Soft Tissue Sarcomas

KIT MUTATION FOR GIST

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Most GISTs characteristically express the KIT receptor tyrosine kinase, and approximately 80% harbor oncogenic mutations within the KIT gene. These primarily involve KIT exon 11, but may also occur in exons 9, 13, and 17. All mutations result in the constitutive activation of KIT, which has led to the use of tyrosine kinase inhibitor drugs (imatinib) as a common therapy for GIST patients. Testing for KIT mutation can aid in the diagnosis of GIST, particularly for tumors that lack KIT expression by immunohistochemistry. Mutation testing may also aid in determining prognosis, and may help predict response to imatinib therapy, both of which have been associated with specific KIT mutations. This DNA sequencing test will detect mutations within exons 9, 11, 13 and 17 of the KIT gene. The tested exons correspond to KIT amino acids 497-513 (exon 9), 550-591 (exon 11), 628-661 (exon 13), and 799-823 (exon 17). Appropriate specimens should contain an adequate proportion of tumor nuclei (>40%) to enable mutation detection.

SYT/SSX TRANSLOCATION (SYNOVIAL SARCOMA) BY PCR

Synovial sarcoma is characterized by the t(X;18)(p11;q11) translocation which occurs in over 90% of cases regardless of histologic subtype. This rearrangement leads to fusion of the SYT (SS18) gene on chromosome 18 with one of several closely related SSX genes located on the X chromosome. Approximately two-thirds of fusions are SYT/SSX1 and one-third SYT/SSX2. Other fusions are rare. Because of their high specificity and prevalence, SYT/SSX fusion transcripts are highly sensitive diagnostic markers for synovial sarcoma. Testing can aid in the differential diagnosis of synovial sarcoma, especially in tumors with unusual histologic or clinical presentations. This test qualitatively detects the SYT/SSX1 and SYT/SSX2 fusion transcripts in fresh/frozen or formalin-fixed paraffin embedded tissues.

PAX/FOXO1 TRANSLOCATION (ALVEOLAR RHABDOMYOSARCOMA) BY PCR

Rhabdomyosarcoma is a member of the group of “small round blue cell” tumors, and must be distinguished from morphologically similar pediatric tumors. Rhabdomyosarcoma includes two major histological subtypes, embryonal and alveolar. Of these, the alveolar type is associated with a worse prognosis. Two recurrent and distinctive chromosomal translocations occur in alveolar rhabdomyosarcoma. The t(2;13)(q35;q14) translocation joins the PAX3 and FOXO1 (FKHR) genes in approximately 60% of alveolar rhabdomyosarcomas, while the less common t(1;13)(p36;q14) joins PAX7 with FOXO1 in approximately 20% of cases. The juxtaposed genes lead to expression of chimeric transcripts consisting of the 5’ portion of PAX3 or PAX7 fused to the 3’ portion of the FOXO1 gene. This test qualitatively detects the PAX3/FOXO1 and PAX7/FOXO1 fusion transcripts in fresh/frozen or formalin-fixed paraffin embedded tissues. Testing can aid in distinguishing alveolar rhabdomyosarcoma from other similar tumors.
EWSR1/WT1 TRANSLOCATION (DESMOPLASTIC SMALL ROUND CELL TUMOR) BY PCR

The histologic and immunophenotypic characteristics of desmoplastic small round cell tumor (DSRCT) can overlap with that of other “small round blue cell” tumors. The recurrent t(11;22)(p13;q12) chromosomal translocation is characteristic of DSRCT and leads to fusion of the EWSR1 gene at 22q12 and the WT1 gene at 11p13. The overwhelming majority of DSRCT cases harbor this specific translocation. Because of its high prevalence, the EWSR1/WT1 fusion transcript is a highly sensitive diagnostic marker for DSRCT. Its detection can aid in the diagnosis of these tumors, especially in those with unusual histologic features or atypical presentations. This test qualitatively detects the EWSR1/WT1 fusion transcript in fresh/frozen or formalin-fixed paraffin embedded tissues.

EWSR1/ATF1 TRANSLOCATION (CLEAR CELL SARcoma) BY PCR

Greater than 90% of clear cell sarcomas harbor the reciprocal chromosomal translocation t(12;22) (q13;q12). This rearrangement joins the EWSR1 and ATF1 genes and leads to expression of EWSR1/ATF1 fusion transcripts. This test detects three EWSR1/ATF1 fusion transcript types: Type 1 (EWSR1 exon 8/ATF1 exon 4), Type 2 (EWSR1 exon 7/ATF1 exon 5), and Type 3 (EWSR1 exon 10/ATF1 exon 5) which collectively account for almost all t(12;22)-bearing clear cell sarcoma cases. Testing for EWSR1/ATF1 fusion is a useful diagnostic adjunct in the differential diagnosis of clear cell sarcoma, since malignant melanoma is not associated with this chimeric transcript.

EWSR1/FLI1 & EWSR1/ERG TRANSLOCATIONS (EWING SARCOMA) BY PCR

Ewing sarcoma (ES) is a member of the “small round blue cell” tumor group, and must be differentiated from other morphologically similar tumors. ES is characterized by recurrent chromosomal rearrangements involving the EWSR1 gene. The great majority are the reciprocal translocation t(11;22) (q24;q12), which occurs in approximately 90% of ES cases. This translocation joins the EWSR1 gene on chromosome 22 and the FLI1 gene on chromosome 11, leading to expression of EWSR1/FLI1 fusion transcripts. Alternate translocations involving EWSR1 occur with lower frequency in ES. Of these, the t(21;22)(q22;q12) translocation is the most common, with an incidence of approximately 5-10%. This rearrangement leads to fusion of the EWSR1 and ERG genes, and is also characteristic of ES. This test qualitatively detects the EWSR1/FLI1 and EWSR1/ERG fusion transcripts in fresh/frozen or formalin-fixed paraffin embedded tissues. Testing can aid in the differential diagnosis of ES.

EWSR1 (22q12) REARRANGEMENT BY FISH

This test detects rearrangements involving the EWSR1 gene region (22q12) via fluorescence in situ hybridization (FISH) in formalin-fixed, paraffin-embedded tissue specimens. FISH is performed using a dual color break apart probe (Abbott Molecular) to qualitatively assess for the presence of EWSR1 translocations that occur in soft tissue tumors including Ewing’s sarcoma/peripheral neuroectodermal tumor, desmoplastic small round cell tumor, clear cell sarcoma, angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma, and myxoid liposarcoma. Testing for EWSR1 gene rearrangement may aid in the diagnosis of these tumors. This test will detect rearrangements involving EWSR1, however it will not identify the translocation partner.

HOW TO SEND A SPECIMEN

For assistance 24 hours per day, 7 days per week, call MLabs at 800-862-7284 or visit our website at www.mlabs.umich.edu.

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