Unipath
SPECIALTY LABORATORY Ltd.

MOLECULAR ANALYSIS OF C-KIT AND PDGFRA MUTATION

Department of Molecular Biology

c-KIT Mutation Testing for GIST/Melanoma

TEST DESCRIPTION:

KIT is a tyrosine kinase receptor that regulates cellular proliferation and differentiation. **Activating mutations in KIT have been identified in approximately 75-80% of gastrointestinal stromal tumors (GISTs)**. These mutations occur in the juxtamembrane domain (Exon 11), the extracellular domain (exon 9), and the tyrosine kinase domain (exons 13 and 17). The presence of a KIT mutation in a spindle cell neoplasm suggests a diagnosis of GIST, but is not specific for this diagnosis.

CLINICAL UTILITY:

Many of the acquired mutations in KIT result in constitutive activation of its tyrosine kinase activity. This makes the use of targeted tyrosine kinase inhibitory agents, such as imatinib, an option for patients with tumors that harbor these mutations. **Approximately 80% of GISTs respond to imatinib therapy.** Patients with GISTs that harbor mutations within the juxtamembrane domain (exon 11) of KIT have better responses to imatinib than patients with GISTs that harbor mutations in the KIT extracellular domain (exon 9). **Patients with C-KIT mutations other than D816V (exon 17) are likely to respond to imatinib (Gleevec) therapy.** Secondary mutations usually occur in c-KIT kinase domains in patients after imatinib treatment resulting in resistance to this drug. Therefore, a sensitive, specific and reproducible method for genotyping c-KIT mutations in clinical samples is required to aid in patient selection for appropriate therapy and potential monitoring of treatment efficacy.

TEST DESCRIPTION:

This assay is Uni-directional Sanger sequencing assays has been tested to identify variation in the c-KIT gene using formalin fixed paraffin embedded (FFPE) tissue samples from tumors such as GIST or melanoma.

The test includes: Exon 9, 11, 13 and 17

1. **c-KIT exon 9** - detects the common Ala502_Tyr503dup and any rare mutations in this exon
2. **c-KIT exon 11** - detects the wide range of deletions, substitutions, insertions, and duplications present in this exon
3. **c-KIT exon 13** - detects the common **K642E and N655K mutations associated with melanoma** and any rare mutations in this exon
4. **c-KIT exon 17** - detects the known D816V/H, Y823D, N822K/H, and D820A/Y/G mutations and any rare mutations in this exon

METHODOLOGY: PCR SEQUENCING

Specimen Requirements: A paraffin block + Clinical History

CANCER RELEVANCE

- GIST
- Melanoma

DRUG RELEVANCE

- c-KIT targeted tyrosine kinase inhibitors

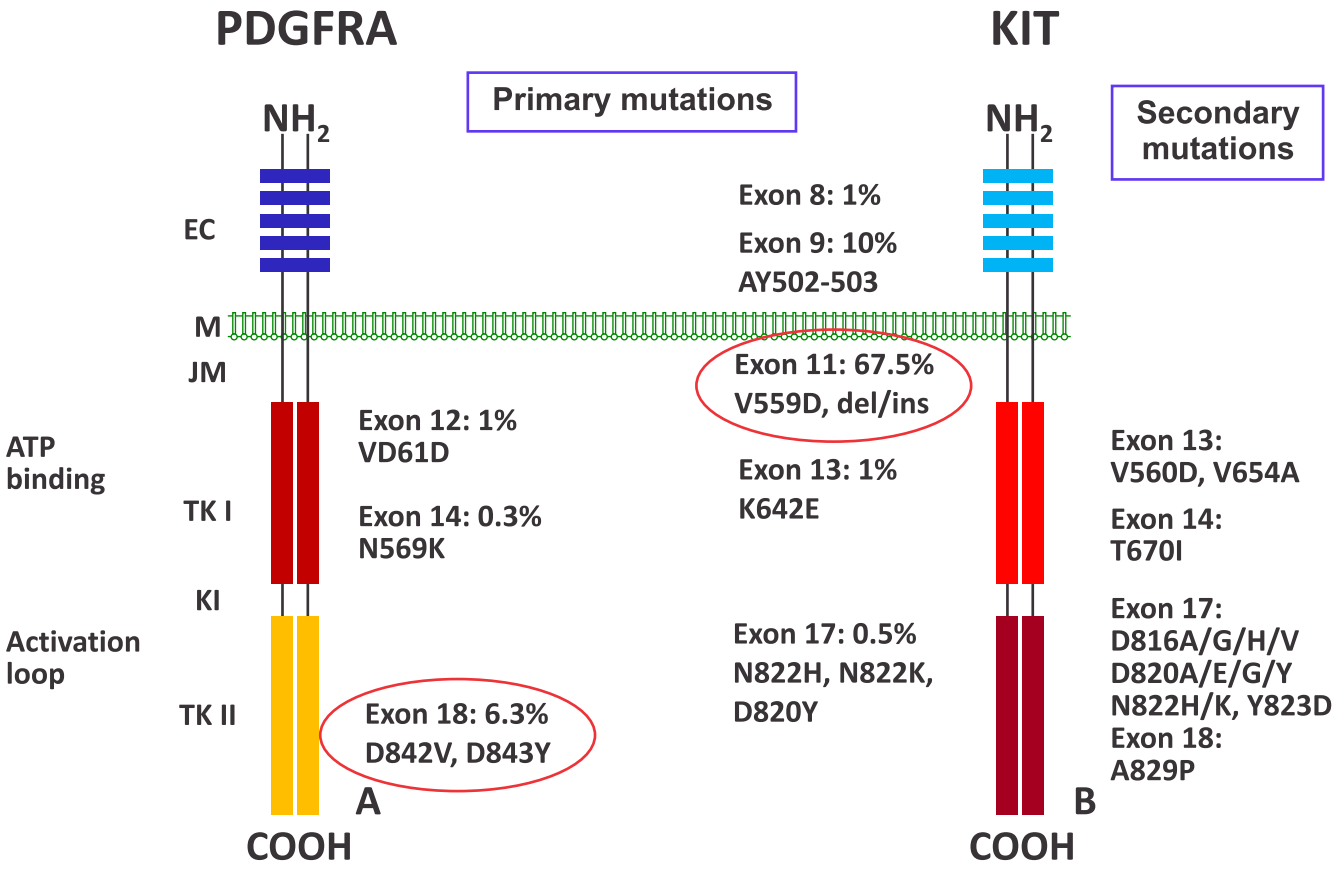
SENSITIVITY

~20% mutant allele

RELATED ASSAYS

- PDGFRα exons 12 and 18 (sequencing assay)
- BRAF codon V600E (Sequencing assay)
- BRAF exon 15 (sequencing assay)
- NRAS exon 2 /codon 61 (sequencing assay)

KIT AND PDFRA MUTATIONS



PDGFRA GENE MUTATION DETECTION

TEST DESCRIPTION:

The platelet-derived growth factor receptor alpha (PDGFRA) gene encodes a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. PDGFRA and c-KIT have approximately 35% homology. They both belong to the PDGFRA subfamily of receptor tyrosine kinases, which are involved in the regulation of cell growth, proliferation, adhesion, migration, differentiation, and apoptosis. **Approximately 5% to 10% of GISTs have a mutation in PDGFRA.** PDGFRA mutations are mutually exclusive with c-KIT mutations but active similar signal transduction pathways that support GIST oncogenesis. The location of c-KIT and PDGFRA mutations in GISTs is associated with the site of origin, histological phenotype, and treatment response to tyrosine kinase inhibitors

CLINICAL UTILITY:

The most common mutation in PDGFRA is **D842V (EXON 18)**, which generates a mutant form of the kinase that is **fully resistant to imatinib**. Tumors with this mutation are generally slow to recur or progress. **GISTs with PDGFRA mutation other than D842V likely to respond to imatinib.**

Exon covered in Test: Exon 12 and 18

INDICATION OF TESTING: This test is performed as a reflex for GISTs that are negative for a cKIT mutation.

METHODOLOGY: PCR SEQUENCING

Specimen Requirements: A paraffin block + Clinical History

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