SDH-deficient GIST Fact Sheet

The Life Raft GROUP

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 an 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 seeing 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 located 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 loss of function in any one of the genes encoding *SDH* subunits. Caused by either *SDHA, B, C, D* or *SDHC* epimutation, SDH-deficiency is identified by immunohistochemical staining (IHC) as a *SDHB* loss.

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

In the more common forms of GIST, a mutation is expressed in the *KIT/PDGRFA* 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 SDH-deficient GIST typically occur in the body?

SDH-deficient GISTs are found nearly exclusively in the stomach. Metastases can occur in the liver and lymph nodes.[2]

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-deficient GIST, an immunohistochemical panel (IHC) 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 promotor, which controls gene expression) has been found mostly in tumors of children and does not appear to be heritable unlike other *SDHx* gene mutations.[3] 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 or *SDHC* epimutations may be at risk for Carney-Stratakis syndrome or Carney triad respectively.

Carney-Stratakis syndrome (CSS)

CSS is an inherited (autosomal dominant) syndrome that affects predominantly 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 mutation.[2] If there is a germline mutation, first-degree relatives should be screened as well.

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

SDH-deficient GIST tumors have been described as indolent, but it may be more accurate to characterize the tumors as having frequent periods of slow growth or stability.[4] They can have high rate of local recurrence and a tendency to metastasize. Due to the rarity of SDH-deficient GISTs, treatment options are currently very limited. Surgery is usually the first course of treatment. There has been some success treating tumors 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/powered/

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://pubmed.ncbi.nlm.nih.gov/29413424/
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.
4. Treatment Responses in SDH-deficient GIST, Patient-reported Treatment Responses in Known/likely SDH-deficient GISTS: And Analysis of The Life Raft Group Observational Registry, LRG Science, July 2019. https://liferaftgroup.org/2019/08/treatment-responses-in-sdh-deficient-gist-2/