Eosinophilia Panel by FISH

Indications for Ordering

- Diagnose and classify specific eosinophilic myeloid neoplasms
  - Acute myeloid leukemia (AML) with inv(16) or t(16;16)
  - Myeloid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1
- Provide prognostic and predictive information for acute or chronic leukemia with eosinophilia
- Monitor therapeutic response

Test Description

- Performed on cultured bone marrow (BM)
  - Peripheral blood may be used
- Multiple fluorescence in situ hybridization (FISH) probes target specific genes
  - FGFR1 rearrangement
  - FIP1L1-PDGFRα region rearrangement
  - PDGFRβ rearrangement
  - CBFB/MYH11 rearrangement
- Probes can be run as a panel or individually

Tests to Consider

Primary test

Eosinophilia Panel by FISH 2002378
- Diagnosis, prognosis, and monitoring for newly diagnosed acute or chronic leukemia with eosinophilia

Related tests

Chromosome Analysis, Bone Marrow 2002292
- Diagnosis, prognosis, and monitoring of eosinophilic leukemia

Chromosome Analysis, Bone Marrow with Reflex to Genomic Microarray 2007130
- Diagnosis, prognosis, and monitoring of eosinophilic disorders
  - If chromosome analysis is “normal” or “no growth,” then genomic microarray testing will be added

Cytogenomic SNP Microarray – Oncology 2006325
- Preferred test for fresh specimens at time of diagnosis for detecting prognostically important genomic abnormalities in leukemias/lymphomas and solid tumors involving
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
- Monitor disease progression and response to therapy

Chromosome FISH, Interphase 2002298
- Specific FISH probes must be requested and include
  - PDGFRα
  - PDGFRβ
  - JAK2
  - +8
  - +9
  - Monosomy 7 or 7q deletion
  - 5q deletion
  - 13q deletion
  - 20q deletion

Myeloproliferative Disorders Panel by FISH 2002360
- Detect specific recurrent genomic aberrations in suspected MPNs
  - BCR/ABL1
  - PDGFRα
  - PDGFRβ
  - FGFR1

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117
- Assess for single gene mutations, including substitutions and insertions and deletions that may have diagnostic, prognostic, and/or therapeutic significance

Disease Overview

Consensus criteria
- 2016 WHO classification of eosinophilic myeloid disorders
  - Myeloid and lymphoid neoplasms with PDGFRα rearrangement
  - Myeloid and lymphoid neoplasms with PDGFRβ rearrangement
  - Myeloid and lymphoid neoplasms with FGFR1 rearrangement
  - Chronic eosinophilic leukemia-not otherwise specified (CEL-NOS)
  - Myeloid and lymphoid neoplasms with PCM1-JAK2 (provisional entity)

Incidence/prevalence
- PDGFRα/B- and FGFR1-related disorders are not well characterized
- inv16; t(16;16)
- 5-8% of AMLs, predominantly in childhood

Diagnostic criteria
- See Table 1
Table 1

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Features</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML with inv(16)(p13.1q22)</td>
<td>Present as AML</td>
<td>Morphology — acute myelomonocytic leukemia with increased eosinophils containing immature eosinophilic granules in the BM</td>
</tr>
<tr>
<td>or t(16;16)(p13.1;q22); CBFB-MYH11</td>
<td>Myeloid sarcomas may be present at initial diagnosis or relapse</td>
<td>o Peripheral eosinophilia is unusual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Diagnosis of AML even if blasts &lt;20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Genetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o inv(16)(p13.1q22) or t(16;16)(p13.1;q22) found in most cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o FISH or PCR may be necessary to document this genetic alteration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Secondary cytogenetic abnormalities +22, +8, del(7q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o KIT mutations may be present</td>
</tr>
<tr>
<td>Myeloid and lymphoid neoplasms with</td>
<td>Most frequently presents as CEL, but may present as AML, T-lymphoblastic</td>
<td>Morphology — peripheral blood and BM eosinophilia (markedly elevated)</td>
</tr>
<tr>
<td>PDGFRA rearrangement</td>
<td>lymphoma, or both</td>
<td>o Typically &lt;20% blasts in peripheral blood and BM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Increased BM mast cells common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Genetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Absence of BCR-ABL1 fusion gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Most commonly associated with FIP1L1-PDGFRB fusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o FISH or PCR is usually necessary to document this genetic alteration;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytogenetic studies are normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Other fusion genes have rarely been identified</td>
</tr>
<tr>
<td>Myeloid and lymphoid neoplasms with</td>
<td>Presents with features of chronic myelomonocytic leukemia (usually with</td>
<td>Morphology — peripheral leukocytosis</td>
</tr>
<tr>
<td>PDGFRB rearrangement</td>
<td>eosinophilia</td>
<td>o Hypercellular BM with typically &lt;20% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Increased BM mast cells common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Genetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Most common rearrangement — t(5;12)(q31-33;p13), resulting in ETV6-PDGFRB</td>
</tr>
<tr>
<td>Myeloid and lymphoid neoplasms with</td>
<td>Often presents with peripheral eosinophilia in the context of lymphadenopathy and lymphoblastic leukemia/lymphoma</td>
<td>Morphology — AML, acute lymphoblastic leukemia (ALL), CEL (usually associated with peripheral blood or BM eosinophilia)</td>
</tr>
<tr>
<td>FGFR1 rearrangement</td>
<td>Slight male predominance</td>
<td>Genetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Presence of t(8;13)(p11;q12) or a variant rearrangement at the 8p11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>breakpoint leading to FGFR1 rearrangement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Secondary cytogenetic abnormalities +21 most often observed</td>
</tr>
</tbody>
</table>

In conclusion, ARUP LABORATORIES provides a comprehensive analysis of genetic markers and their implications in the context of hematological disorders. The table highlights specific features and laboratory findings related to various neoplasms, emphasizing the importance of diagnostic accuracy and the role of genetic testing in clinical decision-making. The use of advanced technologies such as FISH and PCR is crucial for identifying genetic alterations, which can guide therapeutic strategies and patient outcomes.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Structure/Function</th>
<th>Mutations</th>
<th>WHO Disease Association</th>
</tr>
</thead>
</table>
| **CBFB-MYH11** | • CBFB o 16q22 o Core binding transcription factor  
• MYH11 o 16p13.1 o Codes for smooth muscle myosin heavy chain | • inv(16)(p13.1q22) or (t16;16)(p13.1;q22)  
• Inversion results in fusion of CBFB on 16q22 to MYH11 on 16p13.1 | AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); previously FAB M4Eo |
| **PDGFA**  | • Maps to 4q12  
• Cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family  
• Results in a constitutively active tyrosine kinase oncoprotein | • FIP1L1-PDGFA rearrangement is a karyotypically occult 800-kb interstitial deletion (ie, CHIC2 deletion) | Myeloid and lymphoid neoplasms with PDGFA rearrangement |
| **PDGFRB** | • Maps to 5q31-33  
• Cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family  
• Results in a constitutively active tyrosine kinase oncoprotein | • 20 fusion partners reported  
• Most common rearrangement – t(5;12)(q31-33;p13) resulting in ETV6-PDGFRB fusion | Myeloid and lymphoid neoplasms with PDGFRB rearrangement |
| **FGFR1**  | • Maps to 8p11  
• Cell surface tyrosine kinase  
• Rearrangement results in constitutive activation of FGFR1 with the fusion of the FGFR1 C-terminal catalytic domain with unrelated proteins | • >10 fusion partners identified  
• Most common rearrangement – t(8;13)(p11;q12) resulting in ZNF198-FGFR1 fusion | Myeloid and lymphoid neoplasms with FGFR1 rearrangement |