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Prevalence and distribution of *MEFV* mutations among Arabs from the Maghreb patients suffering from familial Mediterranean fever

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Abstract

Familial Mediterranean fever (FMF) is an autosomal recessive inherited disease caused by mutations in *MEFV*. This disease is characterized by recurrent episodes of fever accompanied with topical signs of inflammation. Some patients can develop renal amyloidosis. We prospectively investigated *MEFV* mutations in a cohort of 209 unrelated Arab patients from Maghreb (85 Algerians, 87 Moroccans, and 37 Tunisians) with a clinical suspicion of FMF. FMF is the main cause of periodic fever syndrome in Maghreb. The most frequent *MEFV* mutations in this cohort were M694V and M694I. These mutations account for different proportions of the *MEFV* mutations in Algeria (5%, 80%), Morocco (49%, 37%), and Tunisia (50%, 25%) patients. M694I mutation is specific to the Arab population from Maghreb. Other rare mutations were observed: M680L, M680I, A744S, V726A, and E148Q. We estimated the frequency of *MEFV* mutation carriers among the Arab Maghrebian population at around 1%, which is significantly lower than in non-Ashkenazi Jews, Armenians or Turks. ***To cite this article: L. Belmahi et al., C. R. Biologies 329 (2006).***

Résumé

Prévalence et distribution des mutations de *MEFV* chez des Arabes originaires du Maghreb souffrant de fièvre familiale méditerranéenne. La fièvre méditerranéenne familiale (FMF) est une maladie génétique autosomique récessive due à des mutations dans *MEFV*. Cette maladie de l'inflammation est caractérisée, le plus souvent, par des épisodes récurrents de fièvre, accompagnés de douleurs abdominales et articulaires. Nous avons recherché des mutations dans *MEFV* chez 209 malades Arabes non liés génétiquement et originaires du Maghreb (85 Algériens, 87 Marocains, 37 Tunisiens) ayant un diagnostic clinique de FMF. La FMF est la principale cause de fièvre périodique au Maghreb. Les mutations *MEFV* les plus fréquentes trouvées dans cette population sont M694V et M694I. Leur fréquence est variable selon les populations en Algérie (5%, 80%), au Maroc (49%, 37%) et en Tunisie (50%, 25%). La mutation M694I est spécifique de la population arabe du Maghreb. D'autres mutations rares ont été trouvées : M680L, M680I, A744S, V726A et E148Q. Nous avons estimé que la fréquence des individus hétérozygotes porteurs de la mutation dans la population normale est de l'ordre de 1%, ce qui est significativement beaucoup plus faible que dans les autres

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populations à risque pour cette maladie (Juifs non ashkénazes, Arméniens et Turcs). ***Pour citer cet article : L. Belmahi et al., C. R. Biologies 329 (2006).***

Keywords: Familial Mediterranean Fever; Pyrin/Marenostrin; Inherited inflammatory disorder

Mots-clés : Fièvre méditerranéenne familiale ; Pyrine/Marénostrine ; Syndrome inflammatoire d'origine génétique

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La fièvre méditerranéenne familiale (FMF, MIM 249100) est une maladie autosomique récessive due à des mutations dans *MEFV*. La FMF est caractérisée par des épisodes récurrents de fièvre accompagnés de douleurs abdominales et articulaires. L'amylose rénale est l'une des complications les plus fréquentes et la plus grave. La colchicine prévient les crises inflammatoires ainsi que le développement de l'amylose. La FMF est très fréquente chez les Juifs non ashkénazes, les Arméniens, les Turcs et les Arabes.

Le but de la présente étude est de déterminer les mutations *MEFV* et leurs fréquences au sein de la population arabe du Maghreb. Pour ceci, nous avons étudié 209 patients suspects de FMF originaires d'Algérie (85), du Maroc (87) et de Tunisie (37). Nous avons confirmé le diagnostic de FMF par la présence de deux mutations à l'état, soit homozygote, soit hétérozygote composite, chez 29 Algériens, 33 Marocains et 7 Tunisiens. Un seul allèle a été trouvé chez 11 Algériens, 9 Marocains et 6 Tunisiens. Les deux mutations les plus fréquentes sont M694I et M694V, mais leur répartition dans les trois pays est très différente, M694I représente 80% des allèles mutés en Algérie, 37% au Maroc et 25% en Tunisie, alors que la mutation M694V représente 5% en Algérie, 49% au Maroc et 50% en Tunisie. La mutation M694I est spécifique des populations arabes du Maghreb et n'est pas retrouvée dans les autres populations à risque citées auparavant, contrairement à la mutation M694V. Ces deux mutations sont très anciennes : elles sont apparues il y a plus de 2000 ans. Des études de polymorphisme du chromosome Y dans la population marocaine ont montré que l'arabisation et l'islamisation de la population berbère est un phénomène culturel et que la population actuelle est génétiquement et principalement d'origine berbère. Il semble donc que la mutation M694I soit d'origine berbère et que la mutation M694V ait été amenée dans cette région au cours des différentes migrations de certaines populations et notamment par les Juifs non ashkénazes par l'est et par l'Espagne.

Nous avons, de plus, estimé que la fréquence des allèles mutés de *MEFV* dans la population normale n'excède pas 1%, ce qui est beaucoup plus faible que dans les autres populations à risque. La persistance des mutations *MEFV* chez les Arabes du Maghreb ne semble donc pas s'expliquer par une forte pression de sélection.

1. Introduction

Familial Mediterranean fever (FMF, MIM 249100) is an autosomal recessive disorder of the group of hereditary recurrent inflammatory fevers and are due to mutations in *MEFV* [1,2]. FMF is characterized by recurrent episodes of fever accompanied with topical signs of inflammation mainly in the peritoneal, pleural and articular cavities. Renal amyloidosis is a frequent complication. Colchicine has been shown to be effective in preventing attacks as well as the development of amyloidosis. FMF is very common in populations of the Mediterranean Basin, mainly Non-Ashkenazi Jews, Armenians and Turks. In these populations, the estimated carrier rates are very high (1/6 in Armenians and Turks, 1/7 in Non-Ashkenazi Jews), suggesting heterozygote advantage against an as yet not defined infectious pathogen [3,4]. FMF also affects Arab populations, but the prevalence among the North-African Arabs is still unknown.

The aim of this study was to describe the *MEFV* mutation spectrum frequencies among Arab patients from the Maghreb (Algeria, Morocco and Tunisia) and to estimate the carrier rate among the healthy control population.

2. Subjects and methods

We studied 209 unrelated patients in whom FMF was suspected on a clinical basis according to FMF criteria [5]. Main clinical data were registered on a standardized form [6]. Both parents of the patients were North-African Arabs originating from different countries of the Maghreb: Algeria (85) Morocco (87), and Tunisia (37). Informed consent was given by all patients.

3. Mutation search in *MEFV*

To search for *MEFV* mutations, exons 5 and 10 were PCR amplified and sequenced. The E148Q mutation in

exon 2 was detected by PCR amplification followed by *Ava I* digestion as previously described [6].

4. Results and discussion

We studied a cohort of 209 Arab patients from the Maghreb, with a high suspicious diagnosis of periodic fever syndrome. We searched for mutations in *MEFV* and confirmed the FMF diagnosis by the presence of two mutations in 29/85 (34%) Algerians, 33/87 (38%) Moroccans, and 7/37 Tunisians (19%). Only one FMF allele was found in 11/85 (12%) Algerians, 9/87 (10%) Moroccans and 6/37 (16%) Tunisians. The spectrum of *MEFV* mutations and the patient's genotypes are given in Tables 1 and 2, respectively. The most frequent mutations are M694I and M694V, but their respective frequencies are different in Algeria, Tunisia, and Morocco. Among patients carrying two *MEFV* mutations, the M694I mutation is the more frequent one in Algeria (80%), but not in Morocco (37%) and Tunisia (25%), whereas the M694V mutation is more frequently observed in Morocco (49%) and Tunisia (50%) than in Algeria (5%). In contrast to the M694V mutation, which is shared by the different at risk ethnic groups affected by FMF, the M694I mutation is characteristic of the Arab population of the Maghreb. In this study, we also detected rare mutations such as M680I, M680L, V726A, A744S, and E148Q. The M680L mutation has previously been described in a Berber consanguineous family living in Morocco [6]. A previous report [7] has established that the M694V, V726A, M680I and M694I mutation frequencies among Arabs from the Middle-East were 15%, 30%, 18%, and 8%, respectively, which is very different from those observed here in North African Arabs.

M694I is probably as M694V [2] an ancient mutation based on the following arguments: (*i*) M694I is present in three different countries, (*ii*) M694I is rarely described in other populations, (*iii*) M694I is not a recurrent mutation. A study of Y-chromosome variation among Moroccan Arabs demonstrated that Arabization and Islamization of North Africa starting during the 7th century, was a cultural phenomena without extensive genetic replacement [8] and can explain that the M694I mutation is now still present in the same region where the population remains Berber [9]. The M694V mutation in Arabs of Maghreb could have been inherited from the local Jewish population that came from the Middle East after the destruction of Salomon's temple and from Spain from 1492 onwards. During this second flee, which lasted for more than 200 years, the Jewish population from Spain settled mainly in Morocco.

Table 1
Spectrum of *MEFV* mutations among Arabs from the Maghreb affected by FMF

	Algeria	Morocco	Tunisia
M694I	55	28	5
M694V	4	37	10
M680I	1	1	1
E148Q	6	5	3
M680L	0	2	0
V726A	1	0	0
A744S	2	0	1
Total of alleles	69	75	20

Table 2
MEFV genotypes responsible for FMF among Arabs from the Maghreb

	Algeria	Morocco	Tunisia	Total
M694I/M694I	21	9	0	30
M694V/M694V	1	16	4	21
M680L/M680L	0	2	0	2
M694V/M694I	1	3	1	5
M694I/M680I	1	1	1	3
M694V/V726A	1	0	0	1
M694I/E148Q	4	2	1	7
M694I	7	4	2	13
M694V	0	2	1	3
E148Q	2	3	2	7
A744S	2	0	1	3
?	45	45	24	114
Total	85	87	37	209

These historical data can explain the very different ratios of the M694V and M694I mutations observed in the three countries of the Maghreb.

We estimated the *MEFV* mutation carrier frequency in the Arab from Maghreb general population by studying 113 healthy and unrelated individuals (50 Moroccans, 32 Tunisians and 31 Algerians). Only one Moroccan carried a heterozygous M694V mutation leading a carrier frequency below 1%, which is much lower than in the other FMF at-risk populations (Armenians, Turks, Non-Ashkenazi Jews). In terms of selection pressure, this result argues against a strong heterozygote advantage in the Arab population from Maghreb.

In our series, the high proportion of patients without detected *MEFV* mutations suggest that other genes are involved in these periodic fever syndromes, as previously postulated in the Turkish and Armenians from the Karabakh population [10]. This hypothesis agrees with the observation of two unrelated families from Algeria and Tunisia, with several patients affected by renal amyloidosis associated with periodic fever syndrome without *MEFV* and *TNFRSF1A* mutation [11].

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