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Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever

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ABSTRACT

Familial Mediterranean fever (FMF) is a disease of early onset which can lead to significant morbidity. In 2012, Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched with the aim of optimising and disseminating diagnostic and management regimens for children and young adults with rheumatic diseases. The objective was to establish recommendations for FMF focusing on provision of diagnostic tools for inexperienced clinicians particularly regarding interpretation of *MEFV* mutations. Evidence-based recommendations were developed using the European League against Rheumatism standard operating procedure. An expert committee of paediatric rheumatologists defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey and statements with less than 80% agreement were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique and were accepted if more than 80% agreement was reached. The literature search yielded 3386 articles, of which 25 were considered relevant and scored for validity and level of evidence. In total, 17 articles were scored valid and used to formulate the recommendations. Eight recommendations were accepted with 100% agreement after the consensus meeting. Topics covered were clinical versus genetic diagnosis of FMF, genotype–phenotype correlation, genotype–age at onset correlation, silent carriers and risk of amyloid A (AA) amyloidosis, and role of the specialist in FMF diagnosis. The SHARE initiative provides recommendations for diagnosing FMF aimed at facilitating improved and uniform care throughout Europe.

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease (AID) mainly affecting the populations originating from Mediterranean basin.[1 2] It is the only AID with high prevalence in specific ethnicities, including Turks, Arabs, non-Ashkenazi Jews and Armenians.[3] FMF is characterised by recurrent attacks of fever associated with serositis. Its main long-term complication is amyloid A (AA) amyloidosis, a severe manifestation with poor prognosis. Colchicine remains the therapeutic choice to prevent both FMF attacks and complications,[4] but before committing to daily, lifelong treatment, it is crucial to establish a correct diagnosis. Until recently, FMF was diagnosed in paediatric patients using clinical criteria created for adults. Delay in the appearance of the complete clinical picture in very young children,[5] presence of atypical signs, absence of a suggestive family history and uncertainty of the family provenance may cause additional diagnostic difficulties in this age group.

Mutations in the *MEFV* gene, on chromosome 16 (16p13.3), encoding a protein named marenostrin or pyrin[6 7] were found to underlie FMF in 1997 and the majority of patients demonstrate a Mendelian autosomal recessive pattern of inheritance.[6–8] Over time, the number of mutations recognised as related to FMF has increased.[9] At first, it was believed that genetic testing would enable physicians to completely resolve the diagnostic difficulties associated with FMF and so to prevent its complications. However, over time, it has become clear that diagnostic interpretation can be very complex as some FMF patients may display no or only one of the known *MEFV* mutations,[10] and conversely that the carriage of *MEFV* variants is not always accompanied by clinical symptoms.

In 2012, a European initiative called Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched to optimise management regimens in Europe for children and young adults with rheumatic diseases. For FMF, the aim was to provide a diagnostic tool for inexperienced physicians to optimally manage FMF in their clinical practice and facilitate interpretation of the diagnostic value of *MEFV* gene mutations in predicting FMF phenotype.

METHODS

The development of consensus recommendations for FMF was based on published data extrapolated by a systematic literature review and focused on five main topics:

- Clinical versus genetic diagnosis of FMF
- Genotype–phenotype correlation
- Genotype–age at onset correlation
- Silent carriers and risk for amyloidosis
- Role of the specialist in FMF diagnosis.

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Systematic review

A literature search was performed in the PubMed, Embase and Cochrane databases in June 2013 following the European League against Rheumatism (EULAR) recommendations for developing best practices.[11] Search terms for titles, abstracts and MeSh/EmTree terms included 'Familial Mediterranean Fever', 'periodic fever syndrome/s', 'autoinflammatory disease/s' and synonyms. A manual search of all references in the included articles was performed and reviews were checked for missing articles. Figure 1 summarises the search algorithm. The search was limited to English language papers published after 1970.

Screening and selection of papers

Two authors (NMTH and SO) excluded duplicate articles and selected papers according to predefined criteria (figure 1), including those reporting at least 10 FMF patients and discussed possible discrepancies. When the same patients were described in more than one paper, only the new, relevant information was

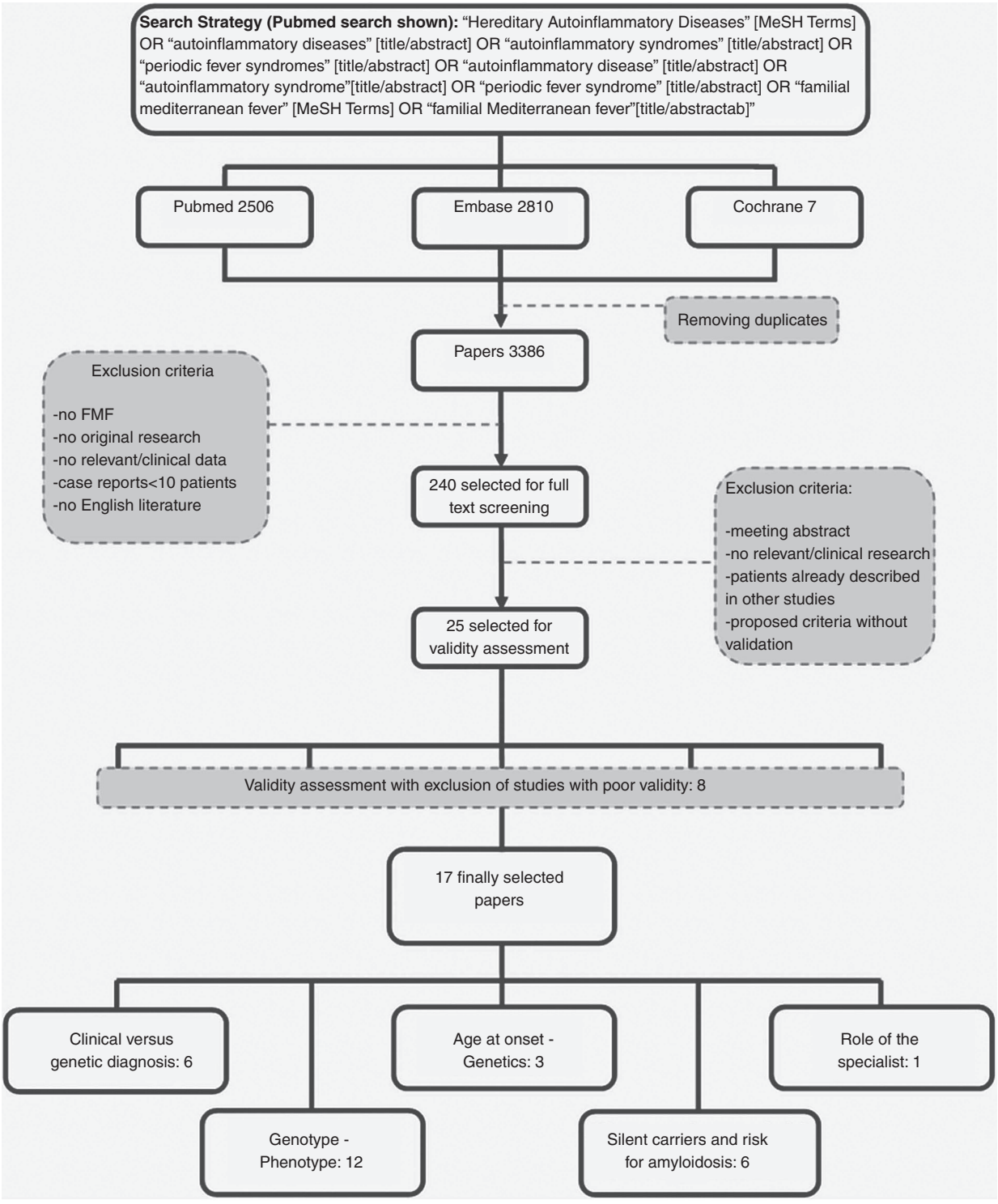

Figure 1 Flowchart of the strategy for search and selection of articles. The total number of papers per category is higher than the total number of papers selected for validity assessment because one paper could be selected for more than one category.

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Table 1 Level of evidence for diagnostic procedures

1A	Meta-analysis of cohort studies
1B	Meta-analysis of case-control studies
2A	Cohort studies
2B	Case-control studies
3	Non-comparative descriptive studies
4	Expert opinion

Table 2 Strength of recommendations

A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

included. If non-validated clinical criteria were proposed, the paper was excluded as well.

Validity assessment

A core group of six FMF experts (SO, YU, VH, TK, KB and HO) from different countries evaluated the selected papers using predefined scoring forms. The forms included both the data required and methodological quality of the papers. The validity of the studies, all diagnostic, was assessed according to Whiting *et al*.[12] Each paper was scored by two experts independently and discrepancies were discussed between them in order to reach a consensus. The level of evidence was assessed according to guidelines for diagnostic procedures furnished by Zhang *et al*[13] (table 1).

Recommendations

Data from the included papers were extrapolated by one author (GG) to formulate statements related to the initial questions and submitted to two FMF experts (SO and YU), appointed as supervisors of the entire process. The resulting statements were resubmitted to a larger group of 21 AID experts of the SHARE project, including the core group of six FMF experts. Experts completed a web-based survey in which they agreed or disagreed with each statement, commenting and reformulating it where necessary. Statements with agreement lower than 80% were considered priorities for further discussion; those with ≥80% agreement were considered preliminarily approved, pending ratification of the final sentence structure at the consensus meeting.

Consensus

Fourteen experts discussed the recommendations in a consensus meeting in Genova (Italy) on 18 March 2014 using nominal group technique (NGT). NGT is a structured face-to-face meeting designed to encourage equal participation from group members and to result in a set of prioritised solutions or recommendations.[14] A moderator (BF) mediated the discussion of each statement according to NGT procedures. For each statement, participants spent approximately 20 min sharing comments and thoughts, explaining disagreement if present, and finally suggesting the official statement of the recommendation. Comments were registered in real time. Each statement was voted on at the beginning, in its original structure, and considered approved when at least 12 of 14 experts agreed (86%). If not, the statement was reformulated and voted on again at the end of the discussion. If agreement was not reached after discussion, the statement was discarded. The strength of each recommendation was graded according to EULAR standardised operating procedures (table 2).[11]

RESULTS

Among 3386 papers on FMF found in the literature search, 240 were considered relevant and selected for full text screening (figure 1), with 25 deemed suitable for validity assessment. Of these 25 papers, 17 were judged valid[15–31] by the three pairs of FMF experts and used for the derivation of the recommendations (figure 1). Nine diagnostic recommendations were suggested in the online survey and eight were accepted with 100% agreement after the consensus meeting.

Clinical versus genetic diagnosis of FMF

In general, the diagnosis of FMF is clinical and despite molecular advances and attempts to validate specific clinical criteria, there are still patients for whom definitive diagnosis or exclusion of FMF remains deeply problematic.

The Tel Hashomer Hospital created the first criteria for FMF based on observations in the adult Israeli population.[32 33] In 1997, new criteria were validated by Livneh *et al*[34] to corroborate some clinical elements included in the Tel Hashomer criteria but excluding other manifestations like amyloidosis, which are less common at onset. Two versions, one more conservative and extensive than the other, were created, both with a sensitivity and specificity above 95%. The evidence that some criteria were of little or no relevance to children with FMF and the differences in some clinical manifestations in younger ages (shorter attacks, not always unilateral chest pain, isolated or missing fever in some patients) prompted the Turkish group to formulate new FMF criteria for the paediatric population in 2009 (the Turkish FMF Pediatric criteria).[35] However, the validation of these criteria in other ethnic groups and/or in more genetically heterogeneous populations is still limited (figure 2).[36] Although clinical criteria represent an invaluable tool for FMF diagnosis, they are ultimately restricted to clinical experience and therefore are somewhat open to interpretation by inexperienced physicians who are not familiar with FMF, even in regions with high prevalence, increasingly favouring genetic confirmation to support a clinical diagnosis. This raises many questions about the role of *MEFV* mutation screening and the interpretation of specific sequence variants in FMF diagnosis.

Among the six papers selected for this topic,[15 16 26 29–31] one retrospective cohort study tried to analyse the relationship between clinical findings and the most common mutated alleles of *MEFV* gene in a paediatric population of 408 patients.[15] Among them, 39 patients without detected *MEFV* mutations met the Tel Hashomer criteria, while 44 carried mutations, but did not meet the clinical criteria. Moreover, FMF phenotype in some patients with one mutant *MEFV* allele was as severe as those in patients with two mutated alleles. The authors concluded that *MEFV* sequence analysis for the diagnosis of FMF should be performed only in selected patients in order to avoid possible overdiagnosis.[15] Furthermore, if there is no genetic confirmation, but the phenotype is consistent with FMF, the physician should not exclude the diagnosis.[15 31] Padeh *et al*[26] supported this evidence through the study of 216 Israeli patients who met clinical FMF diagnostic criteria; only in a third of the cases was a mutation found. Based on this observation, the

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TEL HASHOMER CRITERIA
Major criteria
1. Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis
2. Amyloidosis of the AA type without predisposing disease
3. Favorable response to continuous colchicine treatment.
Minor criteria
1. Recurrentfebrile episodes
2. Erysipelas-like erythema
3. FMF in a first-degree relative
Definite diagnosis: 2 major or 1 major and 2 minor criteria
Probable diagnosis: 1 major and 1 minor criteria

LIVNEH CRITERIA (simplifiedversion)
Major criteria
Typical attacks of:
1. Peritonitis (generalized)
2. Pleuritis or pericarditis (unilateral chest pain)
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Incomplete abdominal attacks
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
Diagnosis: 1 major criterion or 2 minor criteria
Typical attacks: 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: 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

TURKISH PEDIATRIC CRITERIA	
Criteria	**Description**
Fever	Axillary temperature of > 38°C, 6-72 hours of duration, ≥ 3 attacks
Abdominalpain	6-72 hours of duration, ≥ 3 attacks
Chestpain	6-72 hours of duration, ≥ 3 attacks
Arthritis	6-72 hours of duration, ≥ 3 attacks, oligoarthritis
Family history of FMF	
The presence of at least two out of five criteria: sensitivity (86.5%) and specificity (93.6%) for the diagnosis of FMF	

Figure 2 Sets of clinical criteria for familial Mediterranean fever: Tel Hashomer criteria, Livneh criteria, and Turkish Pediatric criteria.

authors recommended the use of genetic testing only in atypical cases when there are doubts about the clinical diagnosis.

Low sensitivity and specificity still limit the diagnostic utility of clinical criteria as demonstrated by other authors who advocate broader indications for genetic testing.[16 29 30] Nevertheless, descriptions of patients with a definite FMF phenotype not associated with known *MEFV* mutations led the same authors to conclude that new mutations could be present and that the indication to perform genetic analysis remains clinical.[16]

During the consensus meeting, the experts confirmed what was reported in the literature and concluded that FMF is a clinical diagnosis, which can be supported but not necessarily excluded by genetic testing (Strength B). A consensus for the identification of evidence-based criteria for the diagnosis of FMF on the basis of the combination of clinical and genetic features is needed.

Genotype–phenotype correlation

There are about 300 known sequence variants of *MEFV*, but only 14 occur commonly in FMF (E148Q, E167D, T267I, P369S, F479L, I591T, M680I, I692del, M694I, M694V, K695R, V726A, A744S, R761H), 80% are in exon 10 and the others in exons 2, 3 and 5.[9] We explored the relationship between FMF phenotypes and the reported *MEFV* variants and extrapolated, through the selected papers,[15–26] recommendations regarding M694V, M694I and M680I in exon 10, and E148Q in exon 2. Data regarding other mutations were too limited to be used to formulate consensus statements. As well, a huge variability was found among the selected papers about the genetic screening methods used to detect mutations, so at present no conclusive statements could be extrapolated on this topic (see online supplementary table S1).

Sequence variants in exon 10

M694V is the most frequently encountered mutation in FMF patients and a number of cohort studies and non-comparative descriptive studies have shown that homozygosity for M694V is related to a severe FMF phenotype.[15 19 24–26] The retrospective cohort study by Ozturk *et al*[15] correlated genetic and clinical criteria by using the severity score created by Pras *et al*.[37] Both patients homozygous and compound heterozygous for M694V were found at increased risk for severe disease compared with one-mutant allele patients and patients not displaying M694V mutations.[15] Mattit and colleagues confirmed these findings in 83 Syrian patients compared with 242 healthy controls, and observed that patients with amyloidosis were all M694V/M694V or M694V/M680I.[19] In 2007, Giaglis and coworkers showed in a Greek population of 152 patients and 140 healthy controls that homozygotes for M694V present with a more severe phenotype than compound heterozygotes.[20] The literature therefore provides evidence of the pathogenic role of M694V as a risk factor for FMF patients developing disease-related complications and concludes that a patient homozygous for M694V should always be considered at higher risk of developing, with very high probability, a severe phenotype (Strength B).

The pathogenic role of M694V has also been studied in relation to the number of mutated alleles. Giaglis *et al* showed that FMF patients carrying two mutated alleles (homozygotes or compound heterozygotes) displayed a more severe phenotype

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than heterozygotes. This is evident in patients homozygous for M694V, but also true for mutations in positions 680–694 on exon 10.[20] This evidence was supported by Grateau *et al* in a population of 303 suspected FMF patients, where, according to the Tel Hashomer criteria, among 127 patients with definite FMF, 85 presented with two mutations, although not specified per exon, compared with only 22 of 137 patients with unlikely FMF.[16]

In conclusion, FMF patients carrying two common mutated alleles (homozygotes or compound heterozygotes), especially the M694V mutation, or mutations in position 680 to 694 on exon 10, must be considered at-risk of having a more severe disease (Strength B).

Sequence variants in exon 2

E148Q in exon 2 is one of the most frequent sequence alterations in the *MEFV* gene[21 38] either as the sole identified variant or in association with known mutated alleles. E148Q is frequently encountered in the general population (up to 30% in the Asian population according to the Ensembl database[39]), but its pathogenic role remains uncertain. A case-control study performed in 2000 analysed the role of E148Q as either a disease-causing mutation or a sequence variant with no functional effect. The authors found a similar E148Q mutation frequency between patients and healthy controls and between patients and their asymptomatic relatives, the same frequency of M694V/E148Q genotype among patients with and without FMF and four patients homozygous for E148Q without any FMF symptoms. They concluded that E148Q is a benign alteration and that in both heterozygous and homozygous patients E148Q appeared as a non-disease causing variant.[21] Nonetheless, the authors could not exclude a possible pathogenic role in heterozygous patients when E148Q is associated with variants with a high functional effect (ie, M694V), thus acquiring an effect of potentiation in compound heterozygous patients or in complex alleles.[21 40]

This conclusion was contradicted by Tchernitchko *et al* who analysed 233 patients and 213 controls among Sephardic Jews. They found that E148Q allele frequency, even when associated with M694V, is comparable among patients and asymptomatic relatives and concluded that E148Q can be considered a benign polymorphism.[22]

However, even though other authors later confirmed these data[19] showing that E148Q is the most frequent variant in the healthy population, the pathogenic role of E148Q remains debateable as demonstrated by the association with other rheumatic diseases[17] or by its role in symptomatic heterozygous patients when the second allele was not known.[15] In conclusion, the E148Q variant is common, of unknown pathogenic significance and as the only *MEFV* variant does not support the diagnosis of FMF (Strength B).

Correlation age at onset: specific sequence variants

Non-comparative, descriptive studies show a correlation between specific sequence variants and an earlier disease onset. In particular, Padeh *et al* observed a younger age at onset in children carrying two mutations (6±4.4 years with two mutations vs 10±6.4 years in those with no mutations), especially if homozygous for M694V (4±0.7 years for M694V/M694V vs 7.6±4.4 for M694V/V726A; 10.8±5.1 years for M694V/E148Q and 9.5±5.2 years for V726A/V726A).[26] Ozturk and coworkers confirmed these results showing that patients with two mutated alleles have a lower age at disease onset than patients with one mutated allele.[15] Dewalle *et al* observed a mean age of 6.4±5 years in patients homozygous for M694V compared with 13.6±8.9 years in non-homozygous patients. More than half of homozygous M694V patients manifested the disease before the age of 5 years.[24] We can conclude that patients homozygous for M694V mutation are at risk for early onset disease (Strength C).

Silent carriers and risk of AA amyloidosis

AA amyloidosis is the most severe complication of FMF. The underlying mechanisms are unclear but recent genetic advances have begun elucidating some of them. M694V appears to be a risk factor for FMF complications and is the most frequently associated mutation with amyloidosis (see paragraph 'Genotype-phenotype correlation' above). Many studies have focused on the importance of genetics in amyloidosis,[41–43] but additional non-genetic factors such as environment are also relevant. In 1974, a study showed that no cases of amyloidosis were found among 100 Armenian FMF patients living in the USA, although M694V was demonstrated to be the most frequent *MEFV* mutation.[44] The relevance of the country of residence in determining risk of AA amyloidosis was analysed by Touitou *et al* in 2482 patient from 14 countries, with renal outcome data available for 2277 patients; amyloidosis was found in 260/2277. They found that the country of recruitment, which is roughly the same as the country of residence, was the most important determinant of risk for the development of amyloidosis. Homozygosity for M694V was the second most important risk factor in Armenians, Israelis and Arabians, but its association with AA amyloidosis was less significant in Turkish patients and undetectable among other ethnicities. The findings suggest that the risk of AA amyloidosis in patients with M694V depends on the country of recruitment. This is very important as it affects risk–benefit considerations on using colchicine prophylaxis in asymptomatic individuals incidentally discovered to be homozygous for M694V. The authors suggest a more conservative approach, such as monitoring by urinalysis every 6 months, might be appropriate in areas such as Western Europe with low risk of renal amyloidosis.[28]

Different conclusions were reached by studies focusing on genetics as the main risk factor for amyloidosis.[16 19 25 26] A meta-analysis of 3505 Turkish patients showed that 189/400 affected by amyloidosis were homozygous for M694V. The authors concluded that asymptomatic or mildly symptomatic patients homozygous for M694V should receive treatment even in countries where amyloidosis is rarely encountered.[27]

In conclusion, the literature reports that both genetic and environmental factors play a decisive role in disease pathogenesis.[45] Accordingly, subjects homozygous for M694V who do not report symptoms, should be evaluated and followed closely in order to consider therapy (Strength A). For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for AA amyloidosis (such as the country, family history and persistently elevated inflammatory markers, particularly serum amyloid A protein), close follow-up should be started and treatment considered (Strength B).

Role of the specialist in FMF diagnosis

The primary importance of a clinical diagnosis, even as genetic testing becomes more generally affordable, together with the often difficult interpretation of *MEFV* gene mutations, raises the issue of the role of the specialist in selecting when genetic testing will aid management. In the first years of genetics for FMF, the diagnostic problem was thought to be solved simply by asking for genetic screening. Then, it became clear that many

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Table 3 Recommendations for familial Mediterranean fever (FMF) genetic diagnosis

	Strength of evidence
1. FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing	B
2. Consider patients homozygous for M694V at risk of developing, with very high probability, a severe phenotype	B
3. FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations at position 680 to 694 on exon 10, must be considered at risk of having a more severe disease	B
4. The E148Q variant is common, of unknown pathogenic significance and, as the only *MEFV* variant, does not support the diagnosis of FMF	B
5. Patients homozygous for M694V mutation are at risk of early onset disease	C
6. Individuals homozygous for M694V who are not reporting symptoms should be evaluated and followed closely in order to consider therapy	A
7. For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for AA amyloidosis (such as the country, family history and persistently elevated inflammatory markers, particularly serum amyloid A protein), close follow-up should be started and treatment considered	B
8. Consultation with an autoinflammatory disease specialist may be helpful in order to aid in the indication and interpretation of the genetic testing and diagnosis	C

patients with FMF might have atypical presentations, with difficulties in understanding the indication for genetic testing, or might be asymptomatic despite carrying sequence variants, raising doubts about prophylaxis and treatment. Among the selected papers, one descriptive study on 446 patients analysed for *MEFV* mutations showed that only 43% of the patients referred by a general practitioner were genetically confirmed versus 76.4% of patients referred by an FMF specialist.[23] Therefore, a consultation with an autoinflammatory specialist may aid in the indication and interpretation of genetic testing and the diagnosis (Strength C).

CONCLUSIONS

The ability to diagnose FMF has improved in recent years, resulting in earlier initiation of treatment for many patients. The role of genetics in supporting the diagnosis is crucial, but it should never be substituted for a clinical diagnosis. Based on this understanding, the specialist must be aware of the indications and limitations of genetic testing, and know how to interpret the results. Additional training in this area is suggested, especially in the era of increased genetic testing in many countries. The need for consensus guidelines for interpretation of genetic testing in AID resulted in the recommendations by Shinar *et al* in 2012. The authors proposed interpreting genetic testing according to classification of gene variants. The value of this was confirmed in a consensus meeting.[46] Our diagnostic recommendations (table 3), together with the indications given by Shinar *et al*, propose a diagnostic algorithm for FMF that can help the inexperienced physician.

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