Technical Brief

FISH for 4q12 Rearrangements *(PDGFRA/FIP1L1)*

Background Information

A *PDGFRA/FIP1L1* fusion gene is present in an atypical myeloproliferative neoplasm that is characterized by a proliferation of eosinophils and mast cells.[1,2] Prior classification schemes have characterized such patients as hypereosinophilic syndrome, chronic eosinophilic leukemia, or systemic mastocytosis with eosinophilia. The 2008 revision of the World Health Organization (WHO) classification now recognizes myeloid neoplasms with *PDGFRA* rearrangements as a distinct diagnostic category.[3] Recognition of the *PDGFRA/FIP1L1* fusion gene also helps guide the choice of therapy, based on the knowledge that patients with this fusion gene are sensitive to imatinib.[1,2]

The *PDGFRA* and *FIP1L1* genes normally are located on chromosome 4q12, which means that this fusion gene cannot be detected by metaphase cytogenetics alone.[1-3] In the presence of a *PDGFRA/FIP1L1* fusion, FISH studies will identify retention of the *PDGFRA* and *FIP1L1* loci with loss of the intervening region of DNA that includes the *CHIC2* gene (Figure 1).

Clinical Indications

FISH for 4q12 rearrangements may be useful for:

1. Evaluation of unexplained eosinophilia or
2. Further classification of patients with systemic mastocysis, especially those with peripheral blood eosinophilia.

Interpretation

200 nuclei are scored.

≥ 8% nuclei exhibit a positive signal pattern = positive for *PDGFRA/FIP1L1*

< 8% nuclei exhibit a positive signal pattern = negative for *PDGFRA/FIP1L1*

Limitations of the Assay

False negative results will occur if the malignant cells represent < 8% of the total cells present.

Methodology

FISH studies are performed on gravity preparations of peripheral blood or bone marrow. Hybridizations are performed using a tri-color fusion probe (Abbott Molecular, Abbot Park, Ill).

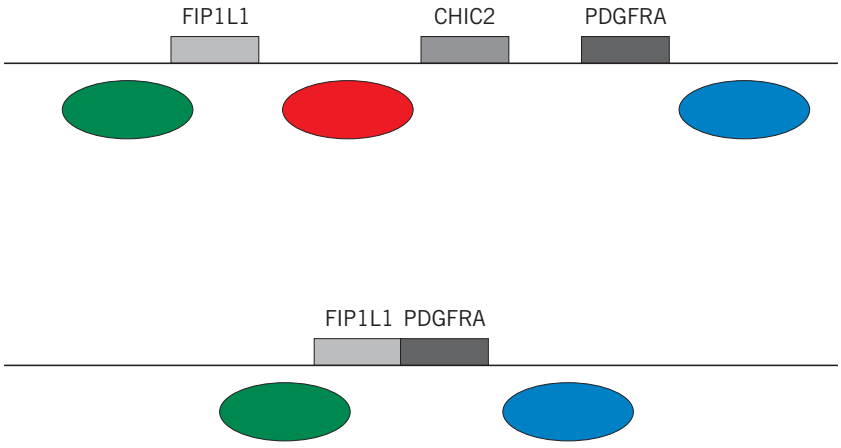

Figure 1. A three-color FISH probe for 4q12 is employed, including a green probe adjacent to *FIP1L1*, an aqua probe adjacent to *PDGFRA*, and a red probe that hybridizes to an intervening region that includes the *CHIC2* gene (Top). In the presence of a *FIP1L1/PDGFRA* fusion gene, the red signal is deleted, and the green and blue signals are retained (bottom).

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References

1. Cools J, DeAngelo DJ, Gotlib J, *et al*. A tyrosine kinase created by fusion of the *PDGFRA* and *FIP1L1* genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *New Engl J Med* 2003;348:1201-14.
2. Pardanani A, Ketterling RP, Brockman SR, *et al*. *CHIC2* deletion, a surrogate for *FIP1L1/PDGFRA* fusion, occurs in systemic mastocytosis with eosinophilia and predicts response to imatinib mesylate therapy. *Blood* 2003;102:3093-3096.
3. Tefferi A and Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic alogorithms. *Luekemia* 2008;22:14-22.

Test Overview

Test Name	FISH for 4q12 Rearrangements or FISH for CHIC2 anomalies
Reference Range	0-7% abnormal nuclei
Specimen Requirements	8 mL whole blood or 5 mL bone marrow in EDTA
Ordering Mnemonic	4q12F
Billing Code	84318
CPT Code	88368 (x3)

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