Project FLAG
Families Learning About GIST

# Information on Hereditary GIST

Hereditary GIST, or gastrointestinal stromal tumor, is very rare – even among people who have GISTs. GISTs are uncommon tumors, and usually do not occur because of inherited factors. Only a small subset of people who develop GIST will do so because of an inherited tendency or "predisposition". Doctors and researchers are beginning to systematically study individuals with GISTs to learn how often GISTs occur because of inherited factors. This research will also identify features of patients or families that would make it easier to recognize hereditary GIST.

### *Genes in Hereditary GIST*

At least two genes are known to play a role in hereditary GIST. They are called *c-kit* and *PDGFRA* (platelet derived growth factor receptor alpha). Alterations (or "mutations") in the *c-kit* gene appear to be more common. If a person has inherited an alteration in either of these genes, then there is a higher chance that a GIST can develop. The risk of developing GIST is inherited, not the GIST itself. GISTs have also been found in individuals with other inherited syndromes in which GIST is not the main tumor. These conditions may be associated with alterations in other GIST-susceptibility genes (see below).

Each family with an inherited form of GIST may have its own unique genetic alteration in one of the GIST-susceptibility genes. Although the precise alteration may be different from one family to another, the alteration will remain constant *within* a family. That is, each member of a family found to carry an alteration in a gene linked to GIST will carry the same specific alteration in the same gene.

A person carrying an alteration in one of his or her *c-kit* or *PDGFRA* genes has a 50% (or 1 in 2) chance of passing on this altered gene to each of his or her children, with an equal chance of passing on the unaltered copy of the gene. An alteration in the *c-kit* and *PDGFRA* genes can be inherited from the mother or father, and may be passed on to daughters and sons equally. This is called an *autosomal dominant* pattern of inheritance.

Relatives who carry an alteration in the *c-kit* or *PDGFRA* genes are at increased risk to develop GIST and can pass that risk on to their children. Relatives who do not carry the familial genetic alteration are not at increased risk to develop GIST and cannot pass it on to their children.

Not everyone with an inherited *c-kit* or *PDGFRA* gene alteration will develop GIST. A study of one large family with an inherited *c-kit* alteration estimated that family members who carried this alteration have up to a 90% risk of developing a GIST by age 70. In other inherited cancer syndromes, there is often a range of risk. Therefore, more data are needed to determine whether the 90% estimate is accurate for all alterations within the *c-kit* and *PDGFRA* genes.

It is also not clear why the symptoms, location, age at diagnosis and clinical course of GISTs may vary even among individuals who carry the same genetic alteration. It is likely that other genetic, lifestyle and/or environmental factors also contribute to the development of a GIST, even in the presence of an inherited susceptibility.

### *GIST in Other Hereditary Syndromes*

Several families have GIST as part of an inherited condition known as "neurofibromatosis type 1" (abbreviated NF1). NF1 is characterized by the development of multiple café-au-lait spots (characteristic pigmented areas) in the skin, and neurofibromas (benign growths), as well as a distinctive pattern of freckling along the armpit and groin. Only a small subset of individuals with NF1 develop GISTs; other tumors may occur in NF1 as well. Heritable mutations in the *c-kit* and *PDGFRA* genes have not been identified in patients with NF1 and GIST to date.

In a rare condition called the *Carney-Stratakis syndrome*, also called the *Carney-Stratakis dyad*,

individuals may develop GIST and a tumor called a paraganglioma. Along with another tumor called a pulmonary chondroma, this grouping of cancers has been referred to as the *Carney triad*. The triad occurs predominantly in young women, and is not thought to run in families. More recent data has suggested that the Carney dyad is actually distinct from the Carney triad. The Carney dyad is thought to be hereditary and occurs equally in men and women. Alterations in *c-kit* and *PDGFRA* have not been detected in families with the Carney dyad or triad. However, recent studies have found that other genes, called *SDHB*, *SDHC*, and *SDHD*, are altered in families with the Carney dyad.

### *Clinical Features of Hereditary GIST*

In addition to GISTs, other milder features have been found in families carrying alterations in the *c-kit* gene. These have included skin findings, such as pigmented or colored spots, areas of loss of coloration ("vitiligo"), multiple moles or "nevi", *melanoma* (a skin cancer of the pigment cells), discoloration around the fingernails, and a rare disorder of mast cells called "mastocytosis". In addition, swallowing disorders that are not related to the GISTs themselves including achalasia (a specific disorder in which the esophagus doesn't help to propel food to the stomach effectively) have also been found in some families with GIST.

**Features that may suggest an inherited form of GIST include (1) the diagnosis of GIST at an unusually early age (before age 50), (2) the development of more than one primary GIST tumor in one person, (3) the development of GIST and another primary cancer in one person, (4) two or more close relatives with GIST, or (5) one relative with GIST and one with another rare cancer or with unusual skin findings or multiple moles.**

### *Genetic Testing for Hereditary GIST*

A physician, genetic counselor, or genetics professional can evaluate an individual's medical and family history for features that signal a hereditary GIST. It may then be recommended that a family member who has had a GIST undergo genetic testing for alterations in the *c-kit* or *PDGFRA* genes. If an alteration is identified, relatives can be tested to see whether they also carry the alteration. Family members who carry an alteration in one of these genes are at increased risk to develop GIST, whereas those who did not inherit the alteration are not at increased risk.

Genetic testing for familial GIST is imperfect at the present time. A family could have an alteration in *c-kit* or *PDGFRA* that would be missed with current testing technologies. Other genes linked to hereditary GIST have not yet been identified. Therefore, in some families that seem likely to have hereditary GIST, genetic testing may not find a genetic mutation, but a hereditary form of GIST could still be present. It is important to understand the current limitations of testing and to work with your physician, genetic counselor, or genetics professional to determine the most appropriate medical care for you and your family. Because there are not yet standard guidelines for the management of families with GIST, your care will be custom-tailored for your particular family and medical history.

### *Screening for Early GIST*

Individuals who carry an alteration in the *c-kit* or *PDGFRA* gene and who have already been diagnosed with a GIST should continue to have treatment and monitoring as recommended by their physician.

Currently, there is no consensus on the most appropriate early detection strategy for early GIST in individuals who carry an inherited alteration in *c-kit* or *PDGFRA*. For this reason, some insurers will not pay for genetic testing for healthy relatives of a GIST patient, although testing may be offered as part of a research study. Current research seeks to obtain additional information about how best to screen unaffected individuals with inherited *c-kit* or *PDGFRA* alterations.