

Recurrent Genetic Abnormalities in Pediatric B-cell Acute Lymphoblastic Leukemia/ Lymphoma (B-ALL), Detected by FISH

Test Highlights

- This test provides significant prognostic information and also supplements diagnosis in pediatric patients with B acute lymphoblastic leukemia (B-ALL). It is suitable for widespread use.
- Specific recurrent genetic changes in B-ALL can be detected by using this test. These genetic abnormalities include hyperdiploidy, translocation 9;22 (*ABL1/BCR*), translocation 12;21 (*ETV6/RUNX1*), and rearrangements of *MLL* and *TCF3(E2A)*.
- FISH is more sensitive than conventional cytogenetics in detecting genomic aberrations.

Clinical Background

- B-ALL is a malignant disease of the lymphoid cell line occurring predominantly in children.
- B-ALL is frequently associated with recurrent cytogenetic abnormalities. Some of these abnormalities are associated with distinctive clinical or phenotypic properties and may also have prognostic value.
- Genetic studies are required at diagnosis not only for identifying specific genetic abnormalities but also for monitoring disease progression and response to therapy.
- Identification of recurrent specific chromosome abnormalities plays an important role in the diagnostic workup of B-ALL and can also provide significant prognostic information.
- Standard chromosome analysis (karyotypic analysis) using metaphase cells requires dividing cells and remains the gold standard for the detection of cytogenetic abnormalities. Cytogenetically visible rearrangements can sometimes be missed due to suboptimal chromosome morphology or lack of dividing cells. In a diagnostic cytogenetics laboratory, FISH analysis has several advantages over chromosome studies. It has a rapid turnaround time, detects small numbers of abnormal cells, and can be performed on nondividing (interphase) cells. In addition, FISH can detect cryptic or subtle rearrangements that might be difficult to detect by routine karyotyping. The breakapart FISH probes are designed to target the critical genes with multiple translocation partners and can detect the rearrangement of the critical gene regardless of the translocation partner; however, identifying the translocation partner correlation with chromosome studies is recommended.

Epidemiology

The incidence of B-ALL in the United States is 3:100,000.

Genetics

- Recurrent genetic abnormalities associated with B-ALL in the pediatric population include:
 - B-ALL with t(9;22)(q34;q11.2)(*BCR/ABL-1*)
 - B-ALL with t(12;21)(p13;q22) (*ETV6/RUNX1*)
 - B-ALL with rearrangement of 11q23 (*MLL*)
 - B-ALL with t(1;19)(q23;p13.3) [*E2A/PBX1-(TCF3-PBX1)*]
 - Hyperdiploidy in association with trisomy, 4, 10, and 17.

Tests Available

- FISH panel for B-ALL with recurrent genetic abnormalities in children:

	CHROMOSOME ABNORMALITIES	PROBE NAMES (GENES INVOLVED)	PROBE TYPE
1.	t(9;22)	<i>ABL1/BCR</i>	Dual fusion, tri color
2.	t(12;21)	<i>ETV6/RUNX1</i>	Extra signal
3.	11q23 rearrangement	<i>MLL</i> *	Breakapart
4.	t(1;19)	<i>TCF3(E2A)</i> *	Breakapart
5.	Hyperdiploidy	CEP4, CEP 10 and CEP 17	Centromeric

*The *MLL* and *E2A* genes, located on 11q23 and 19p13.3 (respectively), have multiple translocation partners. The breakapart FISH probes for these genes can detect the rearrangement but not their translocation partners.

Indications for Ordering

FISH panel testing is indicated in pediatric patients with B-ALL at the time of diagnosis for proper classification and prognostic information. However, selected probe(s) may also be used for follow-up studies to monitor either response to therapy or progression of disease.

Methodology

- Bone marrow cells on unstimulated cultures either from direct harvest or 24-hour culture are analyzed by FISH using a set of commercially available FISH probes.
- Each probe can be run as a panel or individually.
- The FISH probes *ABL1/BCR*, *ETV6/RUNX1*, *MLL*, *TCF3 (E2A)*, CEP 4, CEP 10, and CEP 17 are set up separately for each patient.
- At least two technologists score each case.
- 200 nuclei are evaluated for each probe.
- Bone marrow samples from 20 individuals without apparent hematological diseases and with normal karyotype were used as controls to determine the cutoff value for normal variation of the probe patterns.

Additional Ordering Notes

- A sodium-heparin (green-top) tube with 3–4 mL of bone marrow is required.
- Samples should be stored at room temperature and transported at room temperature to the laboratory within 24 hours of draw.

Limitations

- This probe panel only detects specific imbalances (gain or loss of DNA) and rearrangements at specific loci on the chromosomes of interest.
- Chromosome alterations outside the regions complementary to these FISH probes will not be detected.

References

1. Chromosomal and molecular genetic aberrations of tumor cells. In *Cancer Cytogenetics*, 3rd ed. Heim S and Mitelman F, eds. 2008; Hoboken, NJ: Wiley- Blackwell, 1–736.
2. Swerdlow SH, et al. 2008. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th ed. Lyon: International Agency for Research on Cancer.

Test Information

2002719 Acute Lymphocytic Leukemia (ALL) Panel by FISH, Pediatric

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.