Familial Mediterranean fever (FMF) is a systemic auto-inflammatory disorder, characterized by seemingly unprovoked recurrent episodes of fever and localized inflammation usually involving the peritoneum, pleura and joints accompanied by a marked acute-phase response. The disease primarily affects populations living around the Mediterranean basin (Jewish, Armenian, Arab, Turkish populations) but is also scattered throughout the western world due to extensive population movements of the 20th century [1,2]. Although FMF is an ancient disease and the most common inherited
periodic syndrome, only after the 1970s, were its clinical features understood and the pertinent treatment discovered [3-5]. In 1997, two independent groups defined the gene responsible for FMF (designated MEFV for Mediterranean fever) on chromosome 16p13.3 by positional cloning and this was a major milestone in perceiving this auto-inflammatory disease [6,7].

The discovery of the MEFV gene has led to a molecular approach to diagnosis, aiming at improving the global diagnosis of the disease. MEFV is comprised of ten exons encoding 781 amino acids, and the protein product has been named pyrin (or marenostrin). It is thought that the major role of pyrin is the regulation of caspase-1 activation, and the inflammatory phenotypes of FMF are induced by IL-1β and NF-κB, which are abnormally activated by FMF-associated mutations in the C-terminal domain of pyrin. At a molecular level, FMF associated pyrin mutations might lead to a gain of function, with gene dosage effect, rather than a loss of function, as would be expected for more straightforward recessive diseases [8]. Genotyping has shown that the disease is associated with a wide variety of symptoms. On the other hand, a genotype-phenotype relationship is not well established and the spectrum of the clinical findings may differ considerably from one patient to the other. Any patient with two mutations may be defined to have FMF on genetic grounds but may not always have the phenotype. This situation is more complex for individuals with one MEFV mutation. During genetic analysis of patients with FMF in various countries, besides the presence of patients with homozygous and compound heterozygous mutations, some patients had single mutations and some had none of the studied mutations. Interestingly, patients who bear no MEFV mutations are phenotypically similar to patients with recognizable mutations. Heterozygotes constitute approximately 24%-34% of the patient population in different studies [9-12]. In these patients, it is assumed that there are mutations in other parts of the gene or other genes that have not been identified yet. On the other hand, in the populations of the eastern Mediterranean basin, the carrier frequencies of mutant alleles are extremely high (1:3-1:5 in some populations), the highest rates reported for an autosomal recessive disorder [13-14]. Despite high carrier frequencies in our and other severely affected populations, the prevalence of FMF is less than expected; indicating that the disease is under diagnosed. For example, the estimated prevalence of FMF in Turkey is 0.1% [15]; however the largest series reported from our country included only 5% of the total number of FMF cases in the country [16]. Limited genetic molecular testing for MEFV mutations may explain some of the FMF clinical variability, but is diagnostically ineffective. The value of the molecular approach has been established in patients with a high suspicion of clinical diagnosis and who satisfied proposed criteria. However, the diagnostic value of the molecular tests in patients with atypical or mild signs, especially in those who do not satisfy clinical criteria, is unknown. Furthermore, it is not always possible to obtain genetic analysis and it is expensive. Certain data may need to be shown for the justification of genetic testing for insurance companies in countries where the disease is not endemic. Therefore, the use of clinical criteria remains essential in establishing the diagnosis of FMF.

Given the absence of pathognomical clinical or easily available biochemical abnormalities, the diagnosis of FMF was based on clinical suspicion and the use of criteria. It is crucial to establish the diagnosis of FMF, since it leads to the beginning of a daily and lifelong administration of colchicine, which is an efficient preventive treatment of both the attacks and amyloidosis [1]. Reactive AA amyloidosis is the most devastating complication of FMF. Prior to the discovery of colchicine prophylaxis up to 60% of patients with FMF died of amyloidosis [17,18]. Colchicine changed the course of disease in many patients and prevents the development of systemic amyloidosis in the long term [19]. However, amyloidosis continues to occur in the colchicine era in untreated and noncompliant patients. Recently, it has been reported in 12.9% of patients in a large series from Turkey [16] and also in 11.4% of patients of the metaFMF database [20]. Delay in diagnosis of FMF is one of the most important risk factors for the development of amyloidosis [16]. Furthermore, there was a significant negative correlation between the age at disease onset and duration of delay in diagnosis in pediatric patients. Therefore, the smaller the age of disease onset, the more likely their diagnoses are delayed [21]. Padeh et al [22] reported similar results and showed that diagnostic delay was more common in patients...
with disease onset ≤ 2 years of age. Therefore, evolution of di-
agnostic criteria for FMF patients especially for pediatric pa-
tients is critically important.

Several sets of criteria for adults have been proposed for
the diagnosis of FMF [3, 23-27]. However, many of these cri-
teria are based on personal or institutional experience, but not
on patient-versus-control evaluation and statistical methods
and none became widely accepted. The sole criteria to be vali-
dated were those of Livneh et al [27] and Yalçinkaya et al [28].
We will briefly consider some of these criteria and discuss the
two validated criteria extensively in the following section.

In 1967, Sohar et al [23] emphasized the role of follow-
ing points in the diagnosis of FMF: [1] Short attacks of fever
recurring at varying intervals; [2] painful manifestations in the
abdomen, chest, joints or skin, accompanying the fever; [3]
absence of any causative factor or pathologic finding, in vivo
or postmortem, capable in itself of explaining the picture; [4]
amyloidosis, clinically of the nephropathic and anatomically
of the perireticulin type; [5] features of autosomal recessive
inheritance; [6] preference for people of Mediterranean stock,
particularly Sephardic Jews and Armenians. The first three
points are obligatory for the diagnosis of the common variant
of FMF. A Sephardic ethnic origin, an affected sibling or par-
et, and the presence of amyloidosis are of great value in situa-
tions of diagnostic doubt.

Booth et al [26] proposed their own criteria: major cri-
teria were (a) periodic fever with acute phase response; (b)
absence of any other pathology capable of causing the clini-
cal picture; (c) typical painful manifestations in the abdomen,
chest, joints or skin. Minor criteria were (i) a well-documented
therapeutic response to colchicine; (ii) AA amyloidosis;
(iii) features of autosomal recessive inheritance; (iv) Seph-
ardic Jewish, Levantine Arabic, Armenian or Turkish ancestry.
Patients were designated as classical FMF if all major criteria
were fulfilled plus at least three minor points.

One of the most commonly used criteria is that of Tel
Hashomer which have been established in the Jewish adult
population (Table 1) [25].

In 1997, Livneh et al [27] established a set of criteria for
the classification of FMF in adults (Table 2), which was also
named as Tel Hashomer criteria [1]. Twenty-seven features
and manifestations typical of FMF were studied to determine
their prevalence in 105 patients with FMF and 106 controls.
Diagnosis of FMF in the study group was based on clinical
judgment. Controls were patients with a variety of other dis-
eases who presented to the emergency room or outpatient
clinics with recurrent episodes of pain in body sites usually in-
volved in FMF attacks. Manifestations observed to be signifi-
cantly more common in FMF patients than in controls were
incorporated into the rule proposed for diagnosis of FMF,
based on a model of major, minor, and supportive criteria. Two
sets of diagnostic criteria were established (Table 2A&2B). A
conservative criteria set for diagnosis of FMF was based on the
presence of 1 major or 2 minor criteria, or 1 minor plus 5 sup-
portive criteria, and a simple criteria set for diagnosis of FMF
required 1 major or 2 minor criteria. The sensitivity and speci-
ficity of these 2 criteria sets were >95% and >97%, respectively.
The Livneh’s criteria differ from the previous ones, by defining
the criteria more accurately and excluding rare manifestations
such as amyloidosis from the criteria set. Previously, this seri-
ous manifestation was common at the time of presentation
and during the course of the disease and therefore an impor-
tant diagnostic criterion. But today early diagnosis and colchi-
cine therapy prevent the development amyloidosis and made
amyloidosis an insensitive criterion. We also had to diagnose
FMF prior to amyloidosis development. On the other hand,
some handicaps of these criteria were recognized especially

<table>
<thead>
<tr>
<th>Table 1. Tel Hashomer criteria for the diagnosis of FMF</th>
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<tbody>
<tr>
<td><strong>Major criteria</strong></td>
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<tr>
<td>1. Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis</td>
</tr>
<tr>
<td>2. Amyloidosis of the AA type without predisposing disease</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>1. Recurrent febrile episodes</td>
</tr>
<tr>
<td>2. Erysipelas-like erythema</td>
</tr>
<tr>
<td>3. FMF in a first-degree relative</td>
</tr>
<tr>
<td><strong>Definite diagnosis</strong></td>
</tr>
<tr>
<td>2 major or 1 major and 2 minor criteria</td>
</tr>
<tr>
<td><strong>Probable diagnosis</strong></td>
</tr>
<tr>
<td>1 major and 1 minor criteria</td>
</tr>
</tbody>
</table>
in pediatric patients. Some children could not express the severity and location of the pain, chest pain is not always unilateral, the duration of the attacks can be shorter than 12 hours and fever can be absent in some of the attacks. Moreover, the minor or supportive criteria included features of the disease not associated with the attacks, such as the ethnic origin, the presence of age <20 yrs at disease onset, removal of appendix and consanguinity of the parents. These minor and supportive criteria increase the sensitivity of Livneh's criteria in FMF patients. However, we should keep in mind that minor and supportive criteria also decrease the specificity of Livneh’s criteria in childhood [28].

Recently, in 2009, Yalcınkaya et al [28] established a new set of criteria for the diagnosis of FMF in childhood (Table 3). This is the first attempt to develop classification criteria for FMF to be used in childhood based on a genetically confirmed cohort. The study group consisted of 170 recently diagnosed FMF patients who had mutations at two alleles. Controls were 141 consecutive patients without FMF who had episodes of fever and clinical features mimicking that of FMF. The study began with 35 independent variables. Multiple logistic regres-

### Table 2A. Livneh criteria set for the diagnosis of familial Mediterranean fever*

<table>
<thead>
<tr>
<th>Major criteria</th>
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<tr>
<td>Typical attacks of:</td>
</tr>
<tr>
<td>1. Peritonitis (generalized)</td>
</tr>
<tr>
<td>2. Pleuritis (unilateral) or pericarditis</td>
</tr>
<tr>
<td>3. Monoarthritis (hip, knee, ankle)</td>
</tr>
<tr>
<td>4. Fever alone</td>
</tr>
</tbody>
</table>

**Minor criteria**

1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine

**Supportive criteria**

1. Family history of FMF
2. Appropriate ethnic origin
3. Age ≤20 years at disease onset

**4-7. Features of attacks**

4. Severe, requiring bed rest
5. Spontaneous remission
6. Symptom-free interval
7. Transient inflammatory response, with one or more test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
8. Episodic proteinuria/hematuria
9. Unproductive laparotomy or removal of white appendix
10. Consanguinity of parents

*The requirements for diagnosis of FMF are ≥ 1 major criteria, or ≥2 minor criteria, or ≥1 minor criterion plus ≥5 supportive criteria, or ≥1 minor criterion plus ≥4 of the 5 supportive criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (rectal temperature of 38°C or higher, and short (lasting between 12 hours and 3 days). Incomplete attacks are defined as painful and recurrent attacks that differ from typical attacks in one or two features, as follows: 1) the temperature is normal or lower than 38°C; 2) the attacks are longer or shorter than specified (but not shorter than 6 hours or longer than a week); 3) no signs of peritonitis are recorded during the abdominal attacks; 4) the abdominal attacks are localized; 5) the arthritis is in joints other than those specified. Attacks are not counted if they do not fit the definition of either typical or incomplete attacks.

### Table 2B. Livneh criteria set for the diagnosis of familial Mediterranean fever*

<table>
<thead>
<tr>
<th>Major criteria</th>
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</thead>
<tbody>
<tr>
<td>Typical attacks of:</td>
</tr>
<tr>
<td>1. Peritonitis (generalized)</td>
</tr>
<tr>
<td>2. Pleuritis or pericarditis (unilateral chest pain)</td>
</tr>
<tr>
<td>3. Monoarthritis (hip, knee, ankle)</td>
</tr>
<tr>
<td>4. Fever alone</td>
</tr>
</tbody>
</table>

**Minor criteria**

1-2. Incomplete attacks involving 1 or more of the following sites:

1. Chest
2. Joint
3. Exertional leg pain
4. Favorable response to colchicine

*The requirements for diagnosis of FMF are ≥ 1 major criteria or ≥2 minor criteria. Typical attacks and incomplete attacks are defined in Table 2A. Attacks are not counted if they do not fit the definition of either typical or incomplete attacks.

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Table 3. Yağışkaya criteria for the diagnosis of FMF

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>Fever</td>
<td>Axillary temperature of &gt; 38°C, 6-72 hours of duration, ≥ 3 attacks</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6-72 hours of duration, ≥ 3 attacks</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6-72 hours of duration, ≥ 3 attacks</td>
</tr>
<tr>
<td>Arthritis</td>
<td>6-72 hours of duration, ≥ 3 attacks, oligoarthritis</td>
</tr>
<tr>
<td>Family history of FMF</td>
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</tbody>
</table>

Analysis showed that 5 of the 35 candidate criteria discriminate FMF from controls with a sensitivity and specificity of 88.8% and 92.2%, respectively. The presence of at least two of these five criteria had the highest sensitivity (86.5%) and specificity (93.6%) for the diagnosis of FMF. The sensitivity of the new criteria set is also high in patients who had a mutation at a single allele (93%) [29]. The major advantage of these criteria is that it is practical to use them on an everyday basis and they thoroughly define the characteristics of the attack. The major drawback was the fact that all patients were of Turkish origin and this limited the number of periodic fever syndromes among controls. Thus, these criteria should be validated in other ethnic origins; among homozygous and heterozygous patients. Accordingly, Federici et al. [30] compared the new criteria with Tel Hashomer criteria in a large pediatric cohort of western European children with periodic fever including patients with MEFV, MVK and TNFRSF1A mutations. They found that the pediatric criteria show a higher specificity when compared to Tel Hashomer criteria (76% & 33.2%). Then, the first validation in French patients was published [31]. Kondi et al compared the Tel Hashomer criteria with the new pediatric criteria in 100 FMF patients and in a small control group with 40 patients (28 with the periodic fever, adenitis, pharyngitis, and aphthosis syndrome and 12 with unexplained recurrent fever). Comparison between the Tel Hashomer criteria vs Yağışkaya’s criteria in the FMF group gave a sensitivity of 99% vs 100% and a specificity of 45% vs 50%. However, when they used at least three Yağışkaya’s criteria, they obtained a sensitivity of 77% and a specificity of 95%. Thus, it seems that the sensitivity of the new, easily applicable pediatric criteria was also very high in the French FMF patients. After a period of 10 years without an attempt for diagnostic criteria development, Yağışkaya’s criteria open a new discussion among physicians dealing with FMF throughout the world.

In countries where FMF prevalence is rather low, physicians are not particularly alert for suspecting FMF. In addition, the periodic nature of the disease often prevents the correct diagnosis, especially if different physicians follow the patient. We suggest that usage of easy, universal diagnostic criteria will help physicians interpret the symptoms correctly and think of FMF as a possible diagnosis. Moreover, diagnostic criteria are needed for scientific purposes to serve as standard cornerstones for comparison between patient cohorts.

In conclusion, the diagnosis of FMF is still a clinical one. Mutation analysis of the MEFV gene may fail to show two mutations in some patients and the pediatricians need reliable clinical criteria to guide them.

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