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FISH Panel for Acute Myeloid Leukemia (AML)

inv(3)MECOM/RPN1, 5q, t(6;9)*DEK/NUP214*, 7q, 8 centromere/20q, t(8;21)*RUNX1T1/RUNX1, NUP98, KMT2A* (formerly *MLL*), t(15;17)*PML/RARA,* inv(16) or t(16;16)*CBFB/MYH11.*

Clinical Background

- Acute myeloid leukemia (AML) is a clinically, morphologically and genetically heterogeneous disease that results in clonal expansion of myeloid blasts in the peripheral blood, bone marrow, or other tissue.
- A general AML workup at the time of diagnosis consists of drawing a bone marrow aspirate specimen for morphology, immunophenotyping, and genetic studies including cytogenetic and mutation analyses.
- Detection of cytogenetic abnormalities in AML can aid in the diagnosis of disease and provide prognostic information.
- Although typically associated with a percentage of blast cells exceeding 20%, a diagnosis of AML can be made irrespective of blast cell count if there is an associated t(8;21), inv(16), t(16;16), or t(15;17).

Epidemiology

- Overall incidence of AML – 4.3/100,000 (adults and children)
- inv(3) or t(3;3) – 1 - 2% of individuals with AML (more common in adults)
- t(6;9) – 0.7 – 1.8% of individuals with AML (occurs in both children and adults)
- t(8;21) – 1 - 5% of individuals with AML (more common in younger patients (<65 years)
- inv(16) or t(16;16) – 5 - 8% of younger individuals (<65 years) with AML (less frequent in older adults)
- t(15;17) – 5 - 8% of individuals (all ages) with AML but is more common in adults in mid-life
- NUP98 – 3 – 7% of pediatric AML cases (less frequent in adults)
- KMT2A (MLL) – 5% of individuals with AML (~2% in adults; ~10% in children)
- -5/del(5q) – 5% of elderly individuals with AML (rare in children)
- -7/del(7q) – 7% of individuals with AML (more prevalent in adults)
- Trisomy 8 – 5-6% of AML cases as sole abnormality and common as a secondary alteration
- del(20q) – common in myeloid malignancies

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Genetics

Abnormality	Gene(s) Involved
t(3;3); inv(3)	*MECOM/RPN1*
-5/del(5q)	(Multiple genes)
t(6;9)	*DEK/NUP214*
-7/del(7q)	(Multiple genes)
Trisomy 8/del(20q)	(Multiple genes)
t(8;21)	*RUNX1T1/RUNX1*
t(11p15)	*NUP98*
t(11q23)	*KMT2A (MLL)*
t(15;17)	*PML/RARA*
inv(16) or t(16;16)	*CBFB/MYH11*

Indications for Ordering

- Newly diagnosed patients with AML or patients suspected of a primary or secondary hematological cancer.
- Follow-up of AML patients with a previously identified cytogenetic abnormality.
- This test can ordered as a panel (16 probes) or each probe can be ordered on an individual probe basis.
- This test is typically used in conjunction with conventional cytogenetic analysis.

Interpretation

- **Negative:** No evidence of rearrangement, gains or losses from the probes sets that were tested according to our laboratory standards. The total number of cells analyzed and standard FISH nomenclature are detailed. These results are considered normal. **Limitations:** The probes in this FISH panel detect only specific aberrations. Chromosomal alterations present outside the regions targeted by the probes may not be detected**.**
- **Positive:** Rearrangement or gains and/or losses detected for the probe sets tested is/are present. A description of the abnormality, the number of cells evaluated, the percentage of cells that demonstrate the abnormality, and standard FISH nomenclature are detailed. These results are considered abnormal.

Methodology

- Fluorescence *in situ* hybridization (FISH) is a molecular cytogenetic method that detects fluorescently-labeled DNA/RNA or oligonucleotide probes hybridized to metaphase or

interphase cells. Fluorescent signals are detected with a fluorescence microscope. In general, two hundred interphase cells are analyzed per probe by two readers (100 cells/reader).

- FISH typically serves as an adjunct to conventional karyotype analysis for the detection of cytogenetic abnormalities. FISH studies often provide clarification of G-banded abnormalities or identify cryptic abnormalities not observed by conventional karyotype analysis. However, dividing cells are not required for interphase FISH analysis.
- The high sensitivity and specificity, rapid turn-around time, capacity to analyze large numbers of cells, and ability to obtain adequate data from samples with a low mitotic index or terminally differentiated cells are the main advantages of FISH. This method is most useful when the analysis is targeted toward those abnormalities that are known to be associated with a particular disease.

References

1. Knowles Neoplastic Hematopathology, 3rd ed. Orazi A, Foucar K, Knowles DM, and Weiss LM, Editors. Lippincott Williams & Wilkins: Philadelphia, PA, 2013.

2. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th edition. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Arber DA, Hasserjian RP, Le Beau MM, Orazi A, and Siebert R, Editors. IARC Press: Lyon, France, 2017.