

SDH-deficient GIST Fact Sheet



The LRG strongly suggests *mutational testing* for all patients with a GIST diagnosis as soon as possible. Data has shown that patients can have multiple tumors with multiple mutations. Knowing your mutation(s) gives doctors more information with which to knowledgeably prescribe an effective treatment plan.

Do I need to see a SDH-deficient GIST specialist?

Yes! since SDH-deficient GISTs are of the rarest types of GIST and there is such a small population of cases in the world, we strongly suggest an SDH-deficient GIST specialist. Also, conventional GIST drug treatments may be ineffective with your mutation and therefore a specialist with more information and experience with SDH mutations can more knowledgeably guide you toward other drug combinations or clinical trials.

WHAT IS SDH? SDH (succinate dehydrogenase) is a complex that produces tumor suppressors - a protein that prevents cells from growing and dividing uncontrollably. SDH is localized in the inner mitochondrial membrane and consists of four subunit proteins (*SDHA*, *SDHB*, *SDHC* and *SDHD*, collectively referred to as *SDHx*). The four components, A, B, C, and D form the SDH complex and accelerate the conversion of succinate to fumarate, which plays a critical role in the Krebs cycle, an energy cycle which drives every cell. If one component is faulty, the complex cannot work.

What is SDH-deficiency?

SDH-deficiency is a mutation (loss of function) in one of the genes encoding SDH subunits. Any mutation in the *SDHx* results in SDH-deficiency. SDH-deficient GISTs are a unique class of GIST defined by negative immunohistochemical staining for succinate dehydrogenase B (*SDHB*).

How is 'regular' GIST (KIT/PDGFRA mutant GIST) different from SDH-deficient GIST?

In the more common forms of GIST, a mutation is expressed in the *KIT/PDGFRA* gene (which provides instructions for making a member of a protein family called receptor tyrosine kinases) and stains positive for CD117. In SDH-deficient GIST there are key differences related to the mutations that cause the cancer, specifically affecting tumor suppressor genes, so there is an absence of *KIT* and *PDGFRA* mutations.

How common are SDHx mutations?

SDH-deficient GIST patients make up about 5-7% of approximately 4,000-6,000 GIST diagnoses per year in the United States.¹

Where does SDHx typically occur in the body?

SDH-deficient GISTs are found nearly exclusively in the stomach. Metastases can occur in the liver and lymph nodes².

What are the symptoms of SDH-deficient GIST?

Symptoms of GIST can include abdominal pain, nausea and vomiting, bowel obstruction, feeling very full after eating small amounts, loss of appetite, difficulty swallowing, swelling in abdomen, weight loss. To diagnose SDH-deficiency GIST, an immunohistochemical panel on the tumor tissue must be performed by a pathologist. The use of IHC to analyze loss of SDHB is reliable for detecting these tumors. If testing has not yet been done, an SDH-deficient GIST may be suspected if conventional drug treatments do not work. Mutational testing should be performed on all new GIST cases.

What is an SDH epimutation?

Epimutations occur in the body when chemical groups called methyl groups are added to or removed from DNA or when changes are made to proteins called histones that bind to the DNA in chromosomes. These changes may occur with age and exposure to environmental factors such as diet, exercise, drugs, and chemicals. The *SDHC* epimutation (hypermethylation of the promoter, which controls gene expression) has been found mostly in tumors of children and does not appear to be heritable unlike other *SDHx* gene mutations³. It also appears to affect mostly females and can present with metastases in the liver or lymph nodes.

Are there related issues with SDH deficiency?

Patients who test positive for SDHx mutations may be at risk for Carney triad or Carney-Stratakis syndrome.

Carney-Stratakis Syndrome (CSS)

CSS is an inherited (autosomal dominant) syndrome that affects predominately young, female patients. Patients with this germline mutation (occurring in any of the SDH subunits) are predisposed to GIST and paraganglioma (PGL).

Carney Triad (CT)

Hypermethylation of the SDHC gene promoter region is the molecular signature of CT, which is a syndromic condition that can include GIST, PGL, and pulmonary chondroma. This SDHC epimutation has been found mostly in younger patients and generally does not appear to be heritable, unlike other SDHx gene mutations.

Do I need genetic testing if I've already had mutational testing?

Yes, genetic testing for SDH-deficient GIST patients is advised. More than 80% of SDHx-mutated GISTs have been found to have a germline mutation². If there is a germline mutation, first-degree relatives should be screened as well.

Can SDHx be cured? What treatments work? Will it return?

Due to the rarity of SDH-deficient GISTs, treatment options are currently very limited. SDH-deficient GIST is typically indolent (slow growing) despite a high rate of local recurrence, and has a tendency to metastasize. Surgery is usually the first course of treatment. There has been some success with sunitinib and regorafenib and there are ongoing clinical trials. Your SDH-deficient GIST specialist can help you find treatment options and clinical trials that are appropriate for your type of GIST. A schedule of regular postoperative scans and testing is strongly recommended.

Resources:

SDH-deficient GIST Specialists:

<https://liferaftgroup.org/sdh-deficient-gist-specialists/>

GIST Educational Resources:

<https://liferaftgroup.org/powerd/>

Patient Resource Toolkit:

<https://liferaftgroup.org/patient-resource-toolkit/>

Join the LRG:

<https://liferaftgroup.org/life-raft-group-membership-application-form/>

References:

1. SDH-Deficient Gastrointestinal Stromal Tumor (GIST), MyPART - My Pediatric and Adult Rare Tumor Network, National Cancer Institute of the NIH, February 27, 2019. <https://www.cancer.gov/nci/pediatric-adult-rare-tumor/rare-tumors/rare-digestive-system-tumors/sdh-deficient-gastrointestinal-stromal-tumor-gist>.
2. L. Mei, et al., Gastrointestinal Stromal Tumors: The GIST of Precision Medicine, *Trends in Cancer*, (2017) <https://doi.org/10.1016/j.trecan.2017.11.006>
3. A key molecular defect in a childhood gastrointestinal tumor may have important diagnostic implications, NCI New Note, National Cancer Institute of the NIH, December 24, 2014. <https://www.cancer.gov/news-events/press-releases/2014/SDHCepimutantGIST>.



155 US Highway 46, Suite 202 Wayne, NJ 07470
973-837-9092
fax 973-837-9095
www.liferaftgroup.org
liferaft@liferaftgroup.org