Q & A: Genetic Factors in Gastrointestinal Stromal Tumor (GIST)

GIST Support International asked Genetics Counselors Kelly Branda and Irene Rainville questions about genetic factors predisposing people to develop GIST. Kelly is a Certified Genetic Counselor at the Dana Farber Cancer Institute in Boston, and has been working with GIST patients and families through the sarcoma program at DFCI. Irene recently joined the group as a Genetic Counselor and is interested in research examining genetic factors that contribute to cancer predispositions. They will soon be working with Dr. Judy Garber, a medical oncologist and cancer geneticist, and Dr. Suzanne George, a medical oncologist focusing on GIST, on Project FLAG.

1. **Are hereditary forms of GIST rare? Are they found in any special populations around the world?**

Yes, hereditary GIST is very rare. Most GISTs are considered "sporadic" (occurring without a strong inherited basis). Only a small subset of people who develop GIST will do so because of a strong inherited tendency or "predisposition". More than 15 families with hereditary GIST have been reported in the medical literature to date. These families have been from different countries and have a range of ethnic origins, so it appears that hereditary GIST occurs worldwide.

2. **What is a germ-line mutation and how does it cause hereditary GIST?**

A mutation is a change in the pattern of a gene's DNA that prevents the gene from working properly. If you think of a gene as similar to a sentence, DNA is like the letters that make up the words in that sentence. Just as you can have a misspelling in a word in a sentence, you can have a misspelling (or "mutation") in the DNA of one of your genes. Unlike a somatic mutation (which is acquired over your lifetime and is present only in tumor cells), a *germ-line mutation* is usually passed to you by your mother or father, and can be passed on to your children. Germ-line mutations can, therefore, be carried by multiple family members.

Each family (or "kindred") with hereditary GIST may have its own unique germ-line mutation in a cancer susceptibility gene. Although the location of the germ-line mutation may be different from one family to another, the mutation will remain constant *within* a family: that is, the location of the mutation within the gene is the same for each member of a family.

There have been two genes identified to date that are involved in hereditary GIST. They are called *c-kit* and *PDGFRA* (platelet derived growth factor receptor alpha). So far, mutations in the *c-kit* gene have been found more often. If a person has a germ-line mutation in either of these genes, the gene can no longer function properly, which makes it easier for GISTs to develop. There may also be other cancer susceptibility genes not yet discovered that are associated with GISTs in other families.

GIST can also occur as part of other hereditary syndromes. Germ-line mutations have recently been found in families with inherited GIST and paraganglioma, a rare condition known by several names including Carney-Stratakis syndrome, Carney-Stratakis dyad, or simply, "the dyad". These germ-line mutations were found in three related genes, called *SDHB*, *SDHC*, and *SDHD*. Unlike hereditary GIST, which typically develops in middle age, the Carney-Stratakis syndrome is diagnosed in the young adult years.

3. Does every member of a family with hereditary GIST have the mutation?

No, not every member of a family with hereditary GIST will inherit the familial mutation. We all typically have two copies of every gene: we inherit one copy of a gene from our mother and the other copy from our father. Similarly, if we have children, we pass on one of our two copies of a gene to each child and our partner contributes one of his/her two copies of a gene to make a complete set in a child. A person with a germ-line mutation in one of his or her *c-kit* or *PDGFRA* genes has a 50% (or 1 in 2) chance of passing on the same germ-line mutation to each of his or her children, with an equal 50% chance of passing on his or her unaltered copy of the gene. Mutations in the *c-kit* and *PDGFRA* genes can be inherited from the mother or father, and are passed on to daughters and to sons equally. Relatives who inherit the familial germ-line mutation are at increased risk to develop GIST. In addition, each of their children (or future children) would have a 1 in 2 chance of inheriting the mutation from them and therefore would also be at increased risk to develop GIST. This is called an *autosomal dominant* pattern of inheritance.

Relatives who do not inherit the familial germ-line mutation in a GIST susceptibility gene are not at increased risk to develop GIST as compared to the general population, despite their family history. In addition, because they do not carry the familial mutation, they cannot pass it on to any of their children.

4. Does every person with a germ-line mutation in a GIST- susceptibility gene develop GIST?

No, not everyone with a germ-line mutation in a GIST susceptibility gene will develop GIST. A study of one large family with a germ-line *c-kit* mutation estimated that individuals in the family who carried this alteration might have up to a 90% risk of developing a GIST by age 70. However, more data are needed to determine whether this estimate is true of all possible mutations within GIST susceptibility genes, and whether anything can increase or reduce these risks.

It is also not clear why the symptoms, location, age at diagnosis and clinical course of some GISTs are different from other GISTs, even within the same family in which individuals carry the same germ-line mutation. It is likely that other unknown genetic, environmental and/or lifestyle factors also contribute to the development of a GIST, even in the presence of an inherited susceptibility.

While the overall risk for an individual who carries a germ-line mutation in a GIST-susceptibility gene to develop GIST is not certain, if that individual does develop GIST he or she may be more likely to develop multiple GISTs. If one GIST is rare, then more than one GIST in an individual is extremely rare. Current research is trying to determine how often multiple GISTs are found in hereditary forms of GIST.

5. Can some people have milder effects associated with germ-line mutations?

Beside GISTs, other features have also been reported in some families with germ-line mutations in the *c-kit* gene. These have primarily included:

(a) Skin findings, including pigmented or colored spots, areas of loss of coloration ("vitiligo"), multiple moles ("nevi") and even *melanoma* (a skin cancer of the pigment cells), discoloration around the fingernails, and a group of conditions known as "mastocytosis" or "mast cell disease"

(b) Swallowing disorders that are not related to the GISTs themselves (also called "dysphagia" (difficulty swallowing) or "achalasia" (a specific disorder in which the esophagus doesn't help to propel food to the stomach effectively)

6. Are there other conditions associated with an increased probability of developing GIST?

There have also been multiple families reported with GIST and a heritable condition known as "neurofibromatosis type 1" (abbreviated NF1). NF1 is characterized by the development of multiple café-au-lait spots (specific pigmented spots) and neurofibromas (benign growths) on the skin, 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. Germ-line mutations in the *c-kit* and *PDGFRA* genes have <u>not</u> been identified in patients with both NF1 and GIST to date.

In the rare condition called the Carney-Stratakis *dyad*, individuals are at risk to develop GIST and an even less common tumor called a paraganglioma (see question 2). This grouping of cancers is distinct from another condition, referred to as the Carney *triad*, which also includes a rare tumor not seen in the Carney-Stratakis dyad called a pulmonary chondroma. The Carney triad primarily occurs in young women, and is not thought to run in families. The dyad <u>is</u> known to be hereditary, occurring equally in men and women. At this time, germ-line mutations in *c-kit* or *PDGFRA* have not been detected in families with either the Carney dyad or triad. The distinction between these two conditions has been further clarified with the recent finding of germ-line mutations in a set of related genes known as *SDHB*, *SDHC*, and *SDHD* that are associated with the dyad, but not with the Carney triad.

7. **When would an individual become suspicious that his/her family may have a hereditary predisposition to GIST?**

Any of the following features may suggest that a genetic predisposition to GIST is present:

a. One person in the family who was diagnosed with GIST at an unusually early age (generally before age 50) OR
b. One person in the family who has developed more than one separate primary (new GIST, not a metastasis) GIST tumor OR
c. One person in the family who has had a GIST and another cancer as well OR
d. Two or more close relatives with GIST OR
e. One person in the family with GIST who also has a close relative with another rare type of tumor OR
f. One person in the family with GIST who also has a personal or family history of unusual skin findings, multiple moles, or NF1

Not all families with these features will have a hereditary predisposition to GIST. Similarly, other families who have hereditary GIST may not exhibit these features. However, these combinations of GIST and other findings are rare enough to suggest that additional genetic evaluation may be warranted.

8. **What are the clinical steps for identifying hereditary GIST?**

The first step in identifying hereditary GIST would be to speak with a physician, genetic counselor or other genetics professional to review your personal and family history. Based on the information that you provide, they may be able to help you evaluate the chance that your family has a hereditary form of GIST and determine whether additional genetic evaluation would be warranted.

If appropriate based on your personal and family history, it may then be recommended that your family undergo genetic evaluation. It is ideal to begin by testing an affected family member (someone who has had a GIST) to try and determine whether there is a germ-line mutation in a GIST susceptibility gene, such as *c-kit* or *PDGFRA*, in the family. Genetic tests are performed on a sample of DNA from blood or saliva. If an alteration were identified in one of these genes, other family members could then undergo genetic testing to determine whether they have also inherited the familial mutation. Only those relatives with the familial mutation would be at increased risk to develop GIST. Relatives who did not inherit the mutation would not be at increased risk to develop GIST. If a mutation in a known GIST susceptibility gene were not found, the family might be eligible for other research efforts working to identify other GIST genes.

There are many factors that should be considered before deciding whether to go forward with genetic testing. These can be discussed with a physician or other genetics professional. To locate a genetic counselor in your area, you can contact Project FLAG,

(see question #9 below), or you can also go to the website for the National Society of Genetic Counselors (www.nsgc.org) and click on the 'Find a Counselor' link. However, because so little is known about hereditary GIST, most genetic counselors may not know very much about it at first.

Finally, it is important to recognize that genetic testing for hereditary GIST is imperfect at the present time. It is possible that a family could have a germ-line mutation in *c-kit* or *PDGFRA* that would be missed with current testing technology. It is also possible that there are other genes that have not yet been identified that cause some cases of hereditary GIST. Therefore, even if someone in your family who has had GIST undergoes genetic testing and is not found to have a germ-line mutation in *c-kit* or *PDGFRA*, a hereditary predisposition to GIST could still be present. It is important to understand the current limitations of testing and to work with your physician or a genetics professional to determine the most appropriate medical care for you and your family.

9. If your family has hereditary GIST, what can you do about it?

Because GISTs are rare tumors, and "GIST families" are rare as well, there is not yet a uniform set of recommendations about how to follow families with hereditary GIST.

Individuals who are found to carry a germ-line mutation in a GIST susceptibility gene and who have already been diagnosed with a GIST should continue to undergo treatment and monitoring as recommended by their physician.

At the present time, there is no consensus available about the most appropriate screening for individuals with a germ-line mutation in a GIST susceptibility gene who have not developed a GIST. Individuals who are identified with a germ-line mutation in one of these genes should consult with their physician to review their personal and family history and determine the most appropriate screening for them. In addition, there is research underway to learn how best to screen unaffected individuals with germ-line *c-kit* or PDGFRA mutations, so we would encourage you to check this webpage periodically for updates on this issue.