



REVIEW

Differential mutational profiles of familial Mediterranean fever in North Africa

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Abstract

Familial Mediterranean fever (FMF) is a recessive autoinflammatory disease, mainly occurring in the eastern Mediterranean. In these populations, the five FMF founder mutations are differently distributed. In Algeria, the FMF-causing variants remain poorly explored. This retrospective study aims to report the mutational profile of Algerian FMF patients and to compare it with North African FMF patients. One hundred eighty-three unrelated patients clinically suspected of FMF were recruited from various Algerian hospitals (2007–2015) and tested for mutations in exon 10 of *MEFV* gene. Molecular analysis identified 144 mutant alleles among 87 of 183 patients (47.5%). p.M694I was the most prevalent pathogenic allele, accounting for 63.2% of mutant alleles, followed by p.M694V and p.M680I occurring with a same frequency (14.5%). Others, p.A744S (6.2%) and p.I692del (1.3%), are less frequent. Interestingly, p.M694I was the most recurrent in patients with renal AA-amyloidosis. Our results provide the first genetic data on FMF in Algeria, demonstrating the predominance of p.M694I and the absence of p.V726A, compared to other North African countries (Morocco, Tunisia, and Egypt). In conclusion, North African FMF patients display differential mutational profiles that may result from the difference in ethnic origin and the genetic heterogeneity among these populations.

KEYWORDS

Algeria, familial Mediterranean fever, *MEFV*, North-Africa, p.M694I, renal AA-amyloidosis

1 | INTRODUCTION

Familial Mediterranean fever (FMF; OMIM 249100) is the most recurrent hereditary fever affecting the eastern Mediterranean, namely, Arabs, Sephardic Jews, Turks, and Armenians (Ben-Chetrit & Touitou, 2009; El-Shanti, Majeed, & El-Khateeb, 2006). The first symptoms of FMF appear in early childhood in 50% of cases (Ben-Chetrit & Levy, 1998), and before the age of 20 in about 90% of the patients (Sohar, Gafni, Pras, & Heller, 1967). FMF is an autoinflammatory disease characterized by recurrent, self-limited, episodes of fever, and serosal inflammation (Ben-

Chetrit & Levy, 1998; Padeh & Berkun, 2016). Renal AA-amyloidosis is the most deleterious long-term complication that can lead to renal failure and death in untreated patients (Obici & Merlini, 2012; Scarpioni & Obici, 2018).

Genetically, FMF is a recessive monogenic disease caused by mutations in the *MEFV* gene located on human chromosome 16p13.3 (French FMF Consortium, 1997; The International FMF Consortium, 1997). *MEFV* gene encodes a 781 amino acid protein pyrin/marenostrin, primarily expressed in neutrophils, monocytes, dendritic cells, and fibroblasts (Centola et al., 2000). Pyrin plays

an important role in innate immune system through its interaction with the components of the NLRP3 inflammasome, regulating the production of IL-1 β (Campbell, Raheem, Malemud, & Askari, 2016; Papin et al., 2007), and by its capacity to form the pyrin inflammasome (Park, Wood, Kastner, & Chae, 2016; Schnappauf, Chae, Kastner, & Aksentijevich, 2019). The *MEFV* gene consists of 10 exons, on which more than 370 variants have been reported (<http://fmf.igh.cnrs.fr/infevers>). However, a high fraction of them are of uncertain significance, and mostly located within exons 2 (e.g., p.E148Q, c.442G>C, rs3743930) and 10 (e.g., p.A744S, c.2230G>T, rs61732874) (Van Gijn et al., 2018). The pathogenic variants, p.M680I (c.2040G>A, c.2040G>C, rs28940580), p.M694V (c.2080A>G, rs61752717), p.M694I (c.2082G>A, rs28940578), and p.V726A (c.2177T>C, rs28940579), located in exon 10, are the minimum set recommended to be screened (Shinar et al., 2012; Van Gijn et al., 2018). These pathogenic variants and p.E148Q are responsible of over two-thirds of FMF cases in populations commonly affected by FMF (Ozdogan & Ugurlu, 2019). Several studies reported founder mutations associated with FMF differently distributed among Mediterranean populations (El-Shanti et al., 2006; Papadopoulos, Giaglis, Mitroulis, & Ritis, 2008; Touitou, 2001). In Algeria, the disease-causing variants remain poorly explored. Two molecular studies have been implemented in the Algerian population exploring the profile of mutations in the *MEFV* gene (Ait-Idir, Bouldjennet, Taha, El-Shanti, & Djerdjouri, 2015; Ait-Idir, Khilan, Djerdjouri, & El-Shanti, 2011), while the third study has been focused on *MEFV* mutations associated with renal AA-amyloidosis in suspected FMF patients (Ait-Idir et al., 2017). This genetic retrospective study summarizes our previously published results, aiming to compare the mutational profile to other North African populations.

2 | METHODS

2.1 | Patients

Three investigations of *MEFV* gene included a total of 183 unrelated patients recruited from Algerian hospitals between 2007 and 2015. Molecular studies 1 and 2 were carried out on two cohorts of 71 patients (35 males, 36 females; median age: 10 years [2–65]) (Ait-Idir et al., 2011), and 84 patients (42 males, 42 females; median age: 13.5 years [2–56]) (Ait-Idir et al., 2015). The diagnosis was based on clinical findings of classical FMF symptoms such as recurrent fever, abdominal pain, chest pain, and joint involvement. All patients were evaluated for renal AA-amyloidosis. The third study included 28 patients (15 males, 13 females; median age: 38 years [12–65]) with renal biopsy-proven

amyloidosis (Ait-Idir et al., 2017). In this cohort, the main inclusion criteria were the presence of AA-amyloidosis of unknown origin (after discarding other etiologies of AA-amyloidosis) in the presence of clinical symptoms suggestive of FMF or without clinical symptoms. Other details about all patients were also collected, including demographic data, age of onset of fever attacks, attack duration, the laps between attacks, family history of FMF, and colchicine therapy.

2.2 | Genotyping

Genomic DNA was extracted from peripheral leukocytes using a standard protocol (Miller, Dykes, & Polesky, 1988). The first comprehensive study sequenced the promoter region, all exons, and exon–intron junctions (Ait-Idir et al., 2011). The two other cohorts were screened for exon 10 only (Ait-Idir et al., 2015, 2017). PCR products were purified and subjected to sequencing by BigDye terminator chemistry on an ABI Genetic Analyser (3730xl), according to the protocol of Qatar Biomedical Research Institute (QBRI). Sequences were analyzed by Seq-Scape 2.5 software (Applied Biosystems, Foster City, CA).

Our studies were approved by the ethics committee and deontology of University of Sciences and Technology Houari Boumediene (USTHB, Algiers), which uses the standards and recommendations of the Declaration of Helsinki, and all patients or their legal guardians were consenting.

3 | RESULTS

3.1 | *MEFV* gene mutations in Algerian FMF patients

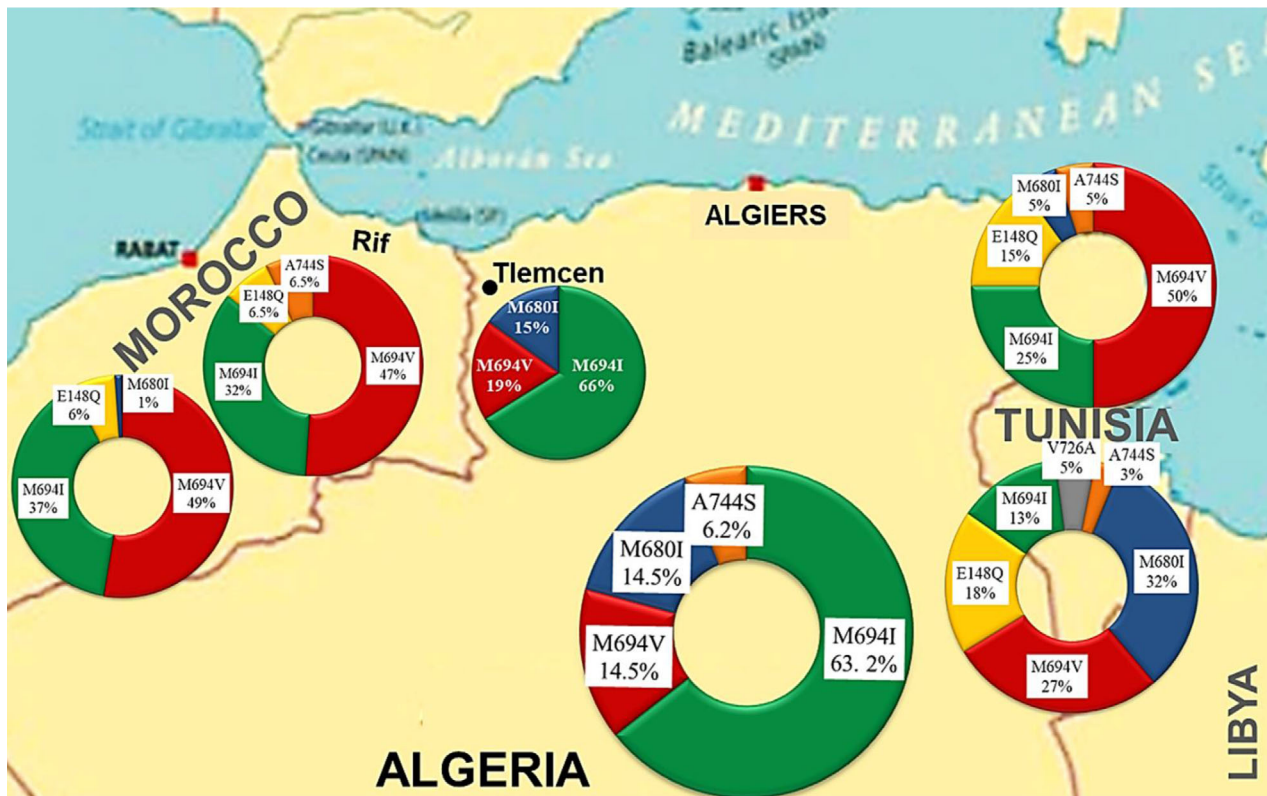
The screening of exon 10 for 183 patients identifies five variants with variable frequencies (Table 1). The results showed a clear predominance of p.M694I in each group of patients with a frequency between 50 and 71.4% of total mutant alleles.

The study 1 identified a total of 50 mutant alleles, mainly located in exon 10 (p.M694I, 50%; p.M694V, 14%; p.A744S, 10%; p.M680I, 8%; and p.I692del, 2%). Other variants were identified in exons 2 (p.E148Q, 12%), 3 (p.P369S, 2%), and 9 (p.I591T, 2%) (Ait-Idir et al., 2011). Studies 2 and 3 have explored exon 10 only. In the study 2, p.M680I (26.4%) was the second identified pathogenic variant, followed by p.M694V and p.A744S at the same frequency (7.5%). The study 3 recruited 28 patients with renal AA-amyloidosis among which p.M694V appeared with a smaller frequency (20.4%) compared to p.M694I (71.4%).

TABLE 1 Allele number and frequencies of mutant alleles identified in Algerian FMF patients

Patients	Mutant alleles, Frequency (%)	Allele number, allelic frequencies (%)					
		Exon 10					Exon 2
		p.M694I	p.M694V	p.A744S	p.M680I	p.I692del	p.E148Q
Study 1 (n = 71)	50/142 (35.2)	25 (50)	7 (14)	5 (10)	4 (8)	1 (2)	6 (12)
Study 2 (n = 84)	53/168 (31.5)	31 (58.5)	4 (7.5)	4 (7.5)	14 (26.4)	Absent	ND
Study 3 (n = 28)	49/56 (87.5)	35 (71.4)	10 (20.4)	Absent	3 (6.1)	1 (2)	ND

Abbreviation: ND, not determined.

**FIGURE 1** Distribution of *MEFV* gene alleles in Maghreb [Colour figure can be viewed at wileyonlinelibrary.com]

Other variants, p.M680I and p.I692del (c.2076_2078del, rs104895093), were rare and p.A744S was absent. Compared to precedent studies, this one identified a high proportion of mutant alleles, which may be explained by criteria used for patients' selection, mainly based on the presence of AA-amyloidosis without a predisposing disease. This complication is one of the major FMF diagnostic criteria, and it is common among untreated patients (Sohar et al., 1967). Indeed, among our patients, the risk for developing AA-amyloidosis secondary to FMF was high because of diagnosis delay, and colchicine therapy missing (Ait-Idir et al., 2017).

Thus, in exon 10, molecular analysis identified 144 mutant alleles among 87 of 183 (47.5%) analyzed patients

pooled from three previous studies. The resultant mutational profile is as follows: p.M694I (91/144; 63.2%), p.M694V (21/144; 14.5%), p.M680I (21/144; 14.5%), p.A744S (9/144; 6.2%), and p.I692del (2/144; 1.3%) (Figure 1). Three pathogenic variants were identified at homozygous state, p.M694I (28 patients), p.M694V (three patients), and p.M680I (three patients).

3.2 | *MEFV* gene mutations in North African patients

The North African region spans six countries, Maghreb-ian countries (Mauritania, Morocco, Algeria Tunisia, and

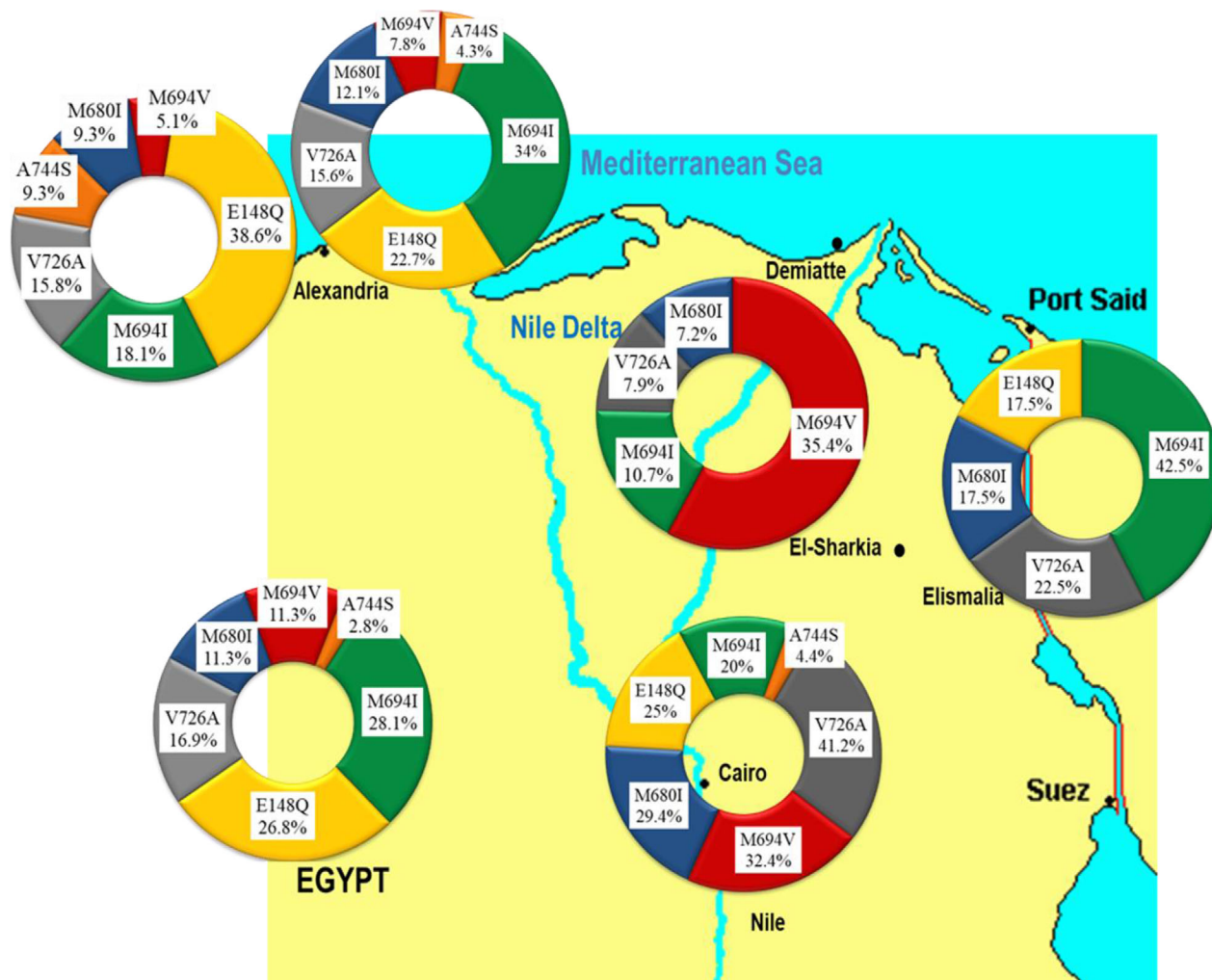


FIGURE 2 Distribution of *MEFV* gene alleles in Egyptian regions [Colour figure can be viewed at wileyonlinelibrary.com]

Libya), and Egypt. The *MEFV* gene has not been explored in Libya and Mauritania.

3.2.1 | *MEFV* mutational profiles in Maghrebian FMF patients

MEFV has been poorly explored in Maghrebian populations. Few available studies indicate they shared p.M694I, p.M694V, p.M680I, p.A744S, and p.E148Q variants, and showed differential distributions between Maghrebian countries (Figure 1).

According to our results, p.M694I is the most recurrent pathogenic variant characterizing Algerian patients, while in Moroccan and Tunisian patients, it is in second position after p.M694V, and represents 37% and 25% of the mutant alleles, respectively (Belmahi et al., 2006) (Figure 1). The predominance of p.M694V among the Moroccan patients has been confirmed later (47%) (Belmahi, Cherkaoui, Hama, & Sefiani, 2012) (Figure 1),

while it occurs with a lower frequency (14.5%) in Algerian FMF patients. For Tunisian, p.M680I appears as the commonest pathogenic variant (32%), followed by p.M694V (27%), p.M694I (13%), and p.V726A (5%) (Chaabouni et al., 2007) (Figure 1). Unlike Algerian and Tunisian patients, p.M680I was very rare to absent in Moroccan patients (Belmahi et al., 2006, 2012), and p.V726A appeared only in Tunisian patients.

3.2.2 | *MEFV* mutational profiles in Egyptian FMF patients

MEFV has been extensively explored in Egypt (Figure 2). Recently, p.E148Q was demonstrated to be the most recurrent (38.6%) among the patients from Alexandria in north-west of Egypt. p.M694I was the second variant to be identified (18.1%), followed by p.V726A (15.8%) and p.A744S (9.3%) (Mansour et al., 2019) (Figure 2). These results contrast with those previously reported for the same region

TABLE 2 Comparison of the frequencies of the five frequent sequence variants in different populations at risk

Regions	Ethnic groups	Sequence variants (%)					References
		p.M694V	p.V726A	p.M694I	p.M680I	p.E148Q	
Western European	Greeks	38.1	12.2	2.7	19.7	10.9	(Giaglis et al., 2007)
	Italians	16		10	8	14	(La Regina et al., 2003)
	Spaniards	37	3.1	12.5	0	16	(Aldea et al., 2004)
Middle-East	Jordanians	30	20	8.3	9	21.5	(Hababbeh et al., 2015)
	Palestinians	49	16	11.9	4	8.5	(Ayesh et al., 2005)
	Lebanese	26.1	21.3	9.6	7.7	22.2	(Sabbagh et al., 2008)
	Syrians	24.1	11.4	8.2	10.3	13.5	(Jarjour & Jamra, 2017)
	Non-Ashkenazi Jews	76.8	11.71	0.8	0.4	9.73	(Sharkia et al., 2013)
Eastern European	Turks	39	11.2	0.2	14.8	23.8	(Yildirim et al., 2019)
		48	12.5	0	15	18	(Cekin et al., 2017)
		25.9	15.8	0	6.8	40.1	(Uluca et al., 2015)

showing the predominance of p.M694I (34%), followed by p.E148Q (22.7%). The p.V726A, p.M680I, and p.M694V pathogenic variants accounted for 15.6%, 12.1%, and 7.8% frequencies, respectively (El Gezery, Abou-Zeid, Hashad, & El-Sayegh, 2010). The predominance of p.M694I (42.5%) was also observed in patients originating from the Suez Canal in north-east Egypt, while p.M694V was absent (Ibrahim et al., 2010) (Figure 2). The results of a survey of FMF in Egypt reported a slight difference between p.M694I (28.1%) and p.E148Q (26.8%) (Ali, Elhady, Abbas, & Mandouh, 2017). In contrast, in FMF patients from middle Delta governorates, p.M694V was the most predominant (35.4%), followed by p.M694I (10.7%), p.V726A (7.9%), and p.M680I (7.2%) (Al-Haggar et al., 2014).

In patients recruited from clinics and university of Cairo, p.V726A has been identified as the most recurrent allele (41.2%), followed by p.M694V (32.4%), p.M680I (29.4%), p.E148Q (25%), and p.M694I (20%) (El-Garf, Salah, Iskander, Salah, & Amin, 2010).

Thus, in Egyptian population, a mutational heterogeneity emerged from the different molecular analyses and between regions. Interestingly, Egyptian FMF patients from some regions of Egypt share with Algerian FMF patients the predominance of p.M694I. In contrast to Egypt and Tunisia, p.V726A is absent in Algerian and Moroccan FMF patients.

Thus, the mutational variability in *MEFV* gene among North African populations could be attributed to the genetic heterogeneity of these populations. Indeed, North Africa has experienced a very complex history characterized by population replacements, extensive continuous gene flow, and differential admixture from neighboring regions, which yielded to a large degree of genetic heterogeneity among North African populations (Arauna & Comas, 2017).

4 | DISCUSSION

The present retrospective compared the published data on FMF in Algeria and in North African countries. It turns out that in Maghreb, p.M694V and p.M694I are the most recurrent pathogenic variants in FMF patients, with the prevalence of p.M694I in Algeria. The latter has been associated with the ARA2 haplotype of North Africans (French FMF Consortium., 1997). Previously, Belmahi et al. (2012) has shown that 85% of patients sharing this variant in Rif northern Morocco are of Berber origin, which suggests p.M694I as a variant characterizing the FMF Berberian patients. Berber populations are considered as the oldest inhabitants of North Africa, and are more important in Morocco and Algeria than in Tunisia, Libya, and Egypt (Harich et al., 2002). Among our positive patients, one-third was from Tlemcen in north-west Algeria, a region bordering the Moroccan Rif. As Riffian patients, p.M694I was the most prevalent mutant allele among Tlemcenean FMF patients (66.03%), followed by p.M694V (18.86%) and p.M680I (15.09%) (Figure 1). This clearly indicates p.M694I as the most prevalent variant shared by a same substratum of FMF population in Tlemcen and Moroccan Rif. Besides, p.M694I is the third most common pathogenic variant carried by ethnic Arab group (El-Shanti et al., 2006). This would allow the hypothesis that p.M694I was introduced by the Arabs in the seventh century and spread to Algeria and other regions of the Maghreb from this founding effect. To support the Arab origin of p.M694I, it will be necessary to date this variant within the Algerian population.

On the European Mediterranean coast, p.M694V is the most prevalent pathogenic variant among patients from Greece (Giaglis et al., 2007), Italy (La Regina et al., 2003), and Spain (Aldea et al., 2004), while p.M694I was poorly identified (Table 2).

In Arab populations, p.M694V is the most recurrent in Jordan (Hababbeh et al., 2015), Palestine (Ayesh, Nassar, Al-Sharef, Abu-Libdeh, & Darwish, 2005), and Lebanon (Medlej-Hashim et al., 2005; Sabbagh et al., 2008). Recently, the distribution of the *MEFV* mutations examined in 14 governorates of Syria reported a heterogeneous mutational profile between the tested regions, and a clear predominance of p.M694V in Damascus (Jarjour & Jamra, 2017) (Table 2). While p.M694V remains less common among Arabs and other populations commonly affected by FMF, non-Ashkenazi Jews had the highest occurrence of this variant (Sharkia et al., 2013) (Table 2).

In Turkey, the same distribution of the following variants p.M694V, p.E148Q, p.M680I, and p.V726A has been showed in patients from central and eastern Anatolia (Etem, Deveci, Erol, Yuce, & Elyas, 2010; Yildirim et al., 2019) and Istanbul (Cekin, Akyurek, Pinarbasi, & Ozen, 2017) (Table 2). Moreover, Etem et al. (2010) reported p.M694V as the most common pathogenic variant in different patients group, except for the Southeast Anatolia where p.E148Q was the most recurrent (Uluca et al., 2015). Interestingly, p.M694I is very rare (Yildirim et al., 2019) or not identified in Turkish FMF patients (Cekin et al., 2017) (Table 2).

5 | CONCLUSION

Our results provided the first genetic data on FMF in Algeria, associating p.M694I mostly to Algerian FMF patients. *MEFV* heterogeneity among North Africans raises the importance of population genetics studies of FMF in North Africa for dating FMF founder mutations, and to define the influence of ancient migrations in *MEFV* mutations spreading in this area.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Djouher Ait-Idir performed data analysis and manuscript preparation. Bahia Djerdjouri performed manuscript revision.

Both the authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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