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Review Article

Familial Mediterranean Fever: Unraveling its Causes, Clinical presentation, and Innovative Treatment Strategies

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ABSTRACT

Auto-inflammatory disorders are recognized as significant in impacting the health of patients. The majority of auto-inflammatory disorders originate from hereditary abnormalities. One of the most significant auto-inflammatory disorders is Familial Mediterranean Fever, which mostly affects populations originating from the Mediterranean region; particularly those of Sephardic Jewish, Armenian, Arab, and Turkish descent. Familial Mediterranean fever typically manifests in childhood due to genetic mutations, mainly the Mediterranean Fever **(***MEFV*) gene. This gene encodes pyrin, which is essential in regulating inflammation. Defects in this particular gene may contribute to higher levels of inflammation, which in turn can cause recurrent episodes of pain and fever. Colchicine, NSAIDs (non-steroidal anti-inflammatory medicines), and medications that target cytokines are the only options for therapy. Finding new remedies is one of the challenges confronting medical research. Therefore, it is critical to provide information on the clinical signs, etiology, available treatments, side effects, and diagnosis of this particular kind of congenital auto-inflammatory ailments. Furthermore, how variations in gender and genetics could impact the prevalence and course of familial Mediterranean fever.

Keywords: *Familial Mediterranean fever (FMF); Auto-inflammatory disorder; The MEFV gene; NSAIDs; Pyrin; Diagnosis.*

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1. Introduction

Familial Mediterranean fever (FMF) is a well-known autosomal recessive disorder characterized by recurrent episodes of fever, widely acknowledged as one of the most prominent syndromes involving recurrent fever globally **[1]**. FMF is an auto-inflammatory disease with recurrent fevers and inflammation associated with pain in multisystem organs such as the abdomen, chest, and joints. It is a genetic disorder affecting the Mediterranean region, mostly Arabs, Armenians, and Turks **[2]**. FMF was first identified as benign paroxysmal peritonitis in 1945. Afterward, FMF may be named “periodic peritonitis”, “family recurring polyserositis”, “Cattan-Mamou illness”, or “Siegel-Cattan-Namou syndrome” **[3]**.

FMF symptoms and signs mainly appear in childhood. They appear as recurrent waves

termed “assaults” that may last one to three days during each episode. The main symptoms include peritonitis, pleuritis, arthritis, rash, and fever **[2]**. However, arthritic flare-ups might last for weeks or months. The peak point of the FMF symptoms mountain is the painful inflammatory episodes. They account for nearly 30% of FMF symptoms and occur even if there are no attacks **[2]**.

FMF's main sign is recurring fever episodes that may be accompanied by one or more symptoms, including pain in the chest, abdomen, joints, and muscles, as well as inflammation in the pelvis. Some FMF episodes may be accompanied by skin edema, headache, pericarditis, and meningitis **[4]**. Each FMF episode may occur from one day to three days. The time between episodes may range from days to even years. The first episode is usually known as the “initial episode”. It occurs mainly in childhood or adolescence. Most patients have no symptoms between episodes **[5] (Table 1)**.

Table 1: List of symptoms FMF patients may experience

Percentage of patients	**1%-4%**	**5%-29%**	**30%-79%**	**80%-99%**
	-Aphthous ulcer	-Arrhythmia	-Chest pain	-Abdominal pain
	-Arthritis	-Ascites	-Diarrhea	-Arthralgia
	-Crohn's disease	-GIT infarctions	-Erysipelas	-Constipation
	-Recurrent fever	-Intestinal obstruction	-Erythema	-Fever
	-Renal amyloidosis	-Lymphadenopathy	-Pleuritis	-Myalgia
	-Vomiting	-Malabsorption	-Proteinuria	-Nausea
		-Meningitis	-Seizures	-Vomiting
		-Nephropathy		
		-Osteoarthritis		
		-Pancreatitis		
		-Splenomegaly		

Since FMF is classified as a type of auto-inflammatory disease due to a genetic disorder, it was reported to occur due to mutations of the Mediterranean fever (*MEFV*) gene. The latter encodes a protein called “pyrin” or “marenostrin” **[5]**. Pyrin is expressed in blood and innate immunity cells. Eosinophils, neutrophils, monocytes, macrophages, dendritic cells, and fibroblasts express the MEFV. Pyrin is part of the inflammasome pathway that regulates the inflammation process and can be inherited through generations. Thus, pyrin can be considered part of the innate immune system. The main role of pyrin is reducing inflammation via autophagy of innate immunity regulators and hence, reducing inflammation **[1]**.

In patients with FMF, the mutated pyrin causes abnormal neutrophil activation, which in turn results in the surplus production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-1 beta (IL-1β), causing an inflammatory reaction. Such inflammation, as previously mentioned, affects mainly the peritoneal cavity, pleural membranes, and joints **[2]**.

2. Main text

2.1.1. Literature search strategy

Electronic databases such as PubMed, PMC, and Google Scholar were utilized to search for literature studies. The following keywords were used to find related literature: "Familial Mediterranean Fever" AND "Auto-inflammatory disorder" OR The MEFV gene" AND "Pathogenesis of FMF" OR "Pyrin gene" AND "Mediterranean fever gene mutations".

2.1.2. Evaluating the retrieved articles and establishing the selection approach

The reviewers carried out the screening process. Initially, studies were assessed based on their titles, followed by an evaluation of their abstracts, and ultimately, a thorough review of the full texts.

2.2. Treatment options

Unfortunately, there is no specific treatment for FMF. Currently, available medications may only improve symptoms, reduce sudden attacks, and prevent inflammation-induced complications (amyloidosis). FMF treatment may be randomized into three main phases: acute attack and amyloidosis prophylaxis (Phase 1), management of acute episodes (Phase 2), and management of comorbidities and complications (Phase 3) (**Fig. 1.)**.

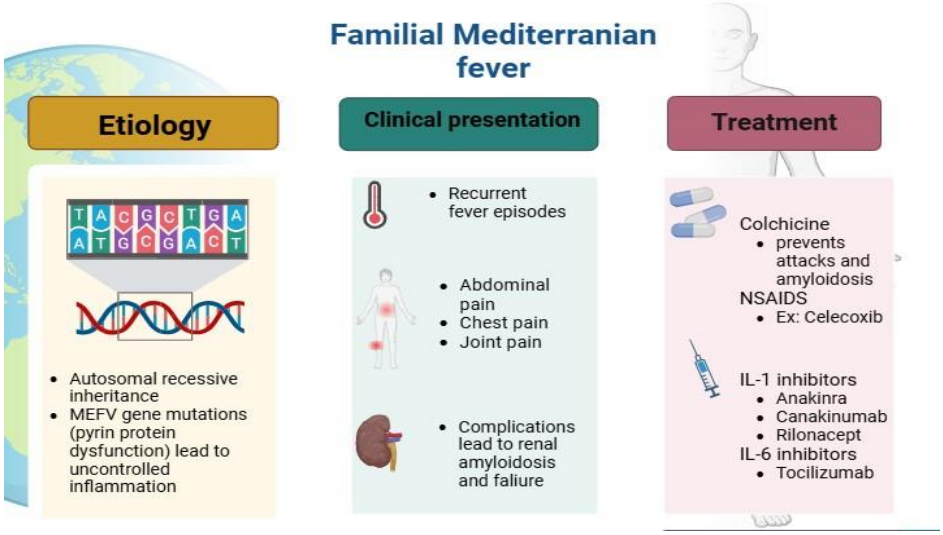

Fig. 1. FMF etiology, clinical presentation, and treatment

2.2.1. Non-steroidal anti-inflammatory Drugs (NSAIDs)

Celecoxib, which is a selective COX-2 inhibitor, is one of the medications used to control the inflammatory symptoms of FMF. Owing to its selectivity, it is the most used NSAID in FMF. In addition, celecoxib's selectivity is associated with fewer gastrointestinal and renal side effects **[6]**.

2.2.2. Colchicine

Being an anti-inflammatory, it prevents pain during episodic attacks and the progression of amyloidosis. Colchicine is structurally related to pyrin. Hence, it binds to tubulin monomers and prevents polymer formation; as a result, colchicine causes a change in the organization of the actin cytoskeleton **[7]**. Additionally, adhesion molecules, neutrophil chemotaxis, and the NOD-like receptor family, pyrin domain containing 3(NLRP3)-mediated inflammasome pathway are all inhibited by colchicine. It is believed that because neutrophils lack the P glycoprotein efflux pump, they selectively accumulate in these cells, which is the reason why it primarily affects them **[8]**.

The pharmacokinetics of Colchicine revealed that its oral bioavailability ranges from 24% to 88%. Moreover, the elimination half-life of Colchicine extends from 20 to 40 h; however, it becomes prolonged in the case of liver and kidney dysfunction. If irreversible glomerular damage is not present, it could reverse proteinuria and stop the further development of amyloidosis **[9]**.

The main side effects following colchicine treatment include gastrointestinal disturbances, azoospermia, transaminase elevation, and leukopenia. However, colchicine is found to be safe during pregnancy and lactation. Colchicine's toxicity becomes enhanced when taken simultaneously with cytochrome P3A4 (CYP3A4) inhibitors. Unfortunately, it was found that the frequency of *M694V*, a mutation in the *MEFV* gene, homozygosity might be closely related to colchicine resistance. Additionally, people with *M694V* homozygous are more likely to be colchicine-nonresponsive **[10]**.

2.2.3. Cytokines targeting drugs

Being an inflammatory disorder, FMF is associated with inflammatory cytokines release including IL-1β and IL-6. Therefore, a treatment option for FMF may be targeting such cytokines **[11]**.

2.2.3.1. Anti IL-1β drugs

2.2.3.1.1. Anakinra

Anakinra is a human recombinant unglycosylated analog of the IL-1 receptor. It serves as an antagonist of IL-1 receptors. It was found to be used for the management of autoimmune diseases **[12]**. It is the most extensively used IL-1 antagonist in FMF treatment. Noteworthy, Anakinra is a very valuable treatment in FMF patients who suffer from amyloidosis as it suppresses the acute-phase proteins. This supports the fact that the FMF pyrin mutant protein directly affects the activation of IL-1β, indicating that increased IL-1 responsiveness may be one reason driving pyrin mutations **[13]**. Due to its brief half-life (4-6 hours), anakinra needs to be injected every day. One benefit of the short half-life is that it can be used to determine whether an uncommon manifestation is related to FMF itself or not, as well as a diagnostic challenge test for suspected IL-1-mediated disorders **[14]**.

A daily dose of 1-2 mg/kg is recommended, reaching a maximum dose of 8 mg/kg/day. It is usually used at a dose of 100 mg/day. Taking into consideration the patient's response, the dose can be elevated **[14]**. As a result, patients rarely endure multiple doses due to painful injections. Individuals suffering from end-stage renal disease (ESRD) need to modify their dosage, beginning with a 100 mg dose every other day. Skin reactions, leukopenia, infections, and weight gain are further noteworthy side effects. Long-term use may lead to a loss of efficacy, which is a sign that canakinumab should be used instead **[15]**.

2.2.3.1.2. Canakinumab

Canakinumab is a monoclonal antibody of

the class IgG1 that is fully humanized and selectively inhibits IL-1 beta. In patients who suffer from complicated FMF due to amyloidosis, it significantly reduces proteinuria **[16]**. It is the only cytokine blocker that the FDA has approved for the treatment of FMF cases that are resistant to colchicine in the US. Due to its mean plasma half-life of 26 days, monthly or biweekly doses are possible **[15]**.

Canakinumab treatment begins at 150 mg/month; additionally, the dose can be escalated to reach a maximum of 300 mg per month or tapered to 150 mg per month. Practically, Anakinra injections are less pleasant than canakinumab injections, which may increase treatment adherence **[15]**.

2.2.3.1.3 Rilonacept

The extracellular domains of type I IL-1 receptor and IL-1 receptor accessory protein are combined to form the fusion protein that is known as Rilonacept **[17]**.

2.2.3.2 Anti IL-6 drugs

2.2.3.2.1 Tocilizumab

Tocilizumab has been widely used for the management of rheumatoid arthritis. FMF amyloidosis patients should take an infusion of 8 mg/kg/month of tocilizumab for a period of three to 16 months. After proteinuria normalization, if tocilizumab is discontinued, proteinuria relapse occurs **[18]**.

3. FMF and Food interaction

Some foods must be reduced from the daily diet, including refined carbohydrates, pastries, French fries, soda-containing drinks, sugar-sweetened beverages, and red meat. By contrast, some foods may help reduce inflammation as tomatoes, olive oil, vegetables, nuts, fatty fish, and fruits **[19-21]**.

4. Diagnosis

Physical examination, appearance of symptoms, and family history represent the cornerstone elements for FMF diagnosis. Family history is a key element for FMF diagnosis, as it is a hereditary disorder.

4.1. Tel-Hashomer criteria

This includes major and minor criteria (Listed below). A patient is diagnosed with FMF if two or more of the major criteria appear or one major and two minor criteria occur **[1] (Fig. 2)**.

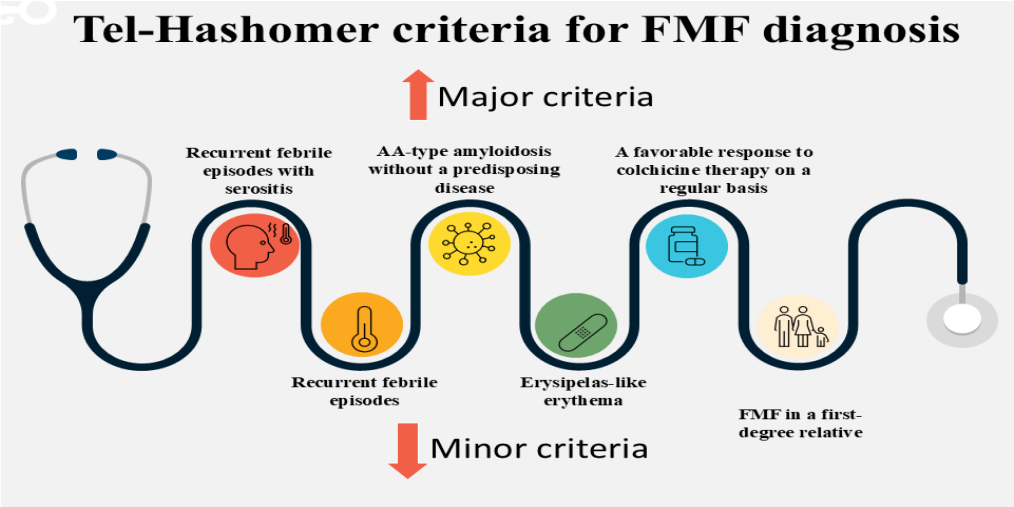

Fig. 2. Tel-Hashomer criteria for FMF diagnosis

4.2. Livneh criteria

This diagnostic tool includes major and minor criteria. The diagnosis of FMF depends on the presence of not less than one major, or two minor criteria has been diagnosed as FMF **[6] (Fig. 3)**.

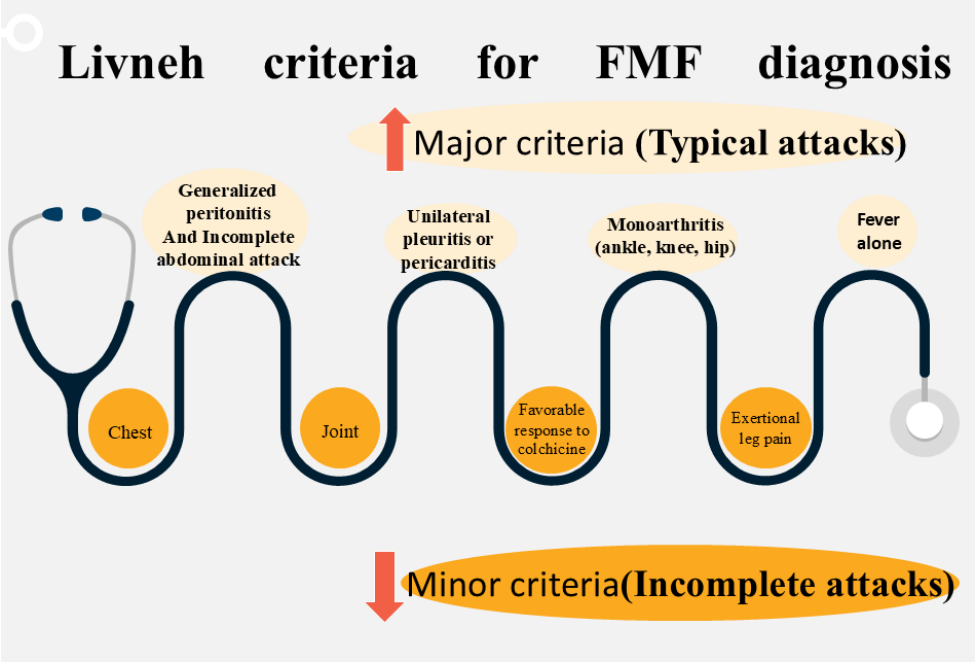

Fig. 3. Livneh criteria for FMF diagnosis

The following two items must be present to ensure a typical attack: they must be recurrent (at least three episodes), febrile (rectal temperature of 38 °C), and brief in length (12 h to 3 days). One or two of the following distinguish incomplete attacks from typical attacks: temperature <38 °C, shorter duration (not less than six hours and not more than seven days), no symptoms of peritonitis, and joint arthritis rather than hip, knee, or ankle inflammation.

4.3 Diagnostic tests

4.3.1 Laboratory tests

Blood and urine analysis for inflammatory markers may help diagnose FMF, especially during an attack. For example, increased neutrophil levels, elevated erythrocyte sedimentation rate (ESR), enhanced plasma fibrinogen, elevated haptoglobin, and C-reactive protein in the blood may indicate FMF presence. Moreover, elevated albumin and amyloidosis in urine, as well as haematuria, may indicate an FMF attack **[6]**.

4.3.2. Genetic testing

Despite genetic testing for MEFV mutations may reveal the FMF occurrence, false negative results may be present for genetic tests. Thus, genetic testing is rarely used as a sole tool for FMF diagnosis. Genetic testing is preferred for first-degree relatives, as well as people at risk of developing FMF **[1]**.

5. Complications

One of the most serious complications of FMF is renal failure, which is indicated by "amyloidosis." In some asymptomatic patients, amyloidosis represents the main symptom of the

disease **[2]**.

5.1 FMF and fertility

5.1.1 Females

Peritoneal adhesions caused by recurrent bouts of peritonitis were thought to be the main reason for infertility in female FMF patients **[22]**. In an earlier study, they found that four out of thirteen patients with fertility issues had varied levels of adhesions in the pelvis or tubal illness, which could have contributed to infertility. However, it remained unclear whether FMF attacks were the individual cause of the adhesions **[23]**. Peritoneal adhesions could easily have been caused by pelvic inflammatory disease in these patients. Visible peritoneal adhesions are uncommon, and this reason of infertility is unusual. The present use of colchicine, which can prevent peritoneal adhesions from forming, is one reason for this discovery **[24]**.

In another facility, a patient with secondary sterility was seen after repeated in vitro fertilization failed. The sperm was discovered to be incapable of penetrating the ovum. A close examination of this patient's eggs revealed that they were covered in a hard material that stained positive for amyloid **[25]**. This discovery led to the evolution of the "X-technique," which involves creating an exterior pore that allows sperm to reach the ovum. As a result, FMF and amyloidosis may have an impact on female fertility. After the initiation of colchicine therapy in FMF, this problem became uncommon **[25]**.

For pregnant women, a higher rate of miscarriage has been discovered in FMF patients who are pregnant. The mechanisms involved, however, are unknown. Even though colchicine is a mitotic inhibitor and has been shown to cross the placenta **[26]**. Before the introduction of colchicine, studies from the 1970s found that women with FMF had a higher risk of abortions and miscarriages (25–30%) than the general population. Today, the course of pregnancies and their outcomes in patients who suffer from FMF is much better, almost comparable to the general female population. This positive change could be attributed to improvements in pregnancy surveillance and colchicine treatment **[27]**.

Cabili et al (1992) investigated 29 pregnancy cases in 17 females with FMF and amyloidosis and discovered that renal function deteriorated in nearly seven of them. These results suggest that people with renal amyloidosis should be counseled not to conceive **[28]**. However, a few people who had both FMF and amyloidosis went on to have healthy pregnancies. There is no increased risk of fetal anomalies in pregnant FMF women who have received colchicine.

5.1.2 Males

FMF progression may lead to testicular impairment and hence, affect spermatogenesis. Generally, sperm pathogenesis in FMF males using a normal dosage of colchicine is extremely low. However, Colchicine may have a negative effect on sperm activity owing to its effect on microtubular function. Ben-Chetrit et al. proved that sperm motility was reduced markedly following incubation with colchicine (10 g/mL) for 18 h **[29]**.

6. Genetics and pathogenesis

FMF results from the gain-of-function alterations and mutations of the MEFV gene, located on chromosome 16 (16p13.3) **[30]**. The 781 amino acid protein pyrin, which MEFV encodes, is found in the nucleus and cytoplasm in several isoforms **[1]**. Not less than four functional domains are present within the pyrin: *PYD*, *bBOX*, *CC*, and *B30.2/SPRY*. Pyrin is activated and then oligomerizes with other proteins in the cell to form the pyrin inflammasome, a macromolecular complex that activates caspase-1, which facilitates the discharge of pro-inflammatory IL-1 and IL-18 from their inactive

precursors and pyroptosis via the gasdermin β D pathway **[31]**. The cytoplasmic pyrin initiates interactions with microtubules within the skeleton of the cell. This pyrin belongs to a family of cytosolic pattern recognition receptors (PRRs) that are assigned to provoke fast innate immune responses via the detection of intrinsic perilous pathogens or extrinsic damage-associated molecular patterns or pathogen-associated molecular patterns (DAMPs and PAMPs) **[32]**.

In contrast to other receptors, pyrin can't directly recognize DAMPs/PAMPs, but it can identify changes in the cytoplasmic homeostasis that are triggered by detrimental stimuli, referred to as "homeostasis-altering molecular processes" (HAMPs). These affect RhoA GTPase in cells. Under normal circumstances, the serine-threonine kinases PKN1 and PKN2, which bind and phosphorylate pyrin, are activated by RhoA GTPase **[32]**. As long as the phosphorylated form of the pyrin binds to the inhibitory 14-3-3 protein, the pyrin inflammasome cannot be formed, as this binding keeps the pyrin in an inactive state. In FMF, mutations that happen in the MEFV gene hinder the pyrin's ability to interact with microtubules, PKN, and 14-3-3 proteins, which in turn help to form a proinflammatory pyrin inflammasome **[33]**.

After the assembly of the pyrin inflammasome, it stimulates caspase-1 to process pro-IL-1 and IL-18, respectively, and cells undergo β and pro-IL-18 to their mature forms IL-1β an inflammatory death termed pyroptosis **[33, 34]**. The typical febrile inflammatory attacks associated with FMF are caused by the excessive stimulation of the pyrin inflammasome and the subsequent inflammation. IL-1 provoked gene expression that is related to the entire IL-1 pathway, hence, triggering its β production, and contributing to an inflammatory burst. Upregulation of pyrin expression is stimulated by various cytokines: interferon (IFN), IL-4, (TNF)-α, and IL-10, as well as Lipopolysaccharides (LPS) **[35]**.

The typical organ sites involved in FMF1 are explained by the fact that pyrin is specifically expressed in innate cells, such as granulocytes, cytokine-activated monocytes, dendritic cells, and synovial and serosal fibroblasts. While the exact cause of FMF's episodic nature remains obscure, during attacks, neutrophil extracellular traps (NETs), i.e., chromatin filaments decorated with neutrophilic proteins and captured IL-1, are formed, restricting further β, via a negative feedback mechanism that could clarify the self-limited β generation of IL-1 nature of FMF attacks **[1]**.

The *MEFV* gene contains ten exons, and more than 370 variants have been found. With the use of genome sequencing, the number of variants is growing. The majority of the variants that are classified as pathogenic or likely pathogenic are found on exon 10, encoding for the B30.2/SPRY domain, which is responsible for activating caspase 1. In regions where FMF is endemic, *M694V* is the most prevalent *MEFV* variant **[5]**.

Other frequent exon 10 variants are *M694I, V726A, M680I,* and *c.2040G*. Approximately 75% of FMF patients have these variations. The usual clinical profile of FMF and more severe disease are linked to the carriage of these variations. The majority of benign and probably benign mutations are found on exon 2 and do not typically result in the classic FMF phenotype **[36]**. A significant proportion of registered variants, approximately two-thirds, are either not classified or classified as variants of unclear significance (VUS) because their clinical connection is unknown **[37]**.

Although FMF has an autosomal recessive

inheritance pattern, about 30% of individuals only have one detrimental variant (monoallelic disease) **[1]**. A high rate of consanguineous marriage accumulation among individuals from subsequent generations may be regarded as a dominant inheritance; however, this is pseudo-dominant transmission in different countries, where FMF is prevalent, while there are also some identified MEFV variants with real dominant inheritance. "Asymptomatic carriers" of the disease are characterized as individuals who have no symptoms and possess one recognizable pathogenic variant of the MEFV gene, whereas "phenotype 3" refers to symptom-free persons who show two pathogenic variants **[38]**.

While genetic factors play a significant role, the environment also contributes to FMF through epigenetic mechanisms **[30]**.

These epigenetic mechanisms are involved: DNA methylation, in which altered DNA methylation patterns influence FMF severity and response to colchicine treatment. In addition, histone modifications as epigenetic changes in histones impact gene expression and inflammatory pathways, and finally, noncoding RNAs, where these molecules regulate gene expression and contribute to FMF pathophysiology.

7. Conclusions

FMF remains a challenging condition; advances in understanding its pathophysiology and treatment options continue to enhance patient care and management. Its etiology is rooted in mutations of the MEFV gene, which encodes the protein pyrin, crucial for regulating inflammation. The treatment of FMF mainly relies on colchicine, which successfully diminishes the frequency and intensity of episodes and helps prevent serious complications like amyloidosis. When colchicine is either ineffective or not well tolerated, alternative options include NSAIDs or biological agents that target particular inflammatory processes. Prompt diagnosis and effective treatment are crucial for enhancing patient outcomes and quality of life.

List of abbreviations:

CYP3A4, Cytochrome P3A4; DAMPs, Damage-associated molecular patterns; ESR, Elevated erythrocyte sedimentation rate; ESRD, End-stage renal disease; FMF, Familial Mediterranean fever; HAMPs, Homeostasis-altering molecular processes; IFN, Interferon; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; LPS, Lipopolysaccharides; MEFV, Mediterranean fever; NETs, Neutrophil extracellular traps; NLRP3, NOD-like receptor, pyrin domain containing 3; NSAIDS, Non-steroidal anti-inflammatory drugs; PAMPs, Pathogen-associated molecular patterns; PRRs, Pattern recognition receptors pathogen; TNF-α, Tumor necrosis factor-alpha.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Availability of the data and Material

Data will be made available on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contribution

A.H.A.: Literature review, Supervision, Data collection, Writing – First draft. N.A., N.A., N.H., N.Y., N.I., N.M., N.M., M.M., N.E.: Data collection, Literature review, Investigation, Writing – First draft. M.Y.G.: Conceptualization, Literature review, Writing - Review & Editing, Supervision. All authors approved the final version of the manuscript.

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