SDHD Gene

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succinate dehydrogenase complex subunit D

genes

1. 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.

2. Health Conditions Related to Genetic Changes

2.1. 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 mutation that deletes the normal copy of the gene is needed to cause hereditary paraganglioma-pheochromocytoma type 1. This second mutation, called a somatic mutation, is acquired during a person's lifetime and is present only in tumor cells.

Most of the inherited *SDHD* gene mutations 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. 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.

2.2. Nonsyndromic paraganglioma

Mutations in the *SDHD* 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 SDHD protein. As in hereditary paraganglioma-pheochromocytoma type 1, 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.

2.3. Cowden syndrome

At least five variants in the *SDHD* 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. When Cowden syndrome and Cowden-like syndrome are caused by *SDHD* gene mutations, the conditions are associated with a particularly high risk of developing breast and thyroid cancers.

The *SDHD* gene variants associated with Cowden syndrome and Cowden-like syndrome change single amino acids in the SDHD 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 *SDHD* 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.

2.4. Other cancers

Mutations in the *SDHD* gene have been found in a small number of people with Carney-Stratakis syndrome. People with this condition have a type of cancer of the gastrointestinal tract called gastrointestinal stromal tumor (GIST) and a noncancerous tumor associated with the nervous system called paraganglioma or

pheochromocytoma (a type of paraganglioma). An inherited *SDHD* gene mutation predisposes an individual to cancer formation. An additional mutation that deletes the normal copy of the gene is needed to cause Carney-Stratakis syndrome. This second mutation, called a somatic mutation, is acquired during a person's lifetime and is present only in tumor cells.

Mutations of the *SDHD* gene lead to loss of SDH enzyme activity, which results in abnormal hypoxia signaling and formation of tumors.

3. 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

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