KIT Exons 8 and 17 Mutation Analysis for Acute Myeloid Leukemia

Background Information

Using 2008 WHO criteria, acute myeloid leukemia is subclassified based upon a combination of clinical, morphologic, phenotypic, cytogenetic and molecular findings. Several cytogenetic and/or molecular abnormalities define distinct clinical entities that are associated with differences in prognosis. For example, acute myeloid leukemias containing the core-binding factor (CBF) translocations, t(8;21)(q22;q22) and inv(16)(p13q22) are recognized as distinct neoplasms with characteristic clinical and morphologic features and an overall favorable prognosis.[1]

Mutations in the *KIT* gene are identified in approximately 20-40% of CBF acute myeloid leukemias. Mutations consist predominantly of point mutations in exon 17 or, less frequently, insertions and deletions occurring in exon 8. The presence of a *KIT* mutation is reported to abrogate the favorable prognosis associated with CBF acute leukemias, especially t(8;21).[2-4]

The identification of *KIT* mutations in CBF leukemias assists in prognostic assessment and selection of appropriate therapy, and *KIT* mutation analysis is recommended for risk stratification of CBF leukemias in current National Comprehensive Cancer Network (NCCN) guidelines.[5] The Cleveland Clinic Department of Molecular Pathology has developed, validated and implemented a sequencing assay for the detection of mutations in *KIT* exons 8 and 17.

Clinical Indications

KIT Exons 8 and 17 Mutation Analysis is useful in the workup of suspected acute myeloid leukemia, especially in cases carrying the CBF translocations, t(8;21)(q22;q22) or inv(16)(p13q22).

Interpretation

Normal results are reported as "*KIT* mutations are not detected." Positive results are reported using Human Genome Variation Society (HGVS) nomenclature, and an interpretation provided.

Methodology

DNA is extracted and *KIT* exons 8 and 17 are amplified by PCR. The PCR product is subjected to bidirectional cycle sequencing using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Carlsbad, CA) on the ABI 3730 Genetic Analyzer. Sequences are aligned to wild type reference sequence and assessed for the presence of mutations.

Limitations of the Assay

The lower limit of reliable mutation detection is 15-20% mutant alleles. Formalin-fixed, paraffin-embedded tissue is not accepted.

References

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3. Cairoli R, Beghini A, Grillo G, *et al*. Prognostic impact of c-*KIT* mutations in core binding factor leukemias: an Italian retrospective study. *Blood*. 2006;107:3463-8.
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6. Levine RL, Wadleigh M, Cools J, *et al*. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7:387-397.
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9. Scott LM, Tong W, Levine RL, *et al*. *JAK2* exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med*. 2007;356: 459-468.

Test Overview

Test Name	*KIT*-AML Exons 8 and 17 Mutation Analysis for Acute Myeloid Leukemia
Reference Range	Normal results are reported as "*KIT* mutations are not detected."
Specimen Requirements	Peripheral Blood: 5mL EDTA (Lavender); Transport Temperature: Refrigerated
Alternative Specimen Requirements	Bone Marrow: 1-2mL. EDTA (Lavender); Transport Temperature: Refrigerated
Ordering Mnemonic	KITAML
Billing Code	84158
CPT Code	81404

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