

FKHR by FISH on Formalin-Fixed, Paraffin-Embedded Tissue

TO DETECT FKHR GENE REARRANGEMENTS FOR THE DIAGNOSIS OF ALVEOLAR RHABDOMYOSARCOMA BY FLUORESCENCE IN-SITU HYBRIDIZATION

Test Highlights

FISH analysis provides a sensitive and specific detection of *FKHR* gene rearrangements used to diagnose alveolar rhabdomyosarcoma.

Disease Overview

- Rhabdomyosarcomas are malignant neoplasms showing differentiation toward striated muscle.
- Rhabdomyosarcoma is the most common soft-tissue sarcoma in children under 15 years of age and is one of the most common soft-tissue sarcomas of adolescents and young adults.
- Rhabdomyosarcomas account for approximately 8 percent of cancer in children. They occur rarely in patients over 45 years of age.
- The most common anatomic sites of origin are the genitourinary tract, head and neck, and retroperitoneum. The pleomorphic variety may arise in the large muscles of the extremities.
- Rhabdomyosarcomas are divided into histomorphologic and prognostic subtypes, including embryonal, alveolar, and pleomorphic. Rhabdomyosarcomas in adults are often of the pleomorphic subtype. The alveolar subtype has a demonstrably poorer prognosis than the embryonal subtype, and its separation from the latter is important for therapeutic decisions. All rhabdomyosarcomas show morphologic and immunohistochemical differentiation towards striated muscle.
- Immunohistochemically, rhabdomyosarcomas will react positively with antisera against desmin, muscle-specific actin, myogenin, and myo-D1. Anatomic site, age at diagnosis, and histopathologic type are all prognostic factors. Favorable factors include young age, orbital or genitourinary location, size under five centimeters, and a botryoid or spindle-cell pattern.

Epidemiology

- Rhabdomyosarcomas are the most common soft-tissue sarcoma in children under 15 years of age. Approximately 5 percent of patients with rhabdomyosarcomas are younger than one year of age at diagnosis, and 2 percent of tumors are present at birth.
- The embryonal, botryoid, and spindle-cell subtypes affect predominately children between birth and 15 years of age. Alveolar rhabdomyosarcoma tends to affect older patients with a peak age of 10–25 years. Hence, the majority of alveolar rhabdomyosarcomas will be found in adolescents and young adults.

Genetics

Alveolar rhabdomyosarcoma is strongly associated with a t(1;13) or t(2;13) translocation; both involve the *FKHR* gene on chromosome 13.

Pathophysiology

- The exact cause of alveolar rhabdomyosarcoma is not known. Most patients with alveolar rhabdomyosarcoma have an acquired t(1;13) or t(2;13) translocation, both of which involve the *FKHR* gene on chromosome 13. These translocations can increase the rate of cell division and growth.
- The distinction of alveolar rhabdomyosarcoma from other sarcomas, especially embryonal rhabdomyosarcoma, is important and provides prognostic and therapeutically relevant information.

Indications for Ordering

Patients diagnosed with or suspected of having alveolar rhabdomyosarcoma based on morphology or immunophenotypic studies.

Contraindications

This test is not recommended for detection of minimal residual disease.

Additional Ordering Notes

The biopsy site and fixative used should be provided. The submitted sample should contain sufficient viable tumor.

Interpretation

Presence of an *FKHR* gene rearrangement is strongly supportive of a diagnosis of alveolar rhabdomyosarcoma.

Limitations

Tissues fixed in alcohol-based or non-formalin fixatives have not been tested using this method.

Methodology

- The detection of *FKHR* gene rearrangements in formalin-fixed, paraffin-embedded tissue uses a commercially available DNA FISH probe.
- The FISH methodology for recognition of the *FKHR* gene rearrangement utilizes a SpectrumGreen-labeled probe centromeric to the *FKHR* gene and a SpectrumOrange-labeled probe telomeric to the *FKHR* gene.
- The presence of two fusion signals per nucleus indicates an intact *FKHR* gene.
- The presence of a single orange and single green signal indicates a rearranged *FKHR* gene.
- This test is conducted by noting the probe-signal configuration within the nuclei and reporting the result as rearranged or normal. The hybridization with the *FKHR* probe will identify the rearrangement or translocation of 13q14, but not the specific translocation partner.

References

1. Vysis® LSI *FKHR* Dual Color Breakapart Probe. Package insert.
2. Anderson J, et al. Detection of the PAX3-FKHR fusion gene in paediatric rhabdomyosarcoma: a reproducible predictor of outcome? *Br J Cancer* 2001;85(6):831–5.
3. Slominski A, et al. Molecular pathology of soft tissue and bone tumors: review. *Arch Pathol Lab Med* 1999;(12):1246–59.
4. Womer RB, Soft tissue sarcomas. *Eur J of Cancer* 1997;33(13):2230–4; discussion 2234–6.

Test Information

2001497

FKHR Gene Rearrangement by FISH

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.