MOLECULAR DIAGNOSIS OF FAMILIAL MEDITERRANEAN FEVER by PCR

Familial Mediterranean Fever (FMF) is the prototype of periodic febrile syndromes. This autosomal recessively inherited disease predominantly affects four Mediterranean ancestral groups: Sephardic Jews, Arabs, Turks and Armenians. In high-risk populations, the carrier frequency of this genetic defect can be as high as one in five to ten. Although molecular genetic testing has become extremely important in suspected cases, the diagnosis of FMF and the exclusion of other diseases remains essentially clinical. The differential diagnoses include hereditary periodic fevers, hyper-immunoglobulinemia-D (HIDS), the tumor-necrosis-factor-1-associated periodic syndrome (TRAPS), the PFAPA syndrome and Behcet's syndrome.

The clinical syndrome of FMF has as its classic hallmarks short, acute, self-limited episodes of fever lasting several days. Up to 90% of patients have an associated peritoneal or abdominal pain syndrome, or a 50% frequency of unilateral pleuritis. Acute synovitis and arthritis are probably the second most common manifestations of FMF, with unusual clinical presentations and durations, including acute short-lived lower extremity monoarthritis to persistent chronic lower extremity arthropy. Approximately half of all affected patients may have an associated dermatologic syndrome (an erysipelas-like erythematous rash particularly over the shins and lower extremities). The great majority of FMF attacks occur under the are of 20; thurs, early onset of the disease helps in its early diagnosis. It is critical to make an early accurate diagnosis so that therapy may be instituted with colchicine to decrease the frequency and/or severity of clinical attacks, decrease the widespread tissue deposition of serum amyloid (SAA) protein, and thus, most importantly, prevent the long-term lethal complications of amyloidosis.

In 1977, two independent groups cloned the specific gene for FMF (MEFV). The gene, localized on the short arm of chromosome 16, encodes a protein (pyrin/marenostrin) involved in polymorphonuclear cell inflammatory events. To date, more than 17 gene mutations have been identified in the four main ethnic groups and they are generally relegated to four of the ten gene exons. Most DNA changes are nucleotide substitutions, with 80% of typical cases appearing within exon 10 (see table 1). In some studies, the clinical expressions of FMF has been associated with one or more of these genetic traits, with another major pathologic allele. To date there has been no consistent correlation between a particular mutation, type of severity of FMF symptomatology or penetrance, and the proven evolution to amyloidosis. There is a suggestion that a significant association does exist between amyloidosis and the M694V mutation. Alternatively, FMF may be suspected in certain clinical syndromes where the genetic diagnosis is heterogenous with either a pre-clinical or low penetrance frequency. Family studies of definite FMF probands may be important in the future for the consideration of more careful follow-up and preventive colchicine therapy.

<table>
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<tr>
<th>Exon</th>
<th>Mutations</th>
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<tbody>
<tr>
<td>2</td>
<td>E148Q, E167D, T267I</td>
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<tr>
<td>3</td>
<td>P369S</td>
</tr>
<tr>
<td>5</td>
<td>R408Q, F479L</td>
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<tr>
<td>10</td>
<td>M680I (x2), T681I, 1692del, M694del, M694V, M694I, K695R, V726A, A744S, R761H</td>
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RDL, Inc. can now identify ten of the most common mutations known to be associated with the clinical syndrome of FMF; our assays detect the presence or absence of the three major mutant genes (M680I, M694V, V726A) responsible for FMF. A negative result does not absolutely exclude FMF in that several other mutant genes can be causative, although rarely, in producing FMF. Our MEFV mutation screening for these ten mutations in individuals suspected of having FMF can confirm the clinical diagnosis. Previous studies have shown that mutational genetic screening can be extremely helpful in corroborating the clinical diagnosis, in the subsequent evaluation for family members at risk for the development of FMF, and in understanding the complex relationship between gene mutations and presence or absence of frank clinical disease.

**Guide to Interpretation**

Genetic testing is only an adjunct to the clinical suspicion and/or diagnosis of FMF. Limitations to genetic mutational testing include the presence of only one of the most frequently defined mutations, the presence of no mutational genetic markers currently defined, or potentially incomplete mutational testing in suspected or confirmed cases of FMF. Pre-clincal, low penetrance disease or carrier states may be either homozygous or heterozygous for genetic mutational markers as most frequently defined from exons 2, 3, 5 or 10. Overall, genetic testing may be helpful in approximately 70% of clinically certain FMF patients who are homozygous or compounded heterozygous for any of the MEFV mutations.

**SPECIMEN REQUIREMENTS**

Two ACD Solution A (yellow) tubes at room temperature. Do not spin, separate or refrigerate. Send overnight express mail.

**REFERENCES**


