KIT Molecular Testing

Content Review: July 2020 Last Update: February 2024

Molecular testing for *KIT* mutations is relevant for various types of cancer and can provide diagnostic, prognostic, and predictive information for systemic mastocytosis (SM), gastrointestinal stromal tumors (GIST), melanoma, and acute myeloid leukemia (AML). For GIST and melanoma, *PDGFRA* testing is also often relevant.

Disease Overview

Acute Myeloid Leukemia

KIT mutation testing is important for prognostication.[1] Refer to the ARUP Consult Acute Myeloid Leukemia topic for more information about KIT testing in AML.

Mastocytosis

KIT mutation testing is important for:

- Diagnosis (presence of mutation is a minor criteria for SM)
- Prediction of response to targeted therapy

Gastrointestinal Stromal Tumors

- *KIT* and *PDGFRA* mutation testing is important for prediction of response to targeted therapy and should be performed in all patients considered for targeted therapy
- Mutation presence and type determine if the patient will benefit from targeted therapy
- Detection of secondary resistance mutations in patient already treated with targeted therapy may guide the use of other therapeutic agents
- Mutation testing may be occasionally used to aid in establishing GIST diagnosis in difficult cases (unusual location, morphology, or immunoprofile)
- Immunohistochemistry for c-kit (CD117) is useful for diagnostic purposes but should not be used to predict response to targeted therapy

Melanoma

- KIT mutation testing is important for prediction of response to targeted therapy
- Immunohistochemistry for c-kit (CD117) should not be used to predict response to targeted therapy

Genetics

Gene

KIT

Structure/Function

- Maps to 4q12
- Receptor tyrosine kinase (type III)
- Important in hematopoiesis for regulation of cell proliferation and maturation

Mutations

A variety of >500 mutations have been described, most commonly in juxtamembrane region (exon 11), extracellular region (exons 8, 9), and kinase domain (exons 13, 17). These mutations are commonly detected in patients with:

Featured ARUP Testing

KIT (D816V) Mutation by ddPCR, Quantitative 3002956

Method: Droplet Digital PCR (ddPCR)

- Aids in the diagnosis of mastocytosis in peripheral blood and bone marrow specimens
- The D816V mutation is a diagnostic marker for systemic mastocytosis
- The D816V mutation confers resistance to imatinib

Gastrointestinal Stromal Tumor Mutations 3004279

Method: Massively Parallel Sequencing

- Detects activating mutations in *KIT* and *PDGFRA*
- Predicts response to targeted therapy

KIT Mutations Melanoma 3004283

Method: Massively Parallel Sequencing

- Detects activating mutations in *KIT* and *PDGFRA*
- Predicts response to targeted therapy

- Mastocytosis
  - Adults
    - D816V mutation detected in 95% of patients with SM
    - Rare juxtamembrane mutations
  - Children
    - D816V mutation detected in 30-40% of patients with SM
    - Approximately 40% carry *KIT* mutations that reside outside exon 17 (mainly exons 8 and 9)
  - Mutations other than D816V may be detected in SM-associated hematologic neoplasm (AHN)
- GIST
  - *KIT* mutations present in approximately 85% of cases
    - Primary mutations most common in exon 11 (approximately 70% of cases) and exon 9 (approximately 10-15% of cases); much less common in other exons
    - Secondary resistance mutations occur in exons 13, 14, 17, and 18
  - *PDGFRA* mutations present in approximately 5% of cases
    - Primary mutations most common in exon 18 (approximately 5% of cases)
    - Primary mutations much less common in other exons
- Melanoma
  - *KIT* mutations present in 2-8% of cases overall (more common in mucosal and acral melanomas)
  - Most common in:
    - Exon 11 (70% of *KIT* mutated cases)
    - Exon 13 (20% of *KIT* mutated cases)
  - Much less common in other exons

Test Interpretation

KIT (D816V) Mutation by ddPCR, Quantitative

Sensitivity

- Clinical: occurs in >80% of SM cases
- Analytic: 0.03% variant allele frequency (VAF)

Results

- Detected VAF: *KIT* (D816V) point mutation; allele specific amplification of the c.2447 C>T (D816V)
- Results are reported as a percent mutated allele
  - Supports a diagnosis of SM or SM-associated clonal hematologic nonmast cell lineage disease (SM-AHNMD) in the correct clinical context
  - Therapeutic implications
    - Imatinib: ineffective if mutation is present
    - Dasatinib and Nilotinib: uncertain clinical efficacy
- Not detected: no detectable *KIT* (D816V) point mutation

Limitations

- Mutations other than the D816V mutation are not detected, including other D816 variants
- Mutations below analytic sensitivity will not be detected

Gastrointestinal Stromal Tumor Mutations and *KIT* Mutations, Melanoma

Analytic Sensitivity			
Variant Class	No. Variant Tested	Positive Percent Agreement (PPA)	PPA, 95% Tolerance at 95% Reliability
SNV	177	100%	98.9-100.0%
MNVs	42	95%	85.6-99.0%

[a]≤21 bp

[b]22-60 bp

[c]≥61 bp and ≤64bp

[d]≥61 bp and ≤13547bp

bp, base pair; MNVs, multiple nucleotide variants; SNV, single nucleotide variant

Variant Class	No. Variant Tested	Positive Percent Agreement (PPA)	PPA, 95% Tolerance at 95% Reliability
Small insertions and duplications[a]	42	100%	95.6-100.0%
Medium insertions and duplications[b]	10	100%	82.9-100.0%
Large insertions[c]	1	100%	22.9-100.0%
Small deletions[a]	80	100%	97.6-100.0%
Medium deletions[b]	14	100%	71.2-99.2%
Large deletions[d]	22	64%	42.9-81.1%

[a]≤21 bp

[b]22-60 bp

[c]≥61 bp and ≤64bp

[d]≥61 bp and ≤13547bp

bp, base pair; MNVs, multiple nucleotide variants; SNV, single nucleotide variant

Results

- Detected: *KIT* mutation detected in exons 9, 11, 13, 14, 17, 18
- Detected: *PDGFRA* mutation detected in exons 12, 14, 18
- Not detected: no mutations detected in *KIT* and *PDGFRA*

Limitations

- Mutations outside of targeted exons are not detected
- Test alone cannot be used for diagnosis of malignancy
- Variants below the limit of detection (LOD) of 5% VAF may not be detected
- 10 ng input DNA from extracted tissue sample is minimally required, but 50 ng input DNA is recommended for optimal results
- Large variants (>60bp) may not be detected
- Not intended to detect minimal residual disease
- Does not distinguish between somatic and germline variants

References

1. Swerdlow S, Campo E, Harris N, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. International Agency for Research on Cancer; 2008.