Genetics of Gastrointestinal Stromal Tumors

A Heterogeneous Family of Tumors?

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KEYWORDS

• GIST • KIT • PDGFRA • Succinate dehydrogenase • BRAF

ABSTRACT

Approximately 85–90% of adult gastrointestinal stromal tumors (GISTs) harbor *KIT* and *PDGFRA* mutations. The remaining cases, including the majority of pediatric GISTs, lack these mutations, and have been designated as *KIT*/*PDGFRA* wild-type (WT) GISTs. Nearly 15% of WT GISTs harbor *BRAF* mutations, while others arise in patients with type I neurofibromatosis. Recent work has confirmed that 20–40% of *KIT*/*PDGFRA* WT GISTs show loss of function of succinate dehydrogenase complex. Less than 5% of GISTs lack known molecular alterations ("quadruple-negative" GISTs). Thus, it is important to consider genotyping these tumors to help better define their clinical behavior and therapy.

OVERVIEW

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Since the first report of gain-of-function *KIT* mutations by Hirota and colleagues,[1] our understanding regarding the genetic alterations in GISTs has significantly evolved to a point that GISTs are now best considered as tumors with heterogeneous disease-initiating molecular events. The goal of this review is to elaborate on the latest molecular underpinnings of GISTs and to discuss their implications on clinical management.

GENOTYPES OF GASTROINTESTINAL STROMAL TUMOR

It is now widely accepted that GISTs arise from interstitial cells of Cajal (ICC) or from an ICC precursor.[2,3] Because it was noted that KIT deficiency causes loss of ICC in mouse models, Hirota and colleagues[1] decided to examine GISTs, and found that they showed strong KIT expression, and had activating *KIT* mutations. This seminal study was followed by many subsequent studies that confirmed and expanded this finding.[4] Nearly 75% to 80% of GISTs harbor *KIT* mutations, whereas 10% demonstrate gain-of-function mutations in platelet-derived growth factor receptor alpha (*PDGFRA*). The remaining 10% to 15% of GISTs lack *KIT* and *PDGFRA* mutations, and have previously been designated as wild-type (WT) GISTs. Several studies have now shown that the subgroup of WT-GISTs consists of GISTs that harbor molecular abnormalities in genes encoding succinate dehydrogenase (SDH)-ubiquinone complex II,[5–10] as well as those that carry mutations in *BRAF*[11–14] and *NF-1*.[15] The frequency of these genotypes has been summarized in **Table 1**.

KIT MUTATIONS

KIT mutations found in GIST result in constitutive activation of the receptor tyrosine kinase pathway in the absence of KIT ligand. Exons 9, 11, 13, and

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Table 1
GIST genotypes

Genotype	Relative Frequency	Germline Examples
KIT mutation (relative frequency 70%–80%)		
Exon 8	Rare	Yes
Exon 9 insertion AY502–503	10%	None
Exon 11 (deletions, single nucleotide substitutions and insertions)	67%	Yes
Exon 13 K642E	1%	Yes
Exon 17 D820Y, N822K, and Y823D	1%	Yes
PDGFRA mutation (relative frequency 5%–15%)		
Exon 12	1%	Yes
Exon 14	<1%	None
Exon 18 D842V	5%	None
Exon 18 (such as deletion of amino acids IMHD 842–846)	1%	Yes
KIT and *PDGFRA* wild-type (relative frequency 12%–15%)		
BRAF V600E	3%	None
SDHA, SDHB, SDHC, and *SDHD* mutations	3%	Yes, including Carney-Stratakis
SDHC hypermethylation – Carney Triad	Rare	No
NF1-related	Rare	Yes
Quadruple wild-type	Rare	No

Abbreviations: GIST, gastrointestinal stromal tumor; NF1, neurofibromatosis type 1; *PDGFRA*, platelet-derived growth factor receptor a; SDH, succinate dehydrogenase.

17 are most often mutated in sporadic GISTs. The vast majority of *KIT* mutations (nearly 65%) involve the juxtamembrane domain (exon 11), followed by extracellular domain (exon 9, 9%), tyrosine kinase I: ATP binding pocket (exon 13; 1%) and tyrosine kinase II: kinase activation loop (exon 17; 1%; **Fig. 1**).[16,17] Very rarely, mutations in exons 8, 12, 14, and 18, have been found in primary GISTs.

Exon 11 mutations include missense mutations, in-frame deletions, insertions, or a combination of these alterations. Oncogenic exon 11 mutations are most commonly composed of in-frame deletions of one or more codons; some of these (codons 557–558) are typically associated with poor clinical outcome.[18] Missense point mutations are the next most common type of mutations. Stomach is the most common site of involvement, and these tumors often show a spindled morphology (**Fig. 2**A–C). In gastric GISTs, exon 11 mutations are associated with a better prognosis, and a more reliable response to imatinib therapy.[19] However, no such correlation has been documented with exon 11–mutated small intestinal GISTs.[20,21]

Virtually all exon 9 mutations are characterized by a 6-nucleotide duplication encoding Ala and Tyr at amino acid residues 502 and 503.[22] These mutations are usually associated with small or large intestinal GISTs (especially rectum).[21,23] A meta-analysis of randomized phase 3 clinical trials has shown that patients with *KIT* exon-9 mutant GISTs have a median progression-free survival that is 1 year longer in those treated with 800 mg imatinib versus those treated with a 400-mg dose.[24] More recently, it was shown that in itself, the presence of this mutation does not have any prognostic relevance.[23]

Exon 13 and 17 mutations are very rare (<1%–2%). Exon 13 mutations are almost always a substitution of aspartate for lysine at residue 642, and most commonly arise in the stomach. Exon 17 mutations are mostly substitutions and occur predominantly in small intestinal GISTs.[4] Although in vitro studies have indicated that they may be less sensitive to imatinib, there are reports of clinical responses with imatinib in primary exon 17–mutant GISTs.[4,16]

PLATELET-DERIVED GROWTH FACTOR RECEPTOR ALPHA MUTATIONS

Like KIT, PDGFRA is a type III receptor tyrosine kinase and similar to KIT, activating mutations result in downstream activation of multiple