SDHA gene

succinate dehydrogenase complex flavoprotein subunit A

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.

Health Conditions Related to Genetic Changes

Gastrointestinal stromal tumor

At least 15 mutations in the *SDHA* gene have been found in people with a gastrointestinal stromal tumor (GIST), which is a type of tumor that occurs in the gastrointestinal tract. Mutations in 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. *SDHA* gene mutations are particularly associated with the development of all three tumor types, which is a condition known as Carney triad, although people with these mutations may develop one type of tumor or a different combination of tumors. The combination of GIST and pulmonary chondroma is known as incomplete Carney triad; and the combination of GIST and paraganglioma is known as known as Carney-Stratakis syndrome.

An inherited (germline) mutation in the *SDHA* 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. *SDHA* gene mutations associated with GIST prevent the production of functional SDHA 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.

Nonsyndromic paraganglioma

At least 30 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 a paraganglioma. However, an additional, somatic mutation that deletes the normal copy of the gene is needed to cause tumor formation.

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. Because of the abnormal subunit, the SDH enzyme cannot form or is broken down. With little SDH enzyme activity, succinate accumulates 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

MedlinePlus Genetics provides information about Hereditary paraganglioma-pheochromocytoma

Leigh syndrome

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.

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)

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SDHA (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6389[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SDHA%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+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SUCCINATE DEHYDROGENASE COMPLEX, FLAVOPROTEIN SUBUNIT A; SDHA (https://omim.org/entry/600857)
- LEIGH SYNDROME; LS (https://omim.org/entry/256000)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6389)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SDHA[gene])

References

- Belinsky MG, Rink L, von Mehren M. Succinate dehydrogenase deficiency inpediatric and adult gastrointestinal stromal tumors. Front Oncol. 2013 May17;3:117. doi: 10.3389/fonc.2013.00117. eCollection 2013. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23730622)
- Burnichon N, Briere JJ, Libe R, Vescovo L, Riviere J, Tissier F, Jouanno E, Jeunemaitre X, Benit P, Tzagoloff A, Rustin P, Bertherat J, Favier J,Gimenez-Roqueplo AP. SDHA is a tumor suppressor gene causing paraganglioma. HumMol Genet. 2010 Aug 1;19(15):3011-20. doi: 10.1093/hmg/ddq206. Epub 2010 May 18. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20484225) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2901140/)
- Gill AJ. Succinate dehydrogenase (SDH)-deficient neoplasia. Histopathology.2018 Jan;72(1):106-116. doi: 10.1111/his.13277. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/29239034)
- Horvath R, Abicht A, Holinski-Feder E, Laner A, Gempel K, Prokisch H,Lochmuller H, Klopstock T, Jaksch M. Leigh syndrome caused by mutations in theflavoprotein (Fp) subunit of succinate dehydrogenase (SDHA). J Neurol NeurosurgPsychiatry. 2006 Jan;77(1):74-6. doi: 10.1136/jnnp.2005.067041. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16361598) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2117401/)
- Janeway KA, Kim SY, Lodish M, Nose V, Rustin P, Gaal J, Dahia PL, Liegl B,Ball ER, Raygada M, Lai AH, Kelly L, Hornick JL; NIH Pediatric and Wild-Type GISTClinic; O'Sullivan M, de Krijger RR, Dinjens WN, Demetri GD, Antonescu CR,Fletcher JA, Helman L, Stratakis CA. Defects in succinate dehydrogenase ingastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl AcadSci U S A. 2011 Jan 4;108(1):314-8. doi: 10.1073/pnas.1009199108. Epub 2010 Dec20. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21173220) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3017134/)
- Korpershoek E, Favier J, Gaal J, Burnichon N, van Gessel B, Oudijk L, BadoualC,

Gadessaud N, Venisse A, Bayley JP, van Dooren MF, de Herder WW, Tissier F,Plouin PF, van Nederveen FH, Dinjens WN, Gimenez-Roqueplo AP, de Krijger RR. SDHAimmunohistochemistry detects germline SDHA gene mutations in apparently sporadicparagangliomas and pheochromocytomas. J Clin Endocrinol Metab. 2011Sep;96(9):E1472-6. doi: 10.1210/jc.2011-1043. Epub 2011 Jul 13. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21752896)

- Opocher G, Schiavi F. Genetics of pheochromocytomas and paragangliomas. BestPract Res Clin Endocrinol Metab. 2010 Dec;24(6):943-56. doi:10.1016/j.beem.2010.05.001. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21115163)
- Parfait B, Chretien D, Rotig A, Marsac C, Munnich A, Rustin P. Compoundheterozygous mutations in the flavoprotein gene of the respiratory chain complexII in a patient with Leigh syndrome. Hum Genet. 2000 Feb;106(2):236-43. doi:10.1007/s004390051033. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/10746566)
- Qin Y, Buddavarapu K, Dahia PL. Pheochromocytomas: from genetic diversity tonew paradigms. Horm Metab Res. 2009 Sep;41(9):664-71. doi:10.1055/s-0029-1215590. Epub 2009 Apr 23. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19391076)

Genomic Location

The *SDHA* gene is found on chromosome 5 (https://medlineplus.gov/genetics/chromosome/5/).

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