Review Article

Familial Mediterranean Fever: A Prevalent Condition Amongst the Arabs

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Abstract

Autoinflammatory diseases are a group of disorders characterized by seemingly unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T-cells and include the hereditary periodic fever syndromes. Familial Mediterranean Fever (FMF) is the prototype of the autoinflammatory disorder. It is an autosomal recessive disorder with high prevalence in non-Ashkenazi Jews, Armenians, Turks and Arabs. The classic clinical picture is recurrent acute short-lived febrile and painful attacks with variable periods of remission. It is complicated by amyloidosis that leads to renal failure in a subset of patients. The gene responsible for FMF, *MEFV*, has been identified and its role in inflammation is under study. There appears to be a distinctive clinical picture among Arab FMF patients and the spectrum and distribution of *MEFV* mutations is different from other ethnic groups commonly affected by FMF. The clinical and molecular aspects of FMF in the Arabs are discussed.

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Familial Mediterranean Fever

Introduction

Autoinflammatory diseases are a group of disorders characterized by seemingly unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T-cells. [1] The autoinflammatory diseases include the hereditary periodic fever syndromes and are thought to be due to disturbances in the regulation of the innate immunity. [2]

Familial Mediterranean Fever (FMF) is the prototype of the hereditary periodic fever syndromes and the autoinflammatory diseases.

It is characterized by recurrent self-limiting episodes of fever and painful polyserositis affecting mainly the peritoneum, pleura and synovium. FMF was first described as a distinct disease entity, under the name of benign paroxysmal peritonitis, in 1945. [3]

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The international medical community adopted the name FMF, as suggested by the team led by Heller. [4] Although the disorder had several other names including recurrent polyserositis, recurrent hereditary polyserositis, periodic disease and periodic peritonitis. FMF is an autosomal recessive disorder, [4] with considerable prevalence in specific ethnic groups, namely, non-Ashkenazi Jews, Armenians, Turks and Arabs.

Currently, FMF is established as a common genetic disease among the Arabs and in the early 1980s it has become recognized as a public health concern in some Arab countries. [5,6] Since then, it became increasingly notable that FMF has a considerable impact on the health and welfare of children and adults from the Middle East. FMF may be complicated by amyloidosis which leads to renal failure, it is associated with loss of school days or work hours and is coined with unnecessary hospitalizations and surgeries. In addition, the painful and febrile episodes are extremely uncomfortable for FMF patients. However, the mortality and morbidity associated with FMF are preventable with early identification of affected individuals followed by appropriate treatment and prophylaxis. Clinical and molecular studies involving a variety of Arab subpopulations demonstrate the high prevalence of FMF and high *MEFV* mutation-carrier frequency. [7- 9] However, the clinical and particularly the molecular aspects of FMF is least studied in the Arabs when compared to other ethnic groups commonly affected by FMF.

Clinical Aspects

The classic clinical picture consists of recurrent febrile episodes that are usually of acute onset, variable frequency, sometimes without a recognized triggering factor but often occurring with menstruation, emotional stress or strenuous physical activity. [10]

These febrile episodes are short lived, lasting 1 to 3 days but may last 4 days or longer, and usually abort abruptly. The episodes are often accompanied by pain due to peritonitis, pleuritis or acute synovitis of large joints. The frequency of the attacks varies from once per week to long periods of remission. Over the course of the life-long illness, an affected individual will probably experience several forms of the febrile and painful episodes, but the recurrence of one type over many years is common. [11] During the attack, there is neutophilia and a brisk acute-phase response and histologically there is a massive sterile influx of Polymorphonuclear leukocytes (PMNs) into the affected site. [11] Between attacks, patients feel well, although biochemical evidence for inflammation may persist. [2]

The episodes start, most commonly during childhood, with more than 80% of patients presenting before the age of 20 years and very few after the age of 40 years. [5, 11, 12]

The painful abdominal (peritoneal) attack is the most frequent association with the febrile episode. It is experienced by the majority of patients [12] and is reported in about 50% of patients as the first symptom. [11] The abdominal pain can be diffuse or localized, ranging in intensity from mild bloating to real peritonitis with guarding, rigidity, tenderness and rebound tenderness. [10, 12] The organization of the peritoneal inflammatory exudate may result in fibrous adhesions and may give rise to mechanical intestinal obstruction. [13] These adhesions are probably the cause of sterility in some women affected by FMF. [14-17]

The articular involvement in FMF episodes is the second-most common association with the fever. The articular inflammation presents as an abrupt onset of acute arthritis, accompanied by high fever, redness, warmth, tenderness and swelling. [5, 18- 20]

It is often monoarticular and commonly affects the large joints of the lower limbs. It usually lasts longer than other FMF manifestations and subsides gradually rather than abruptly and leaves no residual damage. [12] The synovial fluid is sterile but contains large numbers of neutrophils. [11, 21] Rarely, FMF patients develop protracted arthritis, synovitis, muscle atrophy, erosions and juxta-articular osteoporosis. [21-24] Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are generally effective in FMF arthritis.

Pleural attacks occur in 15 to 30 % of FMF patients. [25] Usually, the attacks present as an acute one-sided febrile pleuritis resembling the peritoneal attacks in their abrupt onset, unpredictable occurrence and abrupt and rapid resolution. [11, 18, 26] Breathing may be painful, there may be diminished breath sounds on auscultation and there may be radiological evidence of pleural effusion or lung collapse.

The characteristic skin lesion is the erysipelas-like erythema which may sometimes accompany the arthritis. [11, 27]

Histological examination of the lesions reveals edema of the dermis, sparse perivascular infiltrate without vasculitis and C3 deposits seen by immunofluorescence. [28]

Muscle pain occurs in about 10% of FMF patients and is usually mild and confined to the lower extremities. [12] It may be precipitated by physical exertion or prolonged standing, lasts few hours to 1 day and subsides with rest or NSAIDs. [29] Rarely, a syndrome of protracted febrile myalgia may develop. [29-32] It is characterized by severe debilitating myalgia, prolonged fever, abdominal pain without peritoneal involvement, a high Erythrocyte Sedimentation Rate (ESR) and hyperglobulinemia. If treated with NSAIDs alone, the syndrome may last for up to 8 weeks, but it will subside promptly if treated with corticosteroids. [29-32]

Acute inflammation of the tunica vaginalis in FMF patients may mimic torsion of the testis and will present as a unilateral tender scrotal swelling. [33- 35] This is not surprising as the tunica vaginalis is structurally part of the peritoneum. However, these episodes usually do not occur with an acute peritoneal attack and are usually unilateral. [26] Fever and pain are always present with these self limiting and short lived acute scrotum episodes.

Uncommon manifestations include headache; [36,37] meningeal irritation and increased CSF proteins and cells; [37-41] impaired female fertility; [15-17] pericarditis; [42] and transient microscopic hematuria.

Vasculitides are found in FMF at a higher incidence than in the general population. Henoch-Schonlein Purpura (HSP) have been reported in 3 to 11 % of FMF patients [43-46]. A study identified more than expected homozygous and heterozygous FMF mutations among children presenting with HSP. [46] Polyarteritis nodosa also occurs more commonly in patients with FMF. [47] Various types of glomerulonephritis have been reported in FMF, [48] but the data are insufficient to draw conclusions about its higher prevalence in FMF patients when compared to the general population even within the same ethnic group.
The most significant complication of FMF is amyloidosis, which mainly affects the kidneys causing proteinuria and leading to renal failure. [49] Chemically, it is the same type of reactive amyloidosis, with amyloid A deposits, which takes place with chronic infectious and non-infectious inflammatory conditions, such as tuberculosis, bronchiectasis and rheumatoid arthritis. [50] Family history of amyloidosis, as well as consanguinity are factors causing a higher risk of development of amyloidosis in FMF patients. [25, 51] Colchicine treatment greatly influenced the occurrence of amyloidosis as a complication of FMF.

In a group of patients, clinically designated as phenotype II FMF patients, renal amyloidosis develops without being preceded by typical attacks of the disease. [52-55]

A daily regimen of 1-2 mg of oral colchicine remains the recommended treatment since its introduction in 1972. [56-58] Adherence to a daily dose of colchicine produces significant decrease in the frequency and severity of the attacks or even cessation of the attacks all together in about 95 % of FMF patients [59]. Continuous prophylactic treatment with colchicine in FMF patients inhibits the development of amyloidosis, [60] even in non-responders. [61] The diagnosis of FMF remains a clinical bedside diagnosis with well outlined validated diagnostic criteria, [62] however, a positive response to colchicine is supportive of the diagnosis. There is slight predominance of males affected with FMF, due to either reduced penetrance in females [63] or more probably due to underestimation of the disease in females.

The studies that elaborate on the clinical features of Arab patients were carried out either prior to the identification of the *MEFV* as the gene responsible for FMF or did not incorporate molecular data in the analyses. [5,6,9,20,26,29,33,44,48,64-69]

The majority of these studies employed the original diagnostic criteria (short attacks of fever and abdominal pain recurring at varying intervals in the absence of any causative factor) proposed by Heller and coworkers. [70]

However, more recent studies employed the validated diagnostic criteria of Livneh and coworkers [62] as a standard for the diagnosis. [26,29,33,67-69] In addition, most of these studies were done after the establishment of colchicine as an effective treatment and this may have influenced the reported phenotype.

We conclude that different diagnostic standards and colchicine therapy are the primary confounding factors that may have contributed to the reported clinical peculiarities of the FMF phenotype in the Arabs. In addition, several other confounding factors may have contributed to the difference in phenotype, such as under-reporting of symptoms, criteria for patient selection, reliance on family history, chance variations and the lack of a definitive diagnostic test.

About 80% of Arab FMF patients present before the age of 10 years and abdominal pain is the most commonly reported presenting feature. [26] This earlier age at onset is probably explained by the skewed patient selection in the reported case series which is influenced by the clarity of symptoms and the presence of family history. Unlike the higher prevalence in males in other ethnic groups commonly affected by FMF, the male to female ratio in Arabs is almost equal [9,26]. This is probably due to the accurate estimation of the number of affected females, also influenced by patient selection. In addition, this finding does not support the suggestion that FMF may have incomplete penetrance in females [63]. Arthritis is less common in the Arab FMF children and adults, [5,6,20,26] as compared to Jews, [11, 71] however, it is similar to arthritis in Turks [72, 73] and Armenians.[19, 74]The decreased incidence of arthritis in Arabs, Turks and Armenians may be due to under-reporting of the symptoms due to delay in the diagnosis. The pleural attacks [26], peritoneal attacks [5,6,9] and myalgia [29] are not different from other ethnic groups commonly affected by FMF. About 20 % of Jewish and Arab children with functional abdominal pain were homozygous for an *MEFV* mutation [75]. A non-specific purpuric rash is the most commonly reported FMF related skin manifestation in Arab FMF patients, [44] while erysipelas-like erythema is the most common in other ethnic groups commonly affected by FMF.

This unusual finding is probably due to the small number in that series and the erysipelas-like erythema is noted to be a common cutaneous manifestation of FMF in Arabs in a later case series. [26]

The acute scrotal swelling reported in Arab FMF patients sometimes occurred in the absence of peritonitis [26] and is associated with a high colchicine failure rate in Arab and Jewish FMF patients [26,33-35]. This failure rate is alarming due to a report of testicular necrosis following recurrent scrotal attacks in the latter ethnic group [76]. Recurrent hyperbilirubinemia has been described in the early FMF literature but very few patients were clinically icteric. [77] This probably explains why this feature is not mentioned in the large clinical series reported from all ethnic groups commonly affected by FMF. Recurrent hyperbilirubinemia has been described in two Arab patients in 1994 [78] and in 1998. [79] In these two reports, the hyperbilirubinemia was transient, occurring only during a peritoneal attack and clinical jaundice was mild with only a minimal rise in serum bilirubin (mainly conjugated). [26]

It has been noted that amyloidosis and chronic renal disease are less common in the Arab FMF patients when compared to the other ethnic groups commonly affected by FMF. [5,6,9,26,80,81] The incidence of amyloidosis ranged from 0.4 % in Jordanian FMF patients [26] to 10.1 % in Lebanese patients. [80, 82] The low rate of occurrence of FMF-related amyloidosis in the Arab patients is probably due to the fact that these figures were obtained after the establishment of colchicine as the standard of care for FMF patients. [5,6,9,26] This explanation is supported by the higher figure (10.1 %) obtained in two studies done prior to the establishment of colchicine therapy. [80, 82]
In these two studies, some of the Lebanese FMF patients had Armenian ancestry, which may have increased the rate of amyloidosis, as well.

The incidence of amyloidosis in the Arab FMF patients and the factors influencing its occurrence have been studied together with specific *MEFV* mutations and examination of genotype/ phenotype correlation patterns.

Besides amyloidosis, kidney involvement in the form of IgM nephropathy, IgA nephropathy or rapid progressive glomerulonephritis have been described in Arab FMF patients. [48,64-66] However, the numbers in these case series are small to draw firm conclusions but may point to the higher prevalence of vasculitis or glomerulonephritis in FMF patients.

The Genetics

The gene responsible for FMF, *MEFV*, is located on the short arm of human chromosome 16, [83-86] and was independently identified by two positional cloning consortia [87,88]. With the cloning of the gene, 4 missense mutations in exon 10, namely M694V, V726A, M694I and M680I, were identified. [87, 88] These 4 mutations and E148Q in exon 2 are the most common *MEFV* mutations amongst the 59 putative mutations identified to date. [89-91] Exon 10 remains the major site of mutations, with a smaller cluster in exon 2 (available at http://fmf.igh.cnrs.fr/infevers). The FMF carrier rate can be as high as 1 in 3 in the commonly affected ethnic groups, raising the possibility of selective heterozygote advantage. [7, 8, 91- 94] Although FMF is an autosomal recessive disease, pseudodominance is frequently observed, due to the high mutation frequency and also due to consanguinity, which is practiced frequently in the ethnic groups commonly affected by FMF. [95, 96]

Consistent with the biology of FMF, *MEFV* is expressed predominantly in granulocytes, monocytes, dendritic cells and in fibroblasts derived from skin, peritoneum and synovium. [97- 99] *MEFV* encodes a full-length 781 amino acid protein named pyrin or marenostrin. [87, 88] Native pyrin protein is localized in different subcellular compartments in different cell types. [98] Wild-type pyrin is cytoplasmic, co-localizes with microtubules and it is proposed that it regulates inflammatory responses at the level of the cytoskeletal organization. [100, 101] However, nuclear localization of full-length pyrin in synovial fibroblasts, dendritic cells and granulocytes has been demonstrated. [98]
Several alternatively spliced forms have been described. [98, 101] In addition, it appears that pyrin acts as an upstream regulator of interleukin (IL)-1β activation, [102, 103] having both inhibitory and potentiating effects on IL-1β production. There is also evidence that pyrin plays a role in regulating nuclear factor (NF)-$_K$B activation and apoptosis. [102- 106]

The mutation analysis studies that include a substantial number of Arab FMF patients are limited in number and in methodology. [7, 8, 68, 69, 107- 116] All of these studies examined for the five common mutations (E148Q, M680I, M694V, M694I & V726A) using a combination of restriction endonuclease-based test, ARMS (Amplification Refractory Mutation System) test, DGGE (Denaturing Gradient Gel Electrophoresis) and selective exonic sequencing. A few studies examined for additional mutations but also in a selective manner, [107, 109, 115] However, despite their limitations these studies point to the high *MEFV* mutation carrier frequency among the Arabs, which is similar to the other ethnic groups commonly affected by FMF (1 in 3 - 6 individuals).

The most common *MEFV* mutation in the Arabs is the M694V, [7, 8, 68, 69, 107- 116] although it is less common than in other ethnic groups commonly affected by FMF. [74, 117, 118] The V726A is the second most common mutation in Arabs [7, 8, 68, 69, 107- 116] similar to the findings in Armenians, Turks and Jews. [74, 117, 118] M694I is the third most common mutation in Arabs [7, 68, 69, 107, 108, 110, 112, 115] and appears to be found mainly in this ethnic group. [10, 87, 89, 95, 119] The M680I mutation found mostly in Armenians and Turks [74, 118] is the fourth common in Arabs. [7, 68, 69, 107, 108, 110, 112, 115] There are few studies that show that in Arab patient series M680I is more common than M694I. [8, 110, 115] The E148Q mutation is the least penetrant and might be a polymorphism. [91, 120] It has been identified in Arab FMF patients alone or in a complex allele with other exon 10 mutations, [68, 69, 112, 115, 116] but is more commonly identified in healthy carriers. [7]

Table (1) provides a summary of the distribution of the 5 common *MEFV* mutations in the Arab FMF patients in selected studies that provided clear mutant allele frequencies.

Table 1: The distribution of the 5 common MEFV mutations in the Arab FMF patients in selected studies. The percentage value is the contribution of the mutation to the pool of the identified mutant alleles.

	Mutation				
	M694V	***V726A***	***M694I***	***M680I***	***E148Q***
1 [115]	*20.2 %*	*14.3 %*	*1.2 %*	*9.5 %*	*7.1 %*
2 [109]	*36 %*	*0 %*	*55.4 %*	*4.3 %*	*4.3 %*
3 [8]	*17.4 %*	*34.7 %*	*9.9 %*	*21.5 %*	*16.5 %*
4 [110]	*16.7 %*	*26.7 %*	*13.3 %*	*22.5 %*	*5.8 %*
5 [7]	*35.5 %*	*29 %*	*16 %*	*9.7 %*	*0 %*
6 [68]	*37.5 %*	*26 %*	*14 %*	*10 %*	*12.5 %*
7 [107]	*49 %*	*16.7 %*	*11.9 %*	*4 %*	*8.5 %*

Table 2: Distribution of the 5 common mutations, allele frequencies and carrier rates among the healthy adult cohort from 5 Arab countries.

Nationality & Number	***Egyptians (231)***	***Syrians (225)***	***Jordanians* (200)***	***Iraqis (176)***	***Saudis (107)***	***Total (939)***
Number of chromosomes	*462*	*450*	*400*	*352*	*214*	*1878*
M694V	*2*	*6*	*13*	*0*	*0*	*21*
V726A	*8*	*5*	*14*	*9*	*1*	*37*
M694I	*4*	*0*	*2*	*0*	*0*	*6*
M680I	*0*	*1*	*1*	*0*	*0*	*2*
E148Q	*29*	*30*	*23*	*29*	*12*	*123*
Total	*43*	*42*	*53*	*38*	*13*	*189*
Wild type allele frequency "p"	*0.907*	*0.907*	*0.8675*	*0.892*	*0.939*	*0.899*
Mutant allele frequency "q"	*0.093*	*0.093*	*0.1325*	*0.108*	*0.061*	*0.101*
Calculated carriers (rate)	*39 (16.87%)*	*38 (16.92%)*	*46 (23%)*	*34 (19.26%)*	*12 (11.4%)*	*170*
Observed number of carriers	*43*	*42*	*37*	*38*	*13*	*173*

The calculations of the carrier rate and allele frequency is done under the assumption that there are no complex allele.

The distribution of the 5 common *MEFV* mutations among healthy Arab individuals has been the subject of one study to date. [7] In this study, healthy cohorts from Jordan, Egypt, Syria, Saudi Arabia and Iraq were examined for the 5 common *MEFV* mutations. The distribution of each mutation in each Arab population and collectively are shown in Table (2). This study concludes that E148Q has reduced penetrance in the Arab population and thus, a proportion of the genetically affected individuals remain asymptomatic. It is of note that utilizing the restriction endonuclease digestion for the E148Q mutation can lead to misdiagnosis in the presence of the E148V mutation, [116] which may have increased the number of E148Q identified in healthy Arab cohorts. [7]

M694I and M680I are more prevalent in affected individuals when compared to the healthy individuals, which points to their higher penetrance. The overall carrier rate for the 5 common *MEFV* mutations from this study is 1 in 5 which is very similar to the calculated carrier rate. Despite the high carrier rate, the heterozygote advantage for the MEFV mutations could not be demonstrated in the study probably due to the relatively small sample size.

One of the remarkable conclusions from these studies is that the percentage of unidentified disease-causing *MEFV* alleles is the highest in the Arab population when compared to the other ethnic groups commonly affected by FMF.

This is clearly shown in one study that used a combination of methods including direct sequencing of exon 10, DGGE and restriction endonuclease digestion in a cohort of well characterized FMF patients from the 4 commonly affected ethnic groups. [109] While 51 % of the alleles in Arab FMF patients were not identified in this study, only 30 %, 25 % and 9 % of the alleles were not identified in non-Ashkenazi Jews, Turks and Armenians, respectively.

A recent study that employed methods that detect 24 previously described mutations (ARMS test followed by sequencing of exon 10 and exploration of 5 other mutations in exons 2, 3, 4, 5 and 6) in Palestinians failed to detect 51 % of the alleles, which is quite high considering the detailed methodology. [107] It is unlikely that the diagnosis of FMF in these studies is inaccurate, as all published reports follow the validated diagnostic criteria. [62] A summary of selected studies is shown in Table (3) indicating the high percentage of unidentifiable alleles in Arab FMF patients, which suggests the presence of other mutations not identified by the applied methods.

Table 3: Summary of selected MEFV mutational analysis studies that included Arab FMF patients.

		% UNIDENTIFIED			
	Methodology	***Arabs***	***Jews***	***Armenians***	***Turks***
1 [108]	*RE digestion*	*10% P (3/31)*	*4% P (2/49)*	---	---
2 [109]	*Sequence ex 10, RE digestion & DGGE*	*49% P (24/49)*	*18% P (17/93)*	*6.5% P (2/31)*	*17% (4/24)*
3 [115]	*RE digestion & ARMS*	*44% Ch (37/84)*			
4 [112]	*Sequence ex 10, RE digestion, DGGE & ARMS*	*33% Ch (45/143)*	---	---	---
5 [8]	*RE digestion*	*15% Ch (21/142)*	*4% Ch (6/150)*	---	---
6 [69]	*Sequence ex 10 & RE digestion & ARMS*	*55% P (152/278)*	---	---	---
7 [7]	*Sequence ex 10 & RE digestion & ARMS*	*46% Ch (27/58)*	---	---	---
8 [68]	*RE digestion & ARMS*	*41% P (168/407)*	---	---	---
9 [107]	*Sequencing & ARMS*	*51% Ch (518/1022)*			

Ch: chromosomes; P: patients (denotes patients in whom the 2 mutations were not identified, excluded those in whom 1 was identified); RE: restriction endonuclease; ARMS: amplification refractory mutation system, DGGE: denaturing gradient gel electrophores.

Genotype/ Phenotype Correlation Patterns

The Tel Hashomer severity score, [121] has been used to facilitate comparison of FMF phenotype severity among the different ethnic groups. Several studies have examined the correlation between certain mutations and phenotype severity in the different affected ethnic groups.

Most studies showed correlation between M694V and severity of the disease or the presence of amyloidosis across all affected ethnic groups with the exception of the Turkish FMF patients. [31, 69, 74, 108, 112, 118, 122- 125] The results of the selected studies are summarized in Table (4).

Upon reviewing the FMF genotype / phenotype correlation literature, we can conclude that there is no consistency in the correlation between a specific *MEFV* mutation and amyloidosis or other phenotypic feature across all populations, with the exception of M694V and amyloidosis or severity of the FMF symptoms. However, there is a specific pattern of severity or amyloidosis within the same population, such as in homozygosity for M694V in the North African Jews and M694V homozygosity in the protracted febrile myalgia syndrome in the Arabs.

There are a few genotype / phenotype correlation pattern studies involving Arab FMF patients. [69,108,110,112,113] One study that included a mixed Arab and Jewish FMF patients denoted that in Arab patients FMF tends to run a milder course and carries a better prognosis. [108] This was attributed to the fact that M694V is less common among the Arab FMF patient cohort. Another study concluded that Arab FMF patients with the genotypes M694V/M694V or M694V/V726A tend to have a severe clinical course. [69] The genotype M694I/M694I is common in Arab FMF patients and seems to be associated with milder disease. However, this study used a severity score modified from the Tel Hashomer severity score and both have not been statistically validated. Homozygosity of M694V or the complex allele V726A/E148Q was associated with the most severe course and the highest risk for amyloidosis in a mixed Arab, Ashkenazi and Non-Ashkenazi Jewish FMF patients. [110] In Lebanese patients, M694V and M694I were associated with higher risk of amyloidosis. [112, 113] It appears that the phenotype associated with the M694I mutation is not consistent in the limited number of studies. The genotype / phenotype correlation pattern studies performed in Arab FMF patients are mentioned in Table (4).

A new and simple severity score has recently been developed and has been statistically validated. [126] It will be of interest to utilize this tool on several cohorts from different populations commonly affected by FMF, including Arabs, to outline genotype/ phenotype correlation patterns that may be specific for one or more populations.

Needs and Goals for the Future

Since a considerable proportion of the disease-causing *MEFV* alleles in the Arab FMF patients remains unidentified, the need arises to perform extensive studies that take a comprehensive approach to the identification of *MEFV* mutations. These studies should explore regulatory sequences and conserved intronic sequences for disease-causing mutations.

The exploration of other non-traditional mutation mechanisms should also be examined, such as analysis for large deletions or duplication. Furthermore, the exploration of the role of already described or potential modifier genes and polymorphisms within these genes should be explored in conjunction with the appropriate genotype/ phenotype relationship studies.

It is of paramount importance to identify if there is a distinctive pattern of the relationship between *MEFV* and modifier gene genotypes on one hand and the phenotype in the Arab FMF patient population on the other hand. It is of equal importance to identify if there is a correlation between the severity of the disease, its burden and its common complications with any of the mutations in Arab FMF patients. The severity of the disease should be a practical and actual measure of the disease burden and should not be affected by colchicine therapy, which is the standard of care for diagnosed patients. The achievement of these goals will lead to the establishment of adequate population screening protocols for early and presymptomatic identification of patients and the provision of prophylactic colchicine therapy.

There is a paucity of the studies that measure and evaluate FMF as a public health consideration in the Arab countries, and the need for such cross-sectional studies cannot be overstated. There is a need to establish collaborative and standardized study protocols across the Arab countries with substantial numbers of FMF patients to facilitate comparisons and allow the aggregation of data for robust statistical analyses. These protocols will also provide the guidelines for the appropriate screening approaches and the instatement of public policies that provide adequate preventive measures.

The establishment of educational resources parallels the establishment of diagnostic laboratory testing and increases the awareness of physicians and medical personnel to FMF and its complications.

Since diagnostic laboratory testing are not specific and the molecular diagnosis is still limited, the clarity of the clinical diagnostic criteria is the hallmark for making an accurate and precise diagnosis. The development of these diagnostic skills amongst physicians requires the appropriate and continued medical educational resources to be available to health care takers.

There is a need for the utilization of clinically well characterized FMF patients in research endeavors that aim at exploring the pathogenesis of the disorder.

The understanding of the pathogenesis of the disorder will serve all ethnic groups commonly affected by FMF and will promote the understanding of inflammation and the molecular correlates to the innate immunity.

Table 4: Summary of selected genotype / phenotype correlation studies

	Mutation	Ethnic group	Phenotype assessed	Relation
1	*M694V/M694V*	*Non-Ashkenazi Jews*	*Arthritis & Pleuritis*	*Increased 2X* [122]
			Amyloidosis	*Increased*
2	*M694V/M694V*	*Armenians*	*Arthritis*	*Increased* [74]
			Amyloidosis	*Increased*
3	*M694V/M694V*	*Non-Ashkenazi Jews*	*Severity (no specific index)*	*Increased* [108]
		Arabs	*Amyloidosis*	*Increased*
4	*M694V/M694V*	*North African Jews,*	*Amyloidosis*	*Increased* [125]
	Others	*Armenians & Turks*	*Severity*	*No relation*
5	*M694V/M694V*	*Non-Ashkenazi Jews*	*Amyloidosis*	*Increased* [123]
6	*M694V/M694V*	*Mixed Jewish*	*Tel Hashomer Severity score*	*Increased* [124]
7	*M694V/M694V*	*Mixed Jewish*	*Protracted febrile myalgia*	*Increased* [31]
8	*M694V/M694V*	*Turks*	*Severity (12 parameters)*	*No relation* [118]
	M694V/M694V		*Amyloidosis*	*No relation*
	M680I/M680I		*Arthritis*	*Decreased*
9	*M694V/M694V*	*Arabs*	*Amyloidosis*	*Increased* [112]
	M694I/M694I		*Amyloidosis*	*Increased*
	M694V/M694I		*Amyloidosis*	*Increased*
10	*M694V/M694V*	*Arabs*	*Severity (modified score)*	*Increased* [69]
	M694V/V726A		*Protracted febrile myalgia*	*Increased*

Conclusions

FMF is the prototype of the hereditary periodic fever syndromes which are included in the expanding spectrum of autoinflammatory disorders. It is prevalent in specific ethnic groups, non-Ashkenazi Jews, Armenians, Turks and Arabs with high carrier frequency. The burden of FMF in these ethnic groups is measured by the incidence of its common complication, amyloidosis and the severity of symptoms, both are preventable with daily colchicine. The clinical aspects of FMF and the molecular aspect of its causative gene, *MEFV*, are being studied with the least effort being applied to the FMF in Arabs. There appears to be a distinctive clinical picture among Arab FMF patients, specifically in the lower incidence of amyloidosis. Variable diagnostic standards across studies, colchicine therapy, under-reporting of symptoms, patient selection and chance variation probably contribute to this apparent distinctive clinical picture.

The spectrum and distribution of *MEFV* mutations in Arab FMF patients is different from other ethnic groups commonly affected by FMF. Limitations in the methodology applied in the studies that address this issue and the small sample size may have partially contributed to this variation. However, it is clear that the portion of unidentified disease-causing *MEFV* mutations is the highest in Arab FMF patients. There appears to be a need for larger studies applied to Arab FMF patient cohorts that employ a comprehensive mutation detection strategy and utilize standardized clinical measures.

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