



# Topical Update – The Hong Kong College of Pathologists

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## Editorial note:

Gastrointestinal stromal tumor is the commonest mesenchymal tumor in the digestive system. It is a genetically heterogeneous disease with various mutations apart from classical activation mutations in *KIT* and *PDGFRA* genes. In the topical update, Dr. Anthony Chan provided an overview of molecular alterations of gastrointestinal stromal tumor with emphasis on their prognostic and therapeutic significance. We welcome any feedback or suggestions. Please direct them to Dr. Anthony Chan (e-mail: awh\_chan@cuhk.edu.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

## Molecular alterations of gastrointestinal stromal tumor - Prognostic and therapeutic implications

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### The gist of GIST

Gastrointestinal stromal tumor (GIST) is a rare tumor with the annual incidence rate of 10-15/1,000,000, but it is the commonest mesenchymal tumor in the digestive system. It affects both sexes equally and presents at any age from children to elderly with the median age of mid

60s. Stomach (55.6%) is the most frequent primary tumor site followed by small intestine (31.8%), large intestine (6.0%) and esophagus (0.7%). Other uncommon primary sites, such as omentum, mesentery and liver, accounts for 5.5% of all GISTs.(1) Important milestones of GIST in diagnostic, prognostic and therapeutic aspects are briefly summarized in this section.

In the past, GIST was regarded as leiomyoma, leiomyoblastoma or leiomyosarcoma before the era of wide availability of immunohistochemistry. In 1983, Mazur and Clark first applied the term "stromal tumor" to describe a group of gastric mesenchymal tumor lacking ultrastructural features of smooth muscle or schwann cells.(2) In 1989, a short-lived term, gastrointestinal autonomic nerve tumor (GANT), was used to describe a small subset of GIST featured by small intestinal location, epithelioid appearance and focal immunoreactivity towards neural markers (S100, neurofilament and synaptophysin).(3) In 1995, CD34 was found to be the first useful diagnostic immunohistochemical marker to differentiate GIST from leiomyoma and schwannoma although only 60-70% of all GISTs are immunoreactive to CD34.(4) In 1998, the hallmark constitutive activation mutation of *KIT* gene and overexpression of KIT/CD117 protein in GIST were discovered by Hirota et al.(5) This finding also suggested that GIST may be originated from interstitial cells of Cajal, pacemaker cells of intestine, which express KIT and CD34. However, activation mutation of *KIT* gene and overexpression of KIT are not consistently correlated. A subset of KIT positive GISTs was found to lack *KIT* mutation and this observation led to the subsequent discovery of gain-of-function mutation of platelet-derived growth factor receptor alpha (*PDGFRA*) gene in 2003.(6, 7) *KIT* and *PDGFRA* mutations are mutually exclusive. About 5-10% of GISTs, particularly those with *PDGFRA* mutation do not express KIT. In 2004, West et al. identified a novel gene, *DOG1* (discovered on GIST-1), through cDNA microarray, and showed *DOG1* protein was highly expressed in GISTs (97.8%), including those KIT negative GISTs.(8) KIT and/or *DOG1* become crucial diagnostic immunohistochemical markers for GIST. A small subgroup of GISTs with immunoreactivity of KIT/*DOG1* lack neither *KIT* or *PDGFRA* mutation was first designated as wild-type GISTs in the same year.(9) Wild-type GISTs are later shown to be a heterogeneous group with various mutations.(10-13)

Prognosis of patients with GIST is shown to be correlated with tumor size and mitosis. The first

consensus risk stratification was proposed by investigators in National Institutes of Health (NIH) in 2002 (Table 1).(14) Anatomical location of GIST is also an important prognostic factor and firstly integrated to the Armed Forces Institute of Pathology system in 2006 (Table 2)(15). Gastric GIST behaves more indolent than small and large bowel GIST with similar size and mitosis. Tumor rupture is an additional prognosticator for GIST patients and incorporated into the modified NIH system in 2008 (Table 3).(16) Finally, the most widely adopted tumor staging system, American Joint Committee on Cancer (AJCC), include GIST risk stratification composed of tumor size, mitosis, anatomical location, nodal and distant metastases in the 7th edition in 2010, which remains unchanged in the recently released 8th edition (Table 4 and 5).

Surgical resection remains the mainstay of curative therapy for GIST but a substantial portion of GIST patients present in advanced stage beyond surgical intervention. Imatinib, a multi-targeted tyrosine kinase inhibitor specific for c-abl, c-kit and PDGFR, was first used in a patient with metastatic GIST in 2001.(17) The dramatic clinical response from this patient and the subsequent successful phase II clinical trial in 2002 secured the first-line role of imatinib for patients with inoperable GIST and pioneered molecular targeted therapy for sarcoma.(18) Primary and acquired resistance to imatinib among GIST patients led to development of newer targeted agents. Two hallmark phase III randomized controlled trials on sunitinib (NCT00075218) and regorafenib (NCT01271712) for GIST were completed in 2006 and 2013, respectively.(19, 20) Sunitinib and regorafenib are indicated for patients with advanced GIST resistant or intolerant to imatinib.

### **Mutational landscape of GIST**

*KIT* and *PDGFRA* mutations are major driver mutations in GIST tumorigenesis. Both genes encode type III receptor tyrosine kinases with similar structures: extracellular ligand binding domain and dimerization domain, a transmembrane sequence, a juxtamembrane domain and intracellular kinase domain (Figure 1). Binding of corresponding ligands, stem cell factor and

PDGFA, to c-kit and PDGFRA receptor, respectively, dimerizes and activates receptor tyrosine kinases. In GIST, activation mutations in *KIT* and *PDGFRA* lead to uncontrolled ligand-independent receptor activation. Mutation hotspots of *KIT* gene are located at exons 9, 11, 13 and 17, whereas those of *PDGFRA* gene are situated at exons 12, 14 and 18. Mutation of extracellular domain of *KIT* encoded by exon 9 facilitate receptor dimerization. Mutations in the juxtamembrane domain, which is encoded by exon 11 of *KIT* and exon 12 of *PDGFRA*, allow dimerization of receptor without binding of ligands. Mutations of ATP binding region of kinase domain (encoded by exon 13 of *KIT* and exon 14 of *PDGFRA*) enhance kinase activity, while mutations of activation loop (encoded by exon 17 of *KIT* and exon 18 of *PDGFRA*) promote active conformation of kinase.(21) Table 6 and Figure 2 summarize the mutational landscape of GIST based on the data from population-based studies and clinical trials.(22-29) Frequencies of *PDGFRA* mutations are significantly lower among patients in clinical trials (mean 1.7%) than those in population-based studies (mean 14.9%) because GIST patients with *PDGFRA* mutations are associated with better prognosis and earlier stage and hence do not require systemic therapy.(9, 22, 23, 29)

*KIT* mutation accounts for 71.5% (64.8-89.1%) of mutations in GISTs.(24, 25, 27-29) Exon 11 mutation is the commonest mutation (61.1%, range: 56.1-77.1%). Deletion, substitution and duplication contribute to 23-28%, 2-20% and 2-7%, respectively. Deletion in exon 11 is associated with younger age, larger tumor size, higher mitotic count and poor prognosis, whereas duplication is associated with female and stomach predilection and better prognosis. Exon 9 mutation is found in 7.1-10.9% of GISTs, particularly in those arising from small and large intestine, and associated with poor prognosis. Exon 13 and exon 17 are rare mutation hotspots (<1-2%) in GISTs, which are almost exclusively spindle in morphology and more frequently developed in small intestine. GISTs with exon 13 and 17 mutants are associated good and intermediate prognosis, respectively.

*PDGFRA* mutation accounts for 14.9% (4.7-21.1%) of mutations in GISTs.(24, 25, 27-29) About 30-40% of GISTs without immunoreactivity of KIT/CD117 harbour *PDGFRA* mutation. GISTs with *PDGFRA* mutation generally show predilection to gastric location (>90%) and epithelioid/mixed morphology, and favourable prognosis (except non-D842V exon 18 mutation).

Wild-type GIST, which express immunoreactivity of KIT/DOG1 but lack neither *KIT* or *PDGFRA* mutation, contributes to 13-18% of adult GISTs and 85% of pediatric GIST.(10-12) As previously mentioned, it is a genetically heterogeneous group (Figure 3). Wild-type GIST can be further stratified by using succinate dehydrogenase B (SDHB) immunohistochemistry and familial syndromes. On one hand, SDHB deficient wild-type GISTs accounts for about 5% of all GISTs, and can be sporadic or related to Carney triad and Carney-Stratakis syndrome. Carney triad is a constellation of GIST, paraganglioma and pulmonary chondroma with undetermined germline mutation, whereas Carney-Stratakis syndrome is an autosomal dominant disease with dyad of GIST and paraganglioma, and germline mutations in *SDHB*, *SDHC* or *SDHD* genes.(30) SDHB deficient wild-type GISTs are featured by female predominance (except for Carney-Stratakis syndrome), exclusive location in stomach, multifocality, epithelioid/mixed morphology, unpredictable clinical outcome by histology, indolent clinical course despite frequent nodal metastasis, and mutation in SDH subunits (except for Carney triad). On the other hand, SDHB proficient wild-type GISTs make up 10.5% of all GISTs, and are either sporadic (9%) or syndromic (1.5%). Syndromic SDHB proficient wild-type GISTs are associated with neurofibromatosis type 1, absence of sex/age predilection, small intestine in location, multifocality, spindle morphology, and favorable prognosis. Sporadic SDHB proficient wild-type GISTs can be further classified according to *BRAF* mutation. Sporadic SDHB proficient wild-type GISTs with *BRAF* mutation usually occur in 6th decade of age and small intestine with spindle morphology. Prognosis of this subgroup is inconclusive.(10, 29, 31, 32) Sporadic SDHB proficient wild-type GISTs without *BRAF* mutation are also known as

quadruple wild-type GISTs without any mutation in *KIT*, *PDGFRA*, *SDH* and genes in RAS pathway (*BRAF/NF1*).<sup>(12, 13)</sup> They represent the commonest subgroup (7%) of wild-type GISTs and a genetically heterogeneous subgroup harboring *ETV6-NTRK3* translocation, *FGFR1-TACCI* translocation, mutation of *MEN1* and *MAX*, and overexpression of *COL22A1* and *CALCRL*.<sup>(12, 29, 33, 34)</sup> Due to complex genetic heterogeneity, clinicopathological features of this subgroup have not been well characterized.

### Clinical implications of mutations in GIST

Different mutations in GIST have their own characteristic prognostic and therapeutic implications. Prognostic significance of individual mutations have been described by various investigators and briefly mentioned in the previous section. Rossi et al. recently systemically analyzed the prognostic impact of mutations among 451 patients with primary localized treatment-naive GISTs.<sup>(29)</sup> By multivariable Cox regression, mutational status was an independent prognosticator in addition to patient's age, tumor location, tumor size and mitotic count. Three molecular risk groups with prognostic significance were identified: Group 1 with the most favorable outcome is composed of mutations in *KIT* exon 13, *PDGFRA* exon 12 and *BRAF*; Group 2 with the intermediate outcome (hazard ratio 3.06) consists of *KIT/PDGFRA/BRAF* triple negative, and mutations in *KIT* exon 17, *PDGFA* exon 14 and 18 (D842V); and Group 3 with the most unfavorable outcome comprises mutations in *KIT* exon 9 and 11, and *PDGFRA* exon 18 (non-D842V).

Clinical response toward imatinib among GIST patients is closely related to tumor genotype. In a phase III clinical trial (SWOG S0033/CALGB 150105), the investigators demonstrated that patients with *KIT* exon 11 mutation (complete response [CR]/partial response [PR] 71.7%) had better response to imatinib than those with *KIT* exon 9 mutation (CR/PR 44.4%) and wild-type *KIT* (CR/PR 44.6%).<sup>(23)</sup> They also showed that doubling the dose of imatinib (from 400 mg to 800 mg) improved response rates for patients with exon 9-mutant tumors (CR/PR 17% vs. 67%). Double dose of imatinib did not offer any better response

rate among patients with exon 11 mutant or wild-type *KIT*. A subsequent meta-analysis of 1,640 patients with advanced GIST receiving imatinib confirmed that double dose of imatinib improved progression-free survival and objective response rate, but not overall survival, among patients with *KIT* exon 9-mutant GIST.<sup>(35)</sup> *PDGFA* exon 18 (D842V) mutation and *KIT/PDGFRA* wild-type are responsible for primary resistance to imatinib.<sup>(36)</sup> Among patients with advanced GIST receiving imatinib, a substantial proportion of initial responders will develop acquired resistance. Secondary mutations in exon 11 (L576P and V559A), exon 13 (V654A), exon 14 (T670I), exon 17 and exon 18 (A829P) of *KIT*, and exon 18 of *PDGFRA* are related to acquired resistance to imatinib.<sup>(36)</sup>

Clinical response to sunitinib, the second line targeted therapy after imatinib failure, is also considerably affected by primary and acquired mutations of *KIT*. Patients with primary *KIT* exon 9 mutation or wild-type *KIT* had better overall and progression-free survival than those with *KIT* exon 11 mutation, whereas patients with acquired *KIT* exons 13 or 14 mutations had better outcome than those with *KIT* exon 17 or 18 mutations.<sup>(37)</sup> Similarly, clinical response to regorafenib, the third line therapy after imatinib and sunitinib failure, is significantly influenced by tumor genotype. Regorafenib provided better clinical outcome among patients with primary *KIT* exon 11 mutation and *SDHB* deficient GIST, <sup>(38)</sup> as well as those with secondary mutation of *KIT* exon 17, which are resistant to both imatinib and sunitinib.<sup>(39)</sup>

### Summary

GIST is a genetically heterogeneous tumor. Genotypes and phenotypes are closely interrelated. Specific mutations have their characteristic clinicopathological features, prognostication and therapeutic implications. Genetic analyses *KIT* and *PDGFRA* are highly recommended especially among patients with advanced diseases undergoing targeted therapy. Wild-type GISTs are recommended to be further analysed by *SDHB* immunohistochemistry and *BRAF* mutation test.

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Figure 1: Schematic diagram of the structures of KIT and PDGFRA receptor tyrosine kinases

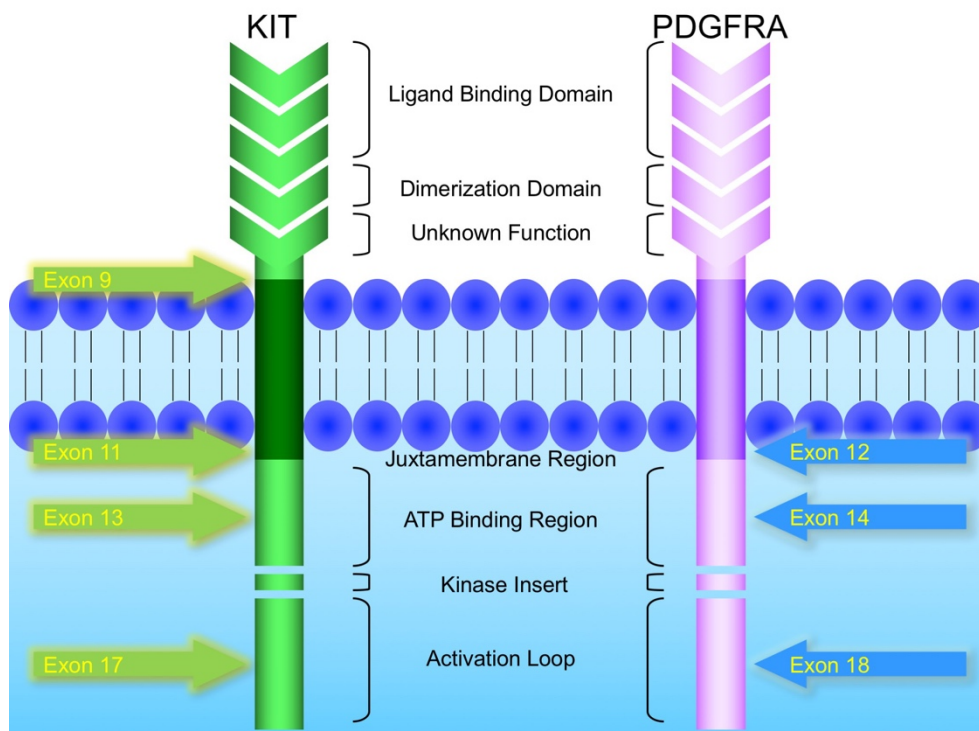


Figure 2: Mutational landscape of GIST

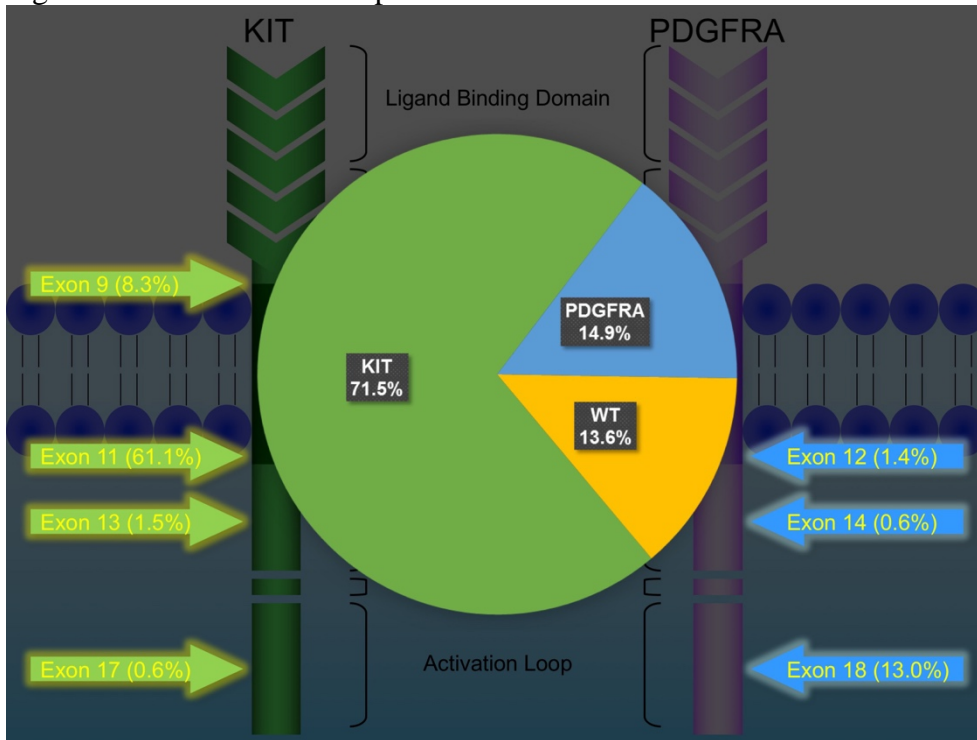
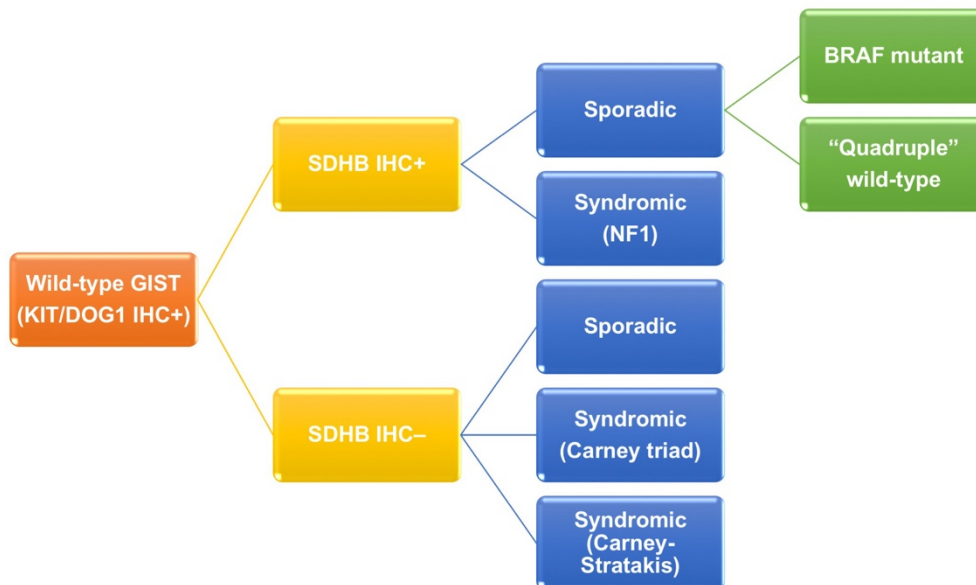


Figure 3: Classification of wild-type GIST





<b>GROUP</b>	<b>SIZE (CM)</b>	<b>MITOSIS (/50 HPF)</b>
Very low risk	<2	≤5
Low risk	2-5	≤5
Intermediate risk	<5	6-10
	5-10	≤5
High risk	>5	>5
	>10	Any
	Any	>10

Table 1: NIH risk stratification for GIST (14)

<b>GROUP</b>	<b>SIZE (CM)</b>	<b>MITOSIS (/50 HPF)</b>	<b>STOMACH</b>	<b>DUODENUM</b>	<b>JEJUNUM /ILEUM</b>	<b>RECTUM</b>
1	≤2	≤5	None	None	None	None
2	>2-5	≤5	Very low	Low	Low	Low
3a	>5-10	≤5	Low	Moderate	-	-
3b	>10	≤5	Moderate	High	High	High
4	≤2	>5	None	High	-	High
5	>2-5	>5	Moderate	High	High	High
6a	>5-10	>5	High	High	-	-
6b	>10	>5	High	High	High	High

Table 2: AFIP risk stratification for GIST (15)

<b>GROUP</b>	<b>SIZE (CM)</b>	<b>MITOSIS (/50 HPF)</b>	<b>PRIMARY SITE</b>
Very low risk	≤2	≤5	Any
Low risk	>2-5	≤5	Any
Intermediate Risk	>2-5	>5	Gastric
	≤5	6-10	Any
	>5-10	≤5	Gastric
High risk	>5	>5	Any
	>10	Any	Any
	Any	>10	Any
	Any	Any	Tumor rupture
	>2-5	>5	Non-gastric
	>5-10	≤5	Non-gastric

Table 3: Modified NIH risk stratification for GIST (16)

GROUP	SIZE (CM)	N	M	MITOSIS (/50 HPF)
IA	≤5	0	0	≤5
IB	>5-10	0	0	≤5
II	≤5	0	0	>5
	>10	0	0	≤5
IIIA	>5-10	0	0	>5
IIIB	>10	0	0	>5
IV	Any	1	0	Any
	Any	Any	1	Any

Table 4: AJCC staging system for gastric and omental GIST

GROUP	SIZE (CM)	N	M	MITOSIS (/50 HPF)
I	≤5	0	0	≤5
II	>5-10	0	0	≤5
IIIA	≤2	0	0	>5
	>10	0	0	≤5
IIIB	>2	0	0	>5
IV	Any	1	0	Any
	Any	Any	1	Any

Table 5: AJCC staging system for small/large bowel, esophageal, mesenteric and peritoneal GIST

Study	Region	n	KIT exon				PDGFRA exon			Wild type
			9	11	13	17	12	14	18	
Wozniak 2012 (24)	Poland	427	7.3%	61.1%	0.5%	0.5%	0.2%	0.7%	11.9%	17.8%
Wozniak 2014 (28)	Europe	1056	7.4%	61.4%	1.8%	0.6%	0.9%	0.3%	12.8%	14.9%
Künstlinger 2013 (25)	Germany	1366	9.2%	59.3%	1.8%	0.8%	1.8%	0.6%	13.8%	12.7%
Wang 2014 (27)	China	275	10.9%	77.1%	1.1%	0.0%	1.1%	0.0%	3.6%	6.2%
Rossi 2015 (29)	Italy	451	7.1%	56.1%	0.9%	0.7%	2.2%	1.6%	17.3%	14.2%
ACOSOG Z9001 (26)		507	6.9%	67.3%	1.8%	0.2%	NA	NA	NA	12.8%
CALGB 150105 (23)		378	8.2%	72.8%	0.8%	1.1%	0.0%	0.0%	1.6%	15.3%
EORTC 62005 (22)		377	15.4%	65.8%	1.6%	0.8%	0.8%	0.0%	1.9%	13.8%

Table 6: Mutational landscape of GIST