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ORIGINAL ARTICLE

MEFV mutation carriage in Israeli Jewish individuals from ethnicities with low risk for familial Mediterranean fever

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Familial Mediterranean fever (FMF) is a disease caused by mutations in the MEditerranean FeVer gene (MEFV), and in Israel it most commonly affects Jews of North African extraction, in whom the mutation carrier rate is as high as 1 in 5. To assess the protective as well as the modulating affect of MEFV mutation carriage on various inflammatory disease states, we sought to define the frequency of MEFV mutations in Israeli Jewish individuals of various ethnicities, including those with low frequency of FMF, which were not in the focus of our attention hitherto. A total of 163 adults of Bucharian, Turkish, Georgian, Yemenite and Bulgarian origin comprised the study group. The prevalence of the most frequent MEFV mutations in the Israeli Jewish population, namely: M694V, V726A and E148Q, was assessed. The association of mutation carriage with a personal history of FMF-like phenomena, as well as various inflammatory and non-inflammatory diseases, was evaluated. A high MEFV mutation frequency was found among Jews of Bucharian, Georgian and Bulgarian origin (20%), whereas intermediate and low rates were detected in Jews of Turkish and Yemenite extraction (14 and 8%, respectively). FMF-like manifestations and related diseases were observed more often in MEFV mutation carriers than in their counterparts. MEFV mutation frequency, directly assessed by DNA analysis, exceeds the rate calculated from disease prevalence in Israeli Jewish individuals originated from ethnicities with a low prevalence of FMF. MEFV mutation carriage in this subgroup is associated with various inflammatory disorders.
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INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory, autosomal recessive disorder, prevalent in the Mediterranean basin and characterized by recurrent attacks of fever and serositis. The MEditerranean FeVer gene (MEFV) encodes a protein, called pyrin/marenostrin, which is involved in the regulation of inflammation and apoptosis.[1] Mutations in MEFV (more than 50 thus far) have been associated with FMF. In Israel, FMF most commonly affects Jews of North African and Iraqi extraction (Sepharadi Jews), in whom disease frequency is 1:200 and 1:1000, respectively,[2] whereas in Ashkenazi Jews, originating from Central Europe, the disorder is rare with a frequency of 1:160 000 only.[3] However, direct assessment of mutation frequency, as reported in several studies, revealed quite surprising results of extremely higher-than-expected rates.[4–6] Furthermore, the mutation rates in these two ethnic groups, so vastly separated by FMF disease frequency, were quite comparable, 1 in 5 vs 1 in 7–8 in Sepharadi and Ashkenazi Jews, respectively. These findings suggest that only direct testing of MEFV mutation frequency is appropriate for the assessment of its role.

This study aims to define the frequency of MEFV mutations in the Israeli-Jewish population with low risk for FMF, specifically those originated from the Jewish diaspora of Buchara, Georgia, Yemen, Turkey and Bulgaria. Knowledge of the prevalence of MEFV mutation carriage may help in elucidating their biological advantage and their role in the modulation of non-FMF inflammatory disorders.

MATERIALS AND METHODS

The study group included 163 Jewish individuals, born to parents, both originating from the same country, Buchara, Turkey, Georgia, Yemen or Bulgaria. They were enrolled, provided they stated no personal or family history of FMF. Participants were interviewed, and a questionnaire focusing on manifestations indicative of inflammatory diseases was completed. The study was approved by the institutional review board, and all participants signed an informed consent.

DNA was analyzed for the three most common Jewish MEFV mutations (M694V, V726A, E148Q), using PCR amplification and restriction enzyme digestion.[7]

Statistical analysis was performed for categorical variables using χ^2-test or Fisher's exact test, according to the size of the cells examined; and for

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continuous variables using the Student's *t*-test. All tests of significance were two-tailed; *P*-values <0.05 were considered statistically significant.

RESULTS

A total of 163 individuals, originating from ethnicities with low rates of FMF, were tested for mutations in the MEFV gene. Baseline demographic data are summarized in Table 1. There were 27 carriers of MEFV mutations, 2 of whom, with no manifestations of FMF, carried two mutations each. The mean age and gender distribution were equal among carriers and non-carriers of an MEFV mutation (58.3 ± 17 vs 61.9 ± 19 years and male/female ratio of 16/11 and 72/64, respectively). Mutation carriage rate and distribution of the three studied mutations by origin are detailed in Table 2. The E148Q mutation was the most prevalent, found in 19/326 chromosomes (6%).

The rate of FMF-like conditions, which may indicate a hitherto unrecognized FMF, amyloidosis, splenomegaly (indicative of subclinical inflammation) and a long list of inflammatory diseases, more commonly encountered in FMF, among mutation carriers and non-carriers, are listed in Table 3. There was a statistically significant excess of the combined frequency of FMF-like manifestations (acute arthritis, pericarditis, erysipelas episodes and Behçet's-like disease) in MEFV mutation carriers ($P=0.001$ for the combination). No difference was noted in the frequency of non-inflammatory diseases aside from hypertension, which was unexplainably overrepresented among non-carriers (67/136 vs 7/27 in carriers, $P=0.03$, respectively).

DISCUSSION

The rate of MEFV mutation carriage in Israeli Jewish individuals from ethnicities with a low risk for FMF may be as high as 20%, reaching the frequencies described in North-African Jews, in which overt FMF is prevalent. The combination, in these ethnicities, of a high mutation frequency, on the one hand, with a low disease prevalence, on the other, indicates low mutation penetrance. Indeed, E148Q and V726A, which are considered 'weak' mutations,[8] were the most commonly found in most ethnic groups except for Georgian individuals, in whom M694V, which is associated with a more severe disease phenotype, as well as amyloidosis,[9] was commonly detected (M694V/E148Q ratio of 4/5).

The finding of a high mutation frequency in Jewish communities immigrated to Israel from Eastern Europe, supports the view that this population has actually emerged originally from an area endemic to a hitherto unrecognized pathogen, from which the mutations protect, comparable with Jewish subgroups with high risk for FMF.

On the basis of our experience at the National Center for FMF, which holds in its registry data on most FMF patients in Israel, the frequency of FMF in Georgian Jews is very low (1:5000). This suggests that Georgian Jews carry a modifier gene or system, or are exposed to an environmental moderating factor, which inhibits the clinical expression of the most penetrant MEFV mutation, M694V.

Finally, our findings reiterate the higher frequency of phenotype 3 (genetic positive, clinically negative individuals) in Jewish individuals and the occurrence of FMF-like symptoms and inflammatory diseases in MEFV mutation carriers. The reduced rate of hypertension in mutation carriers needs to be ascertained and further investigated.

Table 1 Demographic characteristics of study participants by origin

Country of origin	*Number of individuals*	*M/F*	*Age (years ± s.d.)*
Buchara	38	15/23	50.5 ± 19.4
Georgia	41	22/19	64.7 ± 16.0
Yemen	36	18/18	62.6 ± 22.6
Turkey	29	23/6	63.5 ± 14.7
Bulgaria	19	10/9	67.7 ± 15.2
Total	163	88/75	61.1 ± 18.9

Abbreviations: F, female; M, male.

Table 3 Frequency of FMF-related conditions

Condition	*Carriers of MEFV mutations (27)* *Number (%)*	*Non-carriers (136)* *Number*
FMF-like attack manifestations[a]	3 (11.1)	0
Chronic FMF manifestations[b]	0	0
Inflammatory diseases associated with FMF[c]	1 (3.7)	0

Abbreviations: FMF, Familial Mediterranean fever; MEFV, the MEditerranean FeVer gene.
[a]Including abdominal, chest, joint, fever alone and erysipelas attacks. Each of the found manifestations occurred in only one individual, once (pericarditis, knee arthritis) or twice (erysipelas), not conforming with FMF criteria ($P<0.05$ for each or $0<0.004$ for the combined manifestations).
[b]Spelnomegaly or amyloidosis.
[c]Including inflammatory bowel disease, polyarteritis nodosa, glomerulonephritis, Behçet's disease. Only Behçet's disease was found (*P*-value insignificant for Behçet's disease alone but $P=0.001$ for the combination with FMF-like manifestations).

Table 2 MEFV mutation by ethnic origin

		Number of mutations				*Mutation type*		
Country of origin	*Number of subjects*	*0*	*1*	*2*	*Carrier rate*	*M694V*	*V726A*	*E148Q*
Buchara	38	30	8	0	(1:5) 0.2	0	0	8
Georgia	41	33	7	1	(1:5) 0.2	4	0	5
Yemen	36	33	3	0	(1:12–13) 0.08	1	0	2
Turkey	29	25	4	0	(1:7–8) 0.14	1	2	1
Bulgaria	19	15	3	1	(1:5) 0.2	0	2	3
Total	163	136	25	2	(1:5–6) 0.18	6	4	19

Abbreviations: MEFV, the MEditerranean FeVer gene.

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