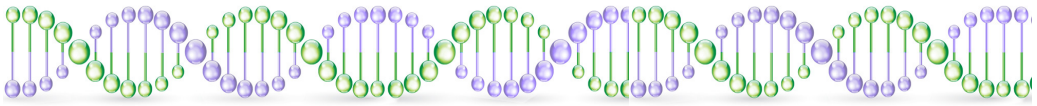
Information Sheet



Gastrointestinal stromal tumours (GIST) and the KIT, PDGFRA and SDH genes

Gastrointestinal stromal tumours (GIST) are rare tumours affecting less than 1: 20,0000 people each year. Familial GIST is even more rare, affecting less than 100 families world wide.

What are Gastrointestinal Stromal Tumours (GIST)?
Gastrointestinal stromal tumours (GIST) are abnormal growths (tumours) that arise in the supporting tissue (stroma). GISTs occur mainly in the stomach and small intestine but can occur anywhere in the gastrointestinal tract.

What causes a Gastrointestinal Stromal Tumours (GIST)?
The genes KIT and PDGFRA are commonly damaged in sporadic (non-hereditary) GIST. This is called a "somatic" mutation. In these cases, the mutation occurred in the GIST as it grew.

The KIT and PDGFRA genes are part of the tyrosine kinase family and they regulate cell growth. While somatic mutations of this kind are almost never passed on, they can be targeted by cancer therapies. All GIST should be tested for somatic mutations in the KIT and PDGFRA genes.

Are Gastrointestinal Stromal Tumours (GIST) inherited?
Familial GIST can be caused by a germline (inheritable) mutation in genes such as KIT and PDGFRA as well as the SDH family of genes.

GISTs that don't have a somatic mutation in the KIT and PDGFRA genes should be screened for loss of the SDHB and SDHA proteins via immunohistochemical testing (IHC) of the GIST itself. If the proteins are missing, it may be because of a germline (inherited) mutation in one of the SDH genes. SDH IHC testing is Medicare funded.

What does loss of staining for SDHB on IHC testing mean?
Loss of staining for the SDHB protein is a clue that an SDH gene has been damaged in that person. While this accounts for only 3 to 5% of all GIST, there is a very high chance that the individual may be at risk of other rare tumours such as paraganglioma and pheochromocytoma.

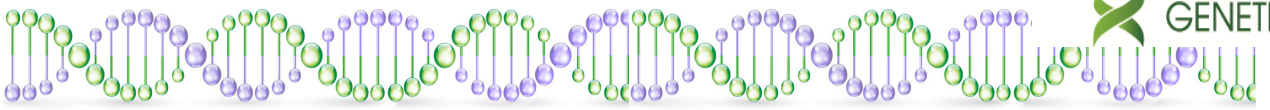
If the mutation was inherited it is called a germline mutation. This used to be known as the Carney-Stratakis Dyad - a clinical description of patients and families having both GIST and paragangliomas and/or pheochromocytomas.

Germline SDH mutations are associated with Hereditary Paraganglioma and Pheochromocytoma syndrome

Sometimes the loss of staining for SDHB on IHC testing is due to hypermethylation. This is known as Carney's Triad

..../2

Gastrointestinal stromal tumours (GIST) and the KIT, PDGFRA and SDH genes



What is Carney's Triad?
Carney's Triad is not an inherited syndrome. It is believed to be caused by a change that occurs in the first few divisions after the egg and sperm meet resulting in one copy of the SDHC gene being "turned off" (hypermethylated or epimutated). Because this change has occurred so early on, it will affect every cell.

SDHC hypermethylation has the same effect on the SDHC gene as a pathogenic inherited mutation – that copy of the gene doesn't work.

GISTs in Carney's Triad are almost always found in the stomach and tend to be multi-focal (more than one GIST may be present) and multi-nodular or lobulated (a particular growth pattern that can be seen by a pathologist).

Carney's Triad includes 3 clinical issues (although all 3 may not be present at diagnosis of the GIST):

Gastrointestinal Stromal Tumours (GIST)
Paragangliomas and/or pheochromocytomas
Pulmonary chondromas, benign growths in the lung

Because paragangliomas and/or pheochromocytomas can cause problems, screening is usually recommended along the same guidelines as for an inherited SDHC mutation

Is genetic testing available for people with GIST?
Yes. If there is loss of staining on SDHB IHC testing, then genetic testing is available.
There is a 50% chance of a person who carries a germline KIT, PDGFRA or SDH mutation, whether male or female, passing the mutation to their son or daughter. If a mutation is identified, then predictive testing is available for blood relatives.

Does this sound like you or your family? Have you had a GIST or has a germline KIT, PDGFRA or SDH mutation been detected in a blood relative? Genetic testing is available.

Make an appointment with Dr Hilda High at Sydney Cancer Genetics. It is a confidential opportunity to discuss your personal and family history of cancer and genetic testing can be organised, if needed.

More information is available on our website, including links to the following:

- Support groups for individuals and families affected by GIST are based overseas but have members worldwide. They include The Life Raft group, GIST Support International and GIST Support UK.
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines
- The US National Library of Medicine website has more information about this syndrome.

Clinics in Sydney. Telehealth throughout Australia including to rural and regional areas
All Correspondence: PO Box 845, Broadway, NSW, 2007
All appointments: (+61 2) 9304 0438 Fax: (+61 2) 9304 0468 E:info@SydneyCancerGenetics.com.au