Ancillary studies (Core)

Immunohistochemistry (IHC) plays a critical role in confirming the diagnosis of gastrointestinal stromal tumour (GIST). The tyrosine kinase receptor KIT (CD117) and the chloride channel ANO1 (DOG1), markers of interstitial cell of Cajal lineage, are highly sensitive and specific markers for GIST.[1-3] KIT expression is observed in 95% of cases, most often with a cytoplasmic staining pattern; a paranuclear dot-like or membranous pattern may also be seen. DOG1 is helpful to confirm the diagnosis in KIT-negative GISTs and those with weak or limited staining.[3,4] KIT-negative GISTs (and those with weak or limited staining for KIT) most often harbor *PDGFRA* mutations.[5,6] Succinate dehydrogenase (SDH)-deficient GISTs show loss of staining for SDHB, irrespective of which *SDHX* gene is mutated (or if there is SDHC promoter hypermethylation; see below).[7,8] SDHB IHC can therefore be used to confirm the diagnosis of SDH-deficient GIST. SDHA loss is only observed in *SDHA*-mutant GISTs.[9] Despite the lack of *KIT* mutations, SDH-deficient GISTs are typically strongly positive for KIT (and DOG1).

KIT mutations are found in about 75% of GISTs, most often in exon 11 (66% overall) and exon 9 (6%); mutations in exon 13, exon 17, and other locations are rare (see Figure 1).[10,11] *PDGFRA* mutations are identified in 10-15% of GISTs, most often in exon 18 (10-12% overall; the most common is p.D842V), rarely in exons 12 or exon 14.[12,13] Genotype predicts response to tyrosine kinase inhibitor therapy; for example, *KIT* exon 11-mutant GISTs have the best response to imatinib mesylate, whereas GISTs with *PDGFRA* D842V mutations show primary imatinib resistance, although such tumours respond to the tyrosine kinase inhibitor avapritinib.[14,15]

SDH-deficient GISTs account for about 5% of GISTs overall, including the majority of gastric GISTs that lack *KIT* and *PDGFRA* mutations and most tumours occurring in paediatric patients.[16] SDH-deficient GISTs typically show indolent behaviour with often late and slowly progressive metastases and show limited response to imatinib. As mentioned previously, conventional risk stratification systems do not apply to SDH-deficient GISTs.[17] SDH-deficient GISTs are often associated with germline mutations in *SDHA*, *SDHB*, *SDHC*, or *SDHD*; these mutations are sometimes associated with Carney-Stratakis syndrome (the dyad of gastric GIST and paraganglioma).[18] SDH-deficient GISTs that lack *SDHX* mutations usually show hypermethylation of the *SDHC* promoter; this epigenetic dysregulation is characteristic of Carney triad (SDH-deficient GIST, paraganglioma, and pulmonary chondroma).[19]

Other genetic alterations in GIST are rare; these include *BRAF* V600E and *EGFR* mutations; biallelic *NF1* inactivation; and tyrosine kinase receptor gene rearrangements.[20,21]

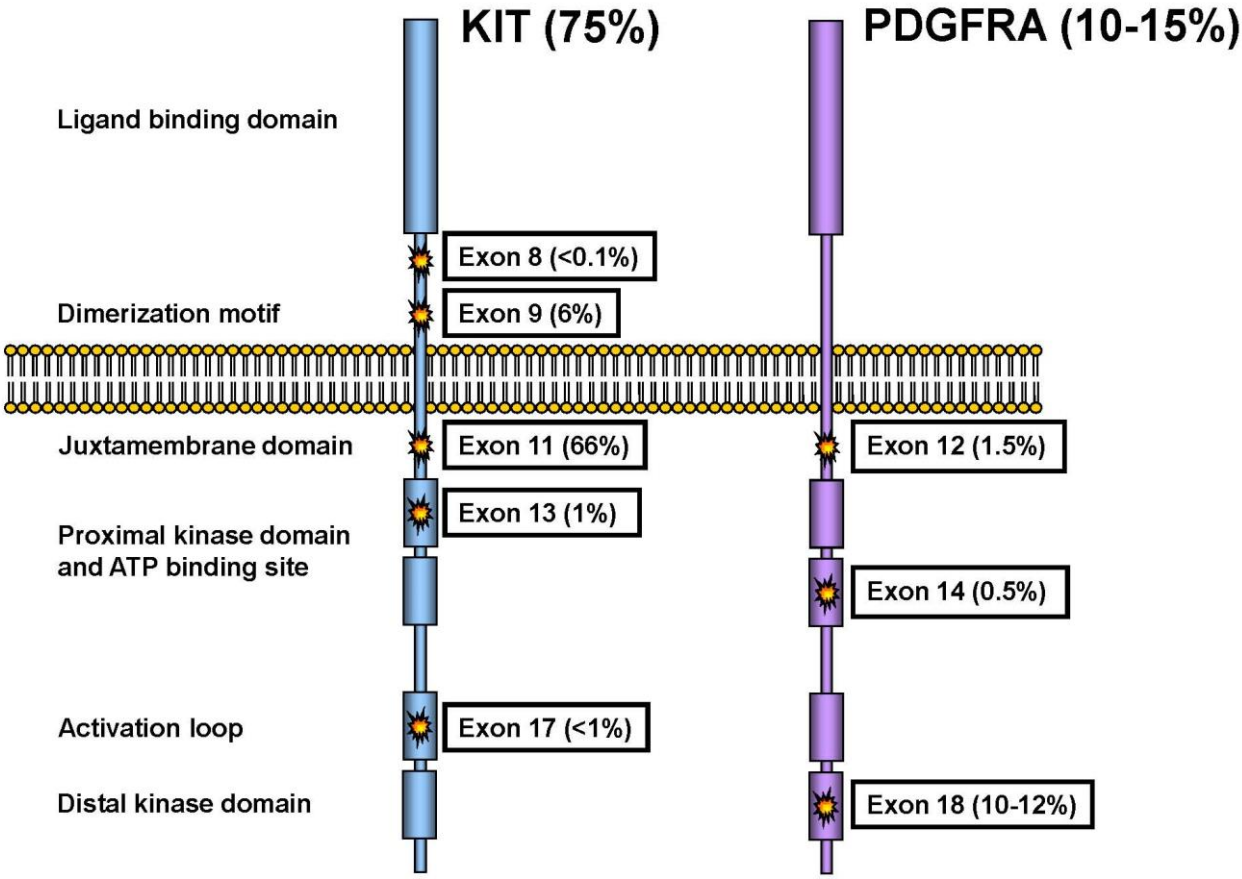

Figure 1: Distribution of *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumours.
Permission courtesy of Professor Jason L. Hornick.

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