subunit B, iron sulfur (Ip)
Additional Information & Resources

Educational Resources

• Biochemistry (5th Edition, 2002): Oxaloacetate Is Regenerated by the Oxidation of Succinate
  https://www.ncbi.nlm.nih.gov/books/NBK22427/#A2401

• National Human Genome Research Institute: The Genomic Services Research Program (GSRP): Study of People with Unexpected Genetic Results
  https://www.genome.gov/Current-NHGRI-Clinical-Studies/Genomic-Services-Research-Program

Clinical Information from GeneReviews

• Hereditary Paraganglioma-Pheochromocytoma Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1548

Scientific Articles on PubMed

• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28SDHB%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

• GASTROINTESTINAL STROMAL TUMOR
  http://omim.org/entry/606764

• PARAGANGLIOMA AND GASTRIC STROMAL SARCOMA
  http://omim.org/entry/606864

• SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT B, IRON SULFUR PROTEIN
  http://omim.org/entry/185470

Research Resources

• Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/SDHBID388.html

• ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SDHB%5Bgene%5D

• HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#/hgnc_id/HGNC:10681

• Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:6390
• NCBI Gene
https://www.ncbi.nlm.nih.gov/gene/6390

• UniProt
https://www.uniprot.org/uniprot/P21912

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